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TRANSMISSION OF PROTEIN HYPERSENSITIVENESS FROM MOTHER TO OFFSPRING[1]

I. CRITIQUE OF PLACENTAL PERMEABILITY

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Rosenau and Anderson (1) were the first to record instances of the transmission of hypersensitiveness or anaphylaxis; this hypersusceptibility was transmitted to young guinea pigs whose mothers had been given diphtheria toxin-antitoxin mixture or normal horse serum two or three months before parturition.

The diphtheria toxin immunity transferred from mother to offspring, demonstrated by Wernicke (2) in 1895, Smith (3) in 1905, Anderson (4) in 1906 and the transmission of hypersusceptibility first shown by Rosenau and Anderson (1) in 1906, led Anderson (5) to question whether female guinea pigs that received toxin-antitoxin, either before or during pregnancy, could give birth to offspring that were both immune to diphtheria toxin and hypersusceptible to horse serum. He readily found that a mother can simultaneously transmit to her young these two properties—the immunity to diphtheria toxin and the hypersusceptibility to horse serum.

Gay and Southard (6) presented evidence that mother guinea pigs, that were thought to be refractory to horse serum, but were later shown by others to be more highly sensitized, still contain the sensitizing substance of the serum unneutralized. The offspring of the so-called refractory animals, born at a period when

[1] This work is being carried on under "The Crane Fund for the Study of Anaphylaxis."

the mother is resistant to the toxic action of horse serum, are sensitive and not resistant.

Otto (7) confirmed the definite transmission of hypersensitivity from a sensitized guinea pig mother to her offspring, and made a further contribution regarding the duration of this passive transfer. He states that "these young guinea pigs, up to the forty-fourth day of life, definitely show the typical hypersensitivity reaction on injection with horse serum. After 72 or 73 days, this reaction was either insignificant or entirely lacking."

Later Lewis (8) and Schenck (9) corroborated the previous work on the transfer of this hypersusceptibility.

Wells (10) indicated that guinea pigs, born of mothers that had been fed oats, were sensitive to oat protein for a short time after birth. This was, however, merely an incidental observation.

We (11) in our preliminary paper, have reported a corroboration of the work on the passive transmission of hypersusceptibility and have shown, that this passive state may exist not only for 44 days as Otto has shown but for at least 77 days. We have, in the same preliminary report, made the statement that beside this passive transfer, we were able actively to sensitize a guinea pig *in utero*. Both of these problems will be discussed at greater length in future studies.

There is therefore evidence that sensitization may be transferred from mother to offspring.

The placenta, which simultaneously accomodates the maternal and fetal circulations, holds them apart physically, but apparently does permit the physiological interchange of some of the substances to take place.

In the main, there are two viewpoints relative to this passage. The vitalists assume that the chorionic villi have a selective function and the mechanists that the wall of the chorionic villi acts passively as a filter. The conception of the earlier investigators as represented by the school of Behring, Pfaundler, and Römer, was that the placenta, irrespective of animal species, was impermeable to protein and did not permit the passage of maternal antibodies. In their opinion, antibodies only appeared in the fetal blood if the placenta was injured either through dis-

ease or heterologous proteins such as horse serum antitoxin which had been used in the course of their experiments. They therefore contended that placental transmission of antibodies was a pathologic and not a physiologic process.

Although we are here concerned with the passage of sensitizing substances from the mother to her offspring, we believe it essential, for a better understanding of our subject, to present the following critical survey of the literature bearing on the passage of other types of substances.

We do assume, however, that this interchange is a physiologic one and is brought about largely by means of mechanical filtration.

PLACENTAL TRANSMISSION IN HUMAN BEINGS

Certain observations are recorded of infants showing resistance to diseases, in cases where the mothers have recovered from the same disease shortly before childbirth. The early observations were those made by Lereboullet and Buchner on variola. Burckhardt (12) made similar observations on infants born of mothers vaccinated during the last weeks of pregnancy. Vaccinating these infants during the first days of their lives, he found that apparent protection against vaccinia had been acquired. Most of the control infants gave positive reactions. This work is of special interest since it is one of the first investigations on the transfer of protective substances from mother to child *in utero*, and, while the results are not conclusive, they offer suggestive data.

