

EXPERIMENTAL INVESTIGATION OF THE PASSAGE OF AGGLUTININS FROM MOTHER TO FETUS

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The well-known low state of immunological reactivity of newborn children suggests the problem of the role of the maternal organism in the production of the natural passive humoral immunity in the fetus and the newborn.

In the animal world there exist two principal mechanisms for transmitting antibodies from mother to offspring: their transplacental passage during the period of intrauterine development, and trophogenesis, with the milk during nursing.

A series of authors studied the possibility of transplacental passage of antibodies from mother to fetus. They obtained substantially different results in animals with the hemochorion type of placenta and in animals with other types (epithelial, endothelial, and syndesmochorion types according to Grosser's classification). It has been shown that in these latter types the intrauterine passage of antibody is not observed [3, 4, 5, 7].

In man and animals with hemochorion placentas, in which as a result of destruction of epithelium and connective tissue of the mucosa the chorionic villi of the blood vessels of the uterus come into direct contact with the maternal blood, there is established transplacental passage from the blood of the mother into the blood of the fetus of antitoxin, lysins, virus-neutralizing and complement-fixing antibodies [1, 3, 8].

As far as agglutinins are concerned, several authors deny their transplacental passage or consider it accidental [2, 6]. This led us to concern ourselves with a study of transplacental passage of agglutinins from mother to offspring.

As a model we chose dysentery, as a bacterial infection in which humoral immunity demonstrates the presence of antibodies, usually agglutinins.

In the first series of investigations the problem before us was: does passage of normal antibody agglutinins from the blood of the mother into the blood of the fetus take place and does the agglutinin level in the maternal serum affect the level in the fetal serum?

METHODS

We had available for observation healthy pregnant women who had not had dysentery or typhoid and who had not been immunized against these infections, so that the antibodies observed should belong in the category of normal antibodies.

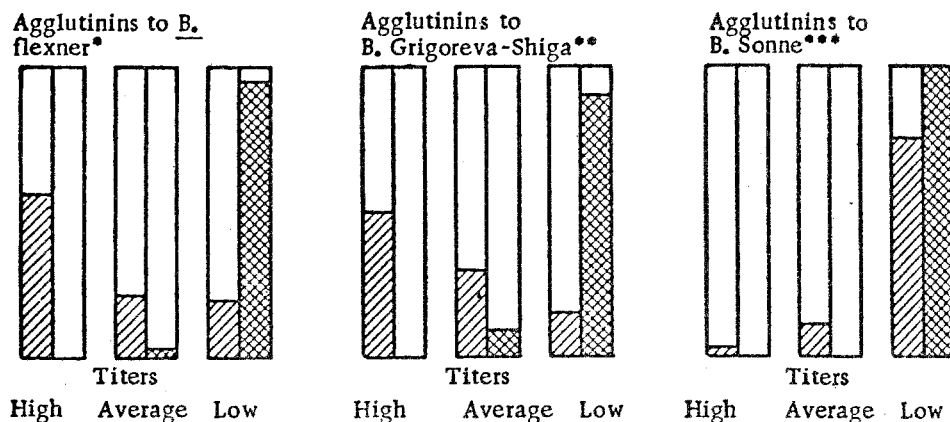
The blood for determination of antibody content was taken, following normal delivery, from the artery and vein of the umbilical cord (before it was tied), from the mother's cubital vein; a sample of the retroplacental blood was also kept.

A comparative study of the agglutinating properties of the blood was carried out on 100 mothers and 100 of their newborn children; in all 400 samples were investigated (4 from each pair). We determined the

agglutinin reaction by the usual methods. However, since the sera of the newborn sometimes contained fine granules, which might be confused with finely granular agglutination, for each dilution of serum to which bacteria were added we set up a control of that dilution of serum without any bacteria.

