PLACENTAL TRANSMISSION OF SHIGELLA ANTIBODIES *

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Introduction

The transmission of certain antibodies through the placenta has been widely investigated. (1 - 5) It is known that in some infections (such as diphtheria, tetanus, pertussis and certain viral diseases) the titer of antibodies so transmitted can be raised sufficiently to indicate that prenatal immunization against these infections is feasible. Less is known, however, about the possible placental transmission of certain other antibodies, including those of the various types of shigella which cause bacillary dysentery in man.

As is well known, bacillary dysentery is one of the major causes of death among small infants in areas with poor hygienic and sanitary conditions where exposure to the disease occurs very early in life. In such areas, of which unfortunately Turkey is one, the disease is often severe in early infancy and more frequently fatal. An indication of the seriousness of the problem is the fact that approximately half of the children with bacillary dysentery seen at Hacettepe Medical Center are under one year old. Bacilli have been successfully isolated from a seven day old infant and from two others, each 45 days old.

Survivors of the disease develop a kind of resistance against frank clinical attacks of the infection in endemic areas. The exact mechanism of this resistance is not yet fully understood nor has it been established that humoral antibodies play a part in it. However, such a possibility cannot be ruled out until the subject has been thoroughly investigated.

The first step in any investigation of the feasibility of prenatal immunization against bacillary dysentery is obviously to determine whether or not the placenta permits passage of shigella antibodies and, if so, in what titers. Some preliminary investigations of this problem have been made but none of them have been very extensive.

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* Presented before the Third Middle Eastern - Mediterranean Pediatric Congress, Beirut, Lebanon, 1963.

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Felsen and Osofsky (6) tested specimens of maternal and cord serum for bacterial agglutinins but used only six out of the 32 known types of shigella. Neter (7) examined serum from 50 mothers together with 50 specimens of cord serum but used only three different shigella types in his tests.

In order to obtain more detailed and comprehensive information, we included all 32 of the known shigella types as antigens in our study. Serum from 104 healthy mothers, and 104 corresponding specimens of cord serum, were tested together with another unrelated series of 52 specimens of cord serum. All specimens were tested for bacterial agglutinins, hemagglutinins and the incomplete type of antibodies. It is not necessary to go into a detailed description of the technique employed in making these tests. For those who are interested the technique applied is given in reference 8 in full detail. But, briefly, the procedure was as follows :

Each specimen was tested against 32 shigella types (heat - killed antigens) in two - fold dilutions using the usual agglutination technique. Four types of sensitized human 0 Rh negative blood cells were used in the hemagglutination tests and each was modified by a mixture of supernates of the shigella types in the four shigella subgroups. These were called A, B, C, and D cells depending on the shigella subgroup involved. Tubes showing no hemagglutination were subjected to incomplete antibody tests, and washed red blood cells taken from these negative tubes were tested with anti-human globulin serum which was also prepared at Hacettepe. A minimum two - fold increase in the titers was considered evidence of the presence of incomplete (or blocking) antibodies in this last test.

Results

1. Bacterial Agglutinins :

Ninety - four (90.3 per cent) of the 104 specimens of mothers' serum were shown to have bacterial agglutinins against 1 to 14 types of shigella in a titer of 1/20 to 1/160. (In only one specimen was a titer as high as 1/320 found). However, only four (3.8 per cent) of the corresponding 104 specimens of cord serum contained any bacterial agglutinins at all and these were against only two types of shigella with a maximum titer of 1/40. None of the 52 specimens of cord serum which were taken independently had agglutinins against any

shigella type in a titer as high as 1/20. These findings are summarized in Tables 1 and 2. In Figure 1, we present a comparison of maternal and cord sera with respect to their maximum bacterial agglutinin titers.