Kayser (13) studied certain cases of diphtheria, wherein he reported an apparent transfer of antitoxin from mothers who had recovered from this disease. Later, Fischl and Wundscheim (14) demonstrated diphtheria antitoxin in a large proportion of specimens of cord blood. Polano (15) demonstrated antitoxin in the cord blood in every instance of women naturally immune to diphtheria. He showed a similar transfer of tetanus antitoxin from mothers injected a few days before delivery. Von Groer and Kassowitz (16) went a step further and titrated the antitoxic content of the maternal and cord bloods. They found that in 84 per cent of the cases the antitoxic content of the maternal

and cord bloods was identical, and, in view of this large percentage, concluded that the human placenta is normally permeable to diphtheria antitoxin. They further compared the Schick tests, but since they omitted adequate Schick controls this particular phase of the problem is unconvincing. In a comparative study of the Schick tests, Zingher (17) found that in infants under three years of age, the reaction in mother and child corresponded in every case except one. Ruh and McClelland (18) corroborated Zingher's work in a study of 95 mothers and their infants who gave corresponding reactions with the Schick test. In four instances, the mothers gave a positive reaction and the babies a negative one. Kuttner and Ratner (19) corroborated the findings of the previous workers by titrations of the antitoxic contents of the maternal and cord bloods with the modified Römer method. They found the content in both to be identical. The Schick tests with adequate controls were also performed by them and they found that out of 50 cases, only 7 did not give corresponding results, there being a positive reaction in the mother and a doubtful or negative one in the infant. In these latter cases, where a discrepancy occurred, these mothers' and their corresponding cord bloods presented identical antitoxic contents. They concluded, therefore, that the transfer of antitoxin occurred in all cases. Where a discrepancy existed in the Schick test, it was shown by them to be due, not to a lack of the passage of antitoxin, but to a peculiar anatomical arrangement of the new-born skin, which does not permit a proper intracutaneous injection.

Ten Broeck and Bauer (20) corroborated the permeability of the human placenta with tetanus antitoxin.

Scholtz (21) reported a strong agglutinating reaction for typhoid in the fluids from a seven-month-old fetus. Schumacher (22), Stäubli (23), Mosse and Daunic (24) obtained positive agglutinin reactions at birth from the fetal end of the cord of infants born from mothers who had suffered from typhoid during the course of pregnancy.

Cooke (25) has shown the complement-fixing antibody of tuberculosis to be transferred from mother to offspring.

Halban and Landsteiner (26) showed maternal bacteriolysins in the infants' serum, but they were present to a lesser degree than in the mothers.

Kingsbury and Sedgewick (27) obtained the same average value for uric acid in the maternal and fetal bloods in a series of 42 cases. Morriss (28) found the average sugar content of the fetal blood of 42 cases to be slightly lower than normal. Plass (29) and Hunter and Campbell (30) agree that the total creatinine is very nearly the same in the maternal and fetal bloods, although the average is slightly higher in the fetal than in the maternal blood. Urea was found by Slemons and Morriss (31) to be practically the same in the two sera in 16 normal cases and in abnormal cases it varied in the same direction. Morse (32), on the other hand, found that the amino acid content of the fetal blood was materially higher than that of the maternal blood in 13 out of 18 cases. Edelstein and Ylppö (33) obtained an average value of 0.032 per cent for sodium and 0.13 per cent for potassium in favor of the fetal blood. Slemons (34) finds non-protein nitrogen in the mother average 25.2 mgm., and in the fetus average 24.9 mgm. In a case of twins, the mother showed 30 mgm. per 100 cc. and each infant showed practically the same. Mendel and Daniels (35) report no interchange of fat.

PLACENTAL TRANSMISSION IN ANIMALS

With the human being, all evidence points to a uniform placental permeability. In analyzing the same condition in animals, one observes that this placental transfer does not occur with the same regularity.

Slightly positive to negative transmission

Gengou (36) obtained a reaction of 1:400 against anthrax in a goat which failed to pass much agglutinin over to her still-born young. The kid's sera reacted in a dilution of 1:10, which is much less than is normally present in the mother's blood before any inoculation. Kraus (37) reported that the transmission of immune hemagglutinins did not take place in a kid born from a

mother who had been immunized against the red blood cells of sheep. Kreidl and Mandl (38), in a preliminary report, stated that the goat, injected with beef blood, might passively transfer the immunity to the fetus, but, from their tests, they concluded that in the majority of cases the specific hemolysins do not pass from mother to fetus through the placenta. Bertarelli (39) reports that he found no specific hemolysins in the blood of the young sheep in the first weeks after birth from mothers immunized by repeated injections of hens' blood during the last weeks of pregnancy. Schumacher (22) found no specific agglutinins in the blood of a kid born from a goat highly immunized late in pregnancy. Römer (40) and Dzierzgowski (41) obtained negative results when they immunized horses, cattle, sheep, swine, and dogs to tetanus antitoxin. Famulener (42) showed a negative placental transmission of hemolysins to sheep corpuscles from mother goat to her kids. Reyman (43) in a study of natural agglutinins with *B. typhosus*, *B. coli*, and horse and rabbit sera, in a series of 14 goats and their new-born kids, found the blood of all but one kid negative. Little and Orcutt (44) observed that calves had no agglutinins to *B. abortus* in their sera at birth from mothers highly immune to this organism as a result of natural infection.