RESULTS

On analyzing the results obtained, the fact emerges that agglutinins are encountered in the serum of the mother definitely more often and in higher titer than in the sera of the newborn. While the majority of the maternal



Correspondence of titers of agglutinins in serum of mothers and of newborn infants (in percents of the average number of positive results; slanting lines, mother; cross-hatched, child).

sera had moderately high titers (1:160-1:320) against the species of bacteria investigated by us, except sonnei, high titers were absent among the children, a medium titer (1:80) was observed in a single instance, and the majority of the positive reactions were obtained at low titers, not exceeding serum dilutions of 1:20.

The explanation of the dependence of the agglutinin content of the blood of each mother and that of her newborn child offers particular interest.

Investigation showed that with increased concentration of normal agglutinins in the maternal serum the frequency of positive reactions and the agglutinin content of the newborn went up. This permits us to state that there is a dependence between the agglutinating power of the mother's serum and that of her newborn child.

Since the method employed by us excluded the possibility of intrauterine and extrauterine active immunization of the fetus, the agglutinins to the dysentery antigen, observed in the serum of newborn infants, could have been acquired only from the mother's blood through the placenta. However, this passage cannot be regarded as a simple filtration through a semipermeable membrane; equality of antibody titers in the bloods of mother and fetus was not observed in a single instance. As a rule the antibody titer of the fetus was lower than the corresponding titer of the mother's blood.

By investigating bloods of mothers and their newborn infants we had the possibility of studying transplacental passage of normal antibodies only. Application of this method did not permit, however, observations of the dynamics of the immunological indicators before and after nursing began. Therefore a series of experiments were carried out on female rabbits subjected to a preliminary immunization, and their newborn leverets.

In setting up the experiment we were guided by the following: 1) in rabbits, as in man, the placenta produced is of the hemochorion type; 2) the leverets are born in a state of incomplete physiological maturity, which offers the possibility of observing in them the establishment of immunological reactivity.

- * *Shigella flexneri*.
- ** *Shigella dysenteriae*.
- *** *Shigella sonnei*.

TABLE 1

Relation of Positive and Negative Results for Agglutination Reaction of Blood Serum of Rabbits and Their Newborn Leverets (in percents)

Species of bacterium	Results of agglutination reaction			
	Positive		Negative	
	Rabbits	Leverets	Rabbits	Leverets
<i>Sh. flexneri</i>	100.0	95.8	—	4.2
<i>Sh. sonnei</i>	81.8	43.6	18.2	56.4
<i>Sh. dysenteriae</i>	96.1	52.7	3.94	47.3

Transplacental passage of antibodies from the mother to the fetus in animals given preliminary immunization was studied in experiments on 26 rabbits and 71 newborn leverets.

To exclude the passage of antigen through the placenta and intrauterine active immunization of the fetus, active immunization of the rabbits chosen for the experiment was carried out with Flexner bacillus before impregnation.

The newborn leverets were taken from their dam. We took blood from them by cardiopuncture.

In order to exclude the influence of normal agglutinins on the results of our study of transplacental passage of antibodies in immunized animals, we used as controls 17 rabbits not previously immunized, and 50 of their newborn leverets.

The experiment showed that in all cases, when the antibody content of the blood of the rabbits exceeded a titer of 1:320, agglutinins were observed in the serum of the newborn leverets, and the percent of negative results for agglutinins for Flexner bacilli, i.e., the antigen to which the dams were immunized, was only 4.2 (Table 1). The agglutinin content of the blood of the immunized animals exceeded in many cases the amount in the blood of the controls.

While in the unimmunized rabbits and their newborn leverets the agglutinins showed extremely low titers, in the immunized rabbits and their offspring the titers were significantly higher (see figure).

Analysis of our material on the agglutinating properties of serums and the agglutinin titer in each pair (female rabbit and her offspring) showed that, as in observations on newborn children, between the titers of agglutinin in the serums of the rabbits and their offspring there existed a direct dependence. This dependence was expressed more sharply in the experiment than in the observations on newborn children (Table 2).

Thus, when agglutinins were present in the blood of the female rabbits they appeared in the leverets during the period of intrauterine development. Inasmuch as immunization of the females was carried out in advance of impregnation, an active mechanism for the appearance of the antibodies in the fetus is ruled out. Therefore we may regard it as established that the appearance of agglutinins in the blood of the fetus is connected with transplacental passage from the blood of the dams.