TABLE 1

TITERS OF BACTERIAL AGGLUTININS AGAINST SHIGELLA ANTIGENS IN MATERNAL AND CORD SERUM

Cord serum No:	Shigella type agglutinated and titers in cord serum specimens		Titers in corresponding maternal serum	Number of Shigella types agglutinated in mothers' sera	Maximum titers in mothers' sera with any Shigella antigen
136	Sh. flexneri—3 Sh. flexneri—4b	1/40 1/20	1/40 1/20	5	1/40
150	Sh. dysenteriae—1	1/20	1/80	7	1/80
262	Sh. flexneri—4b	1/20	1/80	13	1/80
284	Sh. dysenteriae—2 Sh. boydii—1	1/20 1/20	1/80 1/80	10	1/160

TABLE 2

COMPARISON OF THE RESULTS OF BACTERIAL AGGLUTINATION TESTS OBTAINED FOR MOTHERS' AND CORD SERUM

(Summary)

Serum Dilutions	MOTHERS' SERUM		CORD SERUM	
	Number of positives	Per cent	Number of positives	Per cent
1/20	27	25.9	3	2.8
1/40	29	27.8	1	0.9
1/80	24	23.0	—	—
1/160	13	12.5	—	—
1/320	1	0.9	—	—

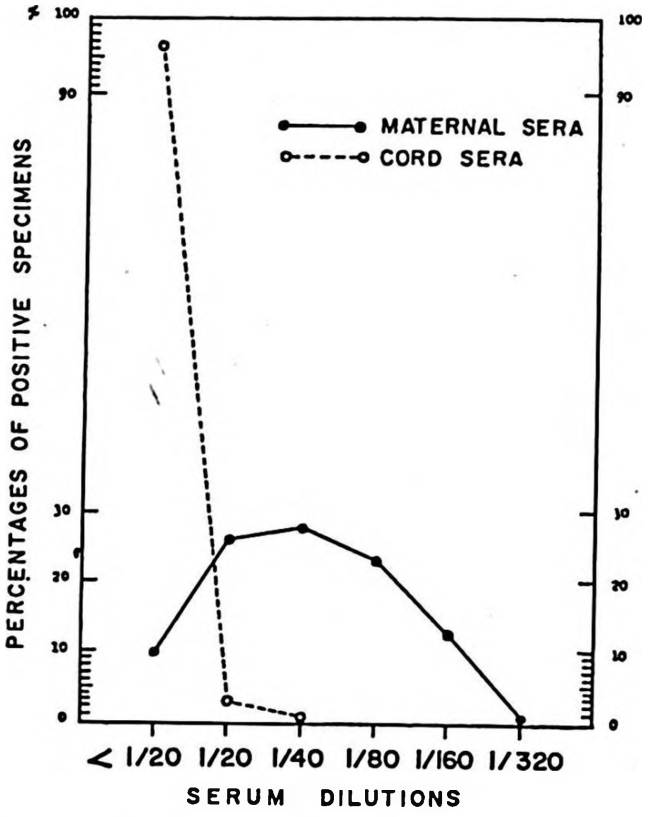

Figure 1. Results of bacterial agglutination tests.

It can be seen that there is little relationship between the agglutinin titers in the maternal circulation and the agglutinin titers in the cord serum. From the practical point of view the placental transmission of bacterial shigella antibodies can be said to be virtually nonexistent. In this respect the blood of newborn infants is *almost* as clean as a photographic plate.

2. Hemagglutinins :

This type of shigella antibody seems to pass through the placenta a little more easily than the bacterial agglutinins do. Out of the 104 specimens of mothers' serum 99 (or 95.1 per cent) were shown to contain hemagglutinins against shigella antigens and 23 (or 22.1 per cent) of the 104 specimens of cord serum contained hemagglutinins against one to several shigella subgroup antigens in a titer of 1/20 or more. The highest titers in maternal and cord serum were 1/640 and 1/80 respectively. (The findings in 52 cord sera taken independently were identical with those already mentioned in hemagglutination and incomplete antibody tests. The addition of the results obtained in this last group of serum makes no difference, so it is not worthwhile to mention them separately here.)

The hemagglutinin titers for both maternal and cord serum are presented in Figure 2. It can be seen that the cord titers are significantly lower than the maternal ones.