Positive transmission

Chauveau, (45) in 1880, found that by vaccinating the slightly susceptible Algerian sheep with anthrax organisms during gestation, their offspring were born immune to this organism. Similar results were reported later by other workers who used symptomatic anthrax—Arloing, Cornevin and Thomas (46) with heifers and Kitasato (47) with the guinea pig.

Ehrlich (48), in 1892, published some fundamental studies which awakened a new interest in the development of this subject. He carried out immunization experiments by feeding the toxalbumins, abrin, ricin, and robin to mice. It was found that the young from immune mothers acquired an immunity which he considered as passive. In opposition to Ehrlich's assertion that this transfer was a placental one and that the immunized

male alone was unable to transmit an acquired immunity to his descendants, several workers brought forth experiments which conflicted with his results. Among these workers may be mentioned Gley and Charrin (49), Tizzoni and Cattani (50) and Tizzoni and Centanni (51).

Ehrlich and Hübener (52) repeated similar experiments using tetanus toxin on both guinea pigs and mice, with results that sustained Ehrlich's first reports. In a critical review of the opposing work, they pointed out certain experimental conditions in each case which they considered invalidated the results of Gley, Tizzoni and their respective collaborators.

In 1895, Wernicke (2), working with guinea pigs, showed the transfer of diphtheria antitoxin from mother to offspring. Vaillard (53), experimenting not only with tetanus but also with anthrax, cholera, and *vibrio metschnikovi*, showed this transfer through the mother in practically all instances, carrying it through four litters from the same mother. He worked with guinea pigs and rabbits. Widal and Sicard (54), in 1897, observed typhoid agglutinins in the offspring of a rabbit immunized against typhoid. Cholera agglutinins were found by Achard (55), and Dieudonne (56) in the offspring of immunized guinea pigs. In 1899, Remlinger (57) reported finding positive transmission of immunity to Eberth bacillus to the young of immunized guinea pigs and rabbits. This transmitted immunity applied to both vaccination and agglutinins.

Ransom (58) actively immunized a mare with tetanus toxin during gestation and within eight hours after the birth of the foal—at a time when it could not have suckled a very considerable amount of milk—the foal's serum showed an antitoxic value of 20 per cent of that of the mother's serum. This rapidly diminished to 10 per cent.

Bulloch (59) approached the same problem with the use of rabbits immunized against the red blood corpuscles of the ox, thereby bringing about the production of specific hemolysins in their blood. He showed these specific hemolysins in the serum of three successive litters. Jurewitsch (60), in 1903, showed the transmission of typhoid agglutinins with rabbits and in

1904, Merkel (61) reported positive results with specific precipitins to human blood. Stäubli (23) observed typhoid agglutinins in the blood of young guinea pigs whose mothers were immune to this disease. Bertino (62) stated, in 1905, that mother rabbits, immunized during pregnancy, transmit the lysins to the fetus. Wegelius (63) reported that goats and rabbits, when immunized either shortly before conception or during gestation, transmit the specific antibodies of vibriolysin to their young.

Bourquin (64) has recently confirmed the permeability of the placenta of guinea pigs and rabbits to diphtheria antitoxin, hemolysins, and agglutinins. Besides showing a passage from mother to fetus, she has, in a very pretty manner, shown a like passage from fetus to mother. Another interesting feature of her work is that she examined the placenta in every instance and found no gross pathologic lesions.

Theobald Smith (3), in 1905, working with the Ehrlich standardized antitoxin unit for diphtheria, found that there was a diphtheria immunity transferred to the young of mother guinea pigs which had received injections of toxin. This increased resistance was observed in all litters until the death of the mother and was nearly constant in amount for any given mother.

Anderson (4) corroborated the work of Smith and former investigators and gave further conclusive evidence that this transfer of immune substances persisted through the life of the mother. He showed the passage through four successive litters, the first and the fourth showing equal resistance. He stated, however, that this passive immunity was not transmitted to the second generation.

Transfer of heterologous proteins

Ascoli (65), in 1902, attempted to answer the question as to whether protein passes through the placental wall. He worked with the antigen-precipitin reaction, injecting rabbits subcutaneously or feeding them with varying amounts of heterologous protein. After a certain time, which fluctuated between one hour and several days, he extracted the young by caesarian section and collected the blood from each separate fetus; he also

took the mother's blood by venesection. The blood serum thus obtained was tested for the protein which had been injected into the mother—this test was against specific precipitins. His results showed that animals injected subcutaneously with a large amount of heterologous protein (egg, inactivated horse or cow serum) gave evidence of this in the maternal and fetal sera. If the protein found in the maternal serum was moderate, as was the case after small subcutaneous injections or after feeding large amounts, then the fetal serum was generally negative.