Summarizing our observations on newborn children and newborn rabbits (first series), we must state that the hemochorial placenta is permeable to agglutinins, and only partly holds them back.

The conditions of the experiment made it possible to obtain repeated samples of blood from one and the same leveret, which permitted study of the duration of retention of the antibodies which had been acquired by them in utero.

We carried out investigations of the properties of the serum of the blood of the developing leverets the day they were born, on the 3rd, 5th, 10th, 20th, 30th, 45th, and 60th days of life. In all we examined repeatedly 50 leverets from 18 immunized dams. Study of the dynamics of retention of agglutinins permitted us to establish that newborn leverets are incapable of retaining antibodies during the course of the first 60 days of life. Between the 10th and 30th days of life in most of the leverets there begins a decrease in the original level of antibodies which were observed at the moment of birth, and by the 60th day agglutinins had disappeared from the blood of the majority of the leverets. This speaks for a passive origin for the agglutinins.

TABLE 2

Agglutinin Content in Newborn Leverets in Relation to the Magnitude of the Titers in Their Mothers (number of cases in percent)

Titers dams' serum Titers leveret serums	Titers dams' serum		
	Low	Medium	High and very high
1:10			
1:20	25.0		
1:40		9.5	
1:80		11.9	
1:160	50.0	11.9	
1:320	25.0	33.3	4.5
1:640		7.2	
1:1280		21.5	13.7
1:2560		4.7	31.8
1:5120			9.0
1:10240			13.7
1:20480			27.3
Totals	100%	100%	100%

Since from the moment of birth of a child there arises the possibility of acquiring antibodies trophogenetically, the study of the mechanism of humoral immunity at various stages of postnatal development naturally includes an investigation of the influence of nursing on the antibody content of the blood.

On the basis of cross experiments, in which immunized females nursed young born to unimmunized dams, and the reverse experiment, it was established that in rabbits, belonging to the hemochorion type of placenta, nursing did not seem to be a direct source of antibodies for the offspring, and did not exert any direct effect on humoral immunity. Natural breast feeding serves as a source of valuable and easily-assimilated proteins, fats, carbohydrates, and vitamins, promoting an increase in the natural nonspecific resistance of the newborn organism.

The reverse relations have been established for animals with other kinds of placentas (syndesmo-, epithelio-endotheliochorion), which must be considered as phylogenetically older than the hemochorion placenta. In these species of animals transplacental passage of antibodies does not go on, while the trophogenetic route seems to be the main route for the acquisition of humoral immunity in the early stages of postnatal development of the offspring. Therefore transplacental passage of antibodies from the mother to the fetus acquires significance phylogenetically as a later mechanism of production of passive humoral immunity in the newborn; in this lies its biological significance.

Summing up the results of these investigations, we believe it is possible to draw the following conclusions. The availability of antibodies in the blood of newborn at the moment of birth under conditions excluding the possibility of active formation as a result of encountering the antigenic stimulus, demonstrates their passive origin from the maternal body.

The investigations showed that in man, and animals with the hemochorion type of placenta the basic mechanism seems to be transplacental passage of antibodies; this latter is supported by the dependence of the agglutinin in the blood of the newborn on the titer in the blood of the mother. This dependence appears especially clear under experimental conditions. Transplacental passage of antibodies is supported also by the absence of trophogenetic transfer of antibodies.

SUMMARY

The agglutinin content of the blood of newborn and their mothers was studied in order to investigate the problem of the transplacental passage of antibodies.

The investigations were carried out post partum in a lying-in hospital. There were observed 100 mothers and the same number of newborn. The results were checked experimentally in female rabbits and their offspring.

It was established that transplacental passage of agglutinins from mother to fetus takes place. However, the titers of antibodies in the blood of the newborn were, as a rule, lower than the corresponding titers in the maternal blood. Consequently this passage of antibody cannot be considered to be simple filtration of antibodies through a semipermeable membrane.

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