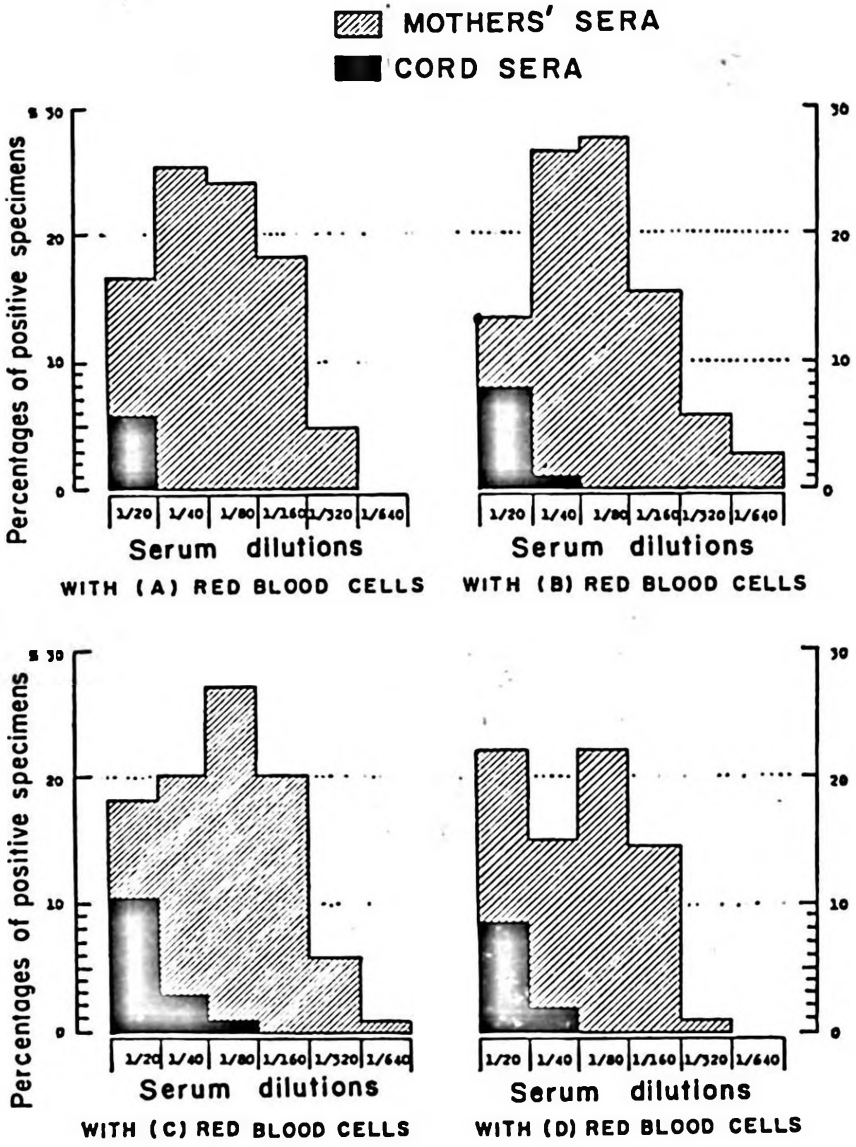

Figure 2. Results of hemagglutination tests.

Most of the maternal serum (71.1 per cent of the specimens) had hemagglutinins against four types (that is, against each subgroup of shigella antigens) of polyvalent modified red blood cells, whereas only 0.9 per cent of the specimens of cord serum displayed hemagglutinins against all types (A, B, C and D) of red blood cells.

3. Incomplete (blocking) Type of Antibodies :

In this last test the results obtained were quite the reverse. These antibodies apparently pass easily through the placenta. In most cases these antibodies could not be detected in maternal serum

because they were masked by the complete agglutinating antibodies. It was possible to detect incomplete shigella antibodies in only 23 out of the 104 maternal specimens (22.1 per cent) but the presence of these antibodies was demonstrated in 89 (or 85.5 per cent) of the 104 specimens of cord serum.

The selective filtration mechanism of the placenta seems to permit virtually unhindered passage of incomplete antibodies since most of the babies in our tests were born with significant amounts of these antibodies in their blood stream.

The results of the incomplete (or blocking) antibody tests are shown in Table 3. It can be seen that incomplete antibodies against

TABLE 3

INCOMPLETE ANTIBODIES IN MATERNAL AND CORD SERUM AGAINST (A), (B), (C) AND (D) SHIGELLA SUBGROUP ANTIGENS

ANTIGEN	SERUM SPECIMENS WHICH HAVE INCOMPLETE ANTIBODIES			
	MATERNAL SERUM		CORD SERUM	
	Number	Per cent	Number	Per cent
(A) Sh. dysenteriae	8	7.6	58	55.7
(B) Sh. flexneri	6	5.7	80	76.9
(C) Sh. boydii	11	10.5	69	66.3
(D) Sh. sonnei	19	18.2	59	56.7

the antigens of subgroup D (Sh. sonnei) are those most frequently found in specimens of maternal serum whereas in cord serum, the incomplete antibodies most frequently found are those against subgroup B antigens (Sh. flexneri). Where incomplete antibodies were detected in a specimen of cord serum there was almost always a high amount of hemagglutinins in the corresponding specimen of maternal serum.

To make these comparisons easier to visualize, the results of all the tests are grouped schematically in Figure 3. As this figure

clearly shows, the degree of permeability of the placenta to the various types of antibodies ranges from close to zero for the bacterial agglutinins, through moderate in the case of hemagglutinins, to high for the incomplete antibodies. These results are in general agreement with those in the small - scale experiments of Neter (7) and of Felsen and Osofsky. (6)

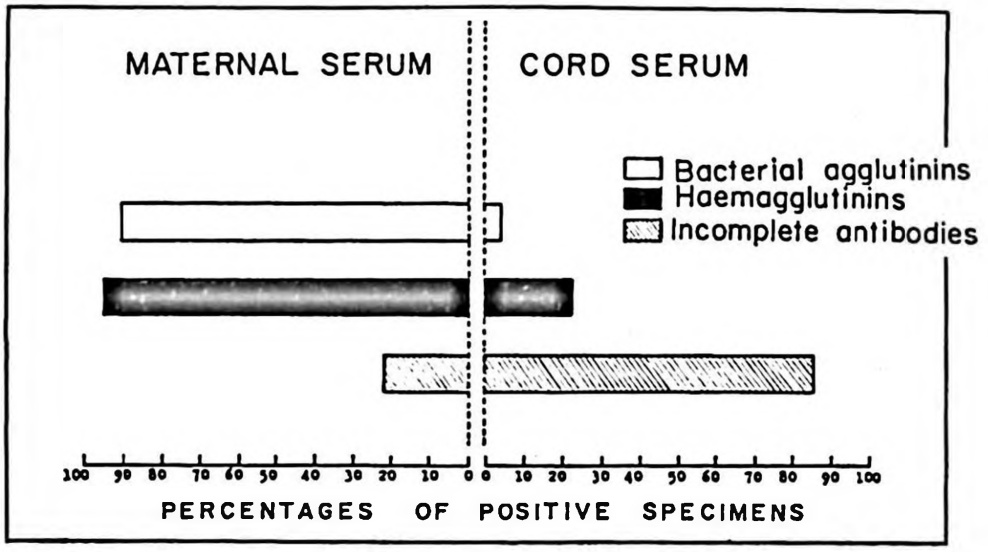

Figure 3. Summary of three tests.

Conclusions and Summary

It is doubtful that immunity to, or the degree of severity of, bacillary dysentery can be explained solely on the basis of humoral antibodies. However, if humoral factors (bacterial agglutinins, hemagglutinins and incomplete antibodies) are to be credited with any role at all in providing immunity or mitigating the severity of the disease, it becomes apparent from our study that this role is probably confined to the bacterial agglutinins. Almost all of the newborn babies in our sample (85.5 per cent) had incomplete shigella antibodies in their blood, a sizeable number (22.1 per cent) had hemagglutinins, but virtually none (3.8 per cent) displayed bacterial agglutinins and these were in very low titers although almost all of the mothers tested had bacterial agglutinins in their blood and in comparatively high titers.

Since these babies and their mothers come from a region where bacillary dysentery is endemic and were, themselves, drawn at random from a population in which the incidence of this type of dysentery is very high, it seems logical to conclude that the presence of incomplete antibodies and hemagglutinins in the blood stream does

not provide any protection against bacillary dysentery. It is possible that the bacterial agglutinins might provide some protection but these are the very antibodies which the placenta will not transmit from mother to child. For this reason prenatal immunization against bacillary dysentery does not seem to be very promising.

It is true that other types of antibodies, such as opsonins, precipitins, and amboceptors, remain to be investigated. We are planning to continue our survey, using tests for these antibodies. However, from the results so far obtained it does not appear that we are going to have much success in minimizing this major hazard of early life by means of prenatal immunization.

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