Holford at a meeting of the Society of American Bacteriologists in December 1925, presented a preliminary report of work which corroborates that done by Ascoli. She injected pregnant rabbits five days before term, with crystalline egg albumin. She showed the presence of antigen in the serum of the new-born which had been removed from the nest immediately after birth. Her work was adequately controlled and greater refinements in technic were used than those employed by Ascoli. Holford's corroboration of Ascoli's work demonstrates beyond doubt that heterologous proteins can be transferred through a normal placenta.

DISCUSSION

That substances pass through the placental partition is demonstrated by an overwhelming number of instances. This placental permeability occurs consistently in the human being with such substances as protein sensitizing antibodies, antitoxins, agglutinins, precipitins, bacteriolysins, chemical blood constituents, etc. But, strangely, in the lower animal kingdom this phenomenon does not occur with the same regularity in all species.

The idea that placental permeability in all cases was due to injury from the injection of heterologous substances has been conclusively contradicted by a number of workers. They excluded this possibility by the immunization of the mother before conception (Stäubli) and by studying the transference of natural immunity to typhoid when no injection of any kind had been made on the mother (Polano). Also Bourquin (64) found no gross pathologic lesions in the placentas of the guinea pigs studied by her. The theory of placental transmission of im-

mune bodies as a result of placental injury has therefore become untenable.

Famulener (42) suggested that perhaps large animals such as goats or sheep do not permit this class of antibodies—hemolysins—to pass the placenta as readily as do some of the smaller animals. He suggested that the negative results may be accounted for by the differences in experimental conditions, such as the nature of the antigen used, the degree of active immunization attained, the time of immunization relative to the birth of the young, the character of the resulting antibody and the time when the blood was taken from the young. He further states that many workers failed to make any distinction between the rôle played by the placenta and that of the milk in the transmission of antibodies. In many cases, the blood of the young was not drawn until after they had had the mother's colostrum and milk. It is of interest to note that Famulener worked with goats and believed that colostrum was the chief agent in bringing about passive immunization of the suckling. Smith and Little (66) also found this to be true with cows and calves.

Bourquin (64) seems to agree with Famulener in explaining these discordant results, as she attributes them to differences in technic for the conditions of immunization and the antigen used, and states that the species of animal does not account for this.

Römer (40) is one of the few investigators who worked with animals of two placental types. In his experiments, the placentas of cows, sheep, and horses were uniformly impermeable to antibodies, whereas in practically every instance with guinea pigs, rabbits and human beings, he found that the antibodies were transmitted through the placenta, although in diminished amounts.

Some workers claim that the placenta is impermeable to antibodies and that the colostrum and milk are the only means of transferring immunity to the young (Famulener (42), Smith and Little (66)); others insist that the placenta is permeable and that placental transmission is the most important mode of transferring antibodies.

Kuttner and Ratner (19), confronted with this apparent in-

consistency, offered an explanation for it, which was based on the histologic structure of the placenta. This structural difference immediately divides the animal kingdom into groups, namely those that have placental partitions of one layer and those with a multiplicity of cell layers separating the maternal from fetal circulations.

TABLE 1*

Variations in cell layers separating maternal from fetal circulation

NOMENCLATURE		PARTITION BETWEEN MATERNAL AND FETAL BLOOD							TYPES	REMARKS
		Maternal (uterine mucosa)				Fetal (chorion)				
Old	New	Endothelium	Connective tissue	Epithelium	Uterus cavum	Endothelium	Connective tissue	Epithelium		
Semi-placentae or Placentae oppositae	Placentae epitheliochorialis	+	+	+	+		+		Pig	True adeciduate
	Placentae syndesmochorialis	+	+†	−‡	−		+		Ruminants	Transition forms
Placentae verae or Placentae conjugatae	Placentae endotheliochoriolis	+	−§	−	−		+		Carnivora	Placentae zonariae (deciduate)
	Placentae hæmochorialis	−	−	−	−		+		Rodentia Insectivora Chiroptera Apes Man	Placentae discordales deciduate)

* Grosser: Eihäute und Placenta, p. 292.
† Partly.
‡ Mostly.
§ Almost entirely.

Table 1, obtained from Grosser's monograph on the structure of the placenta (67) gives a summary of the separating membranes of the various animal species.

In the human placenta, the maternal blood is separated from the fetal by a single cell layer, whereas in the case of ruminants the placenta consists of three cell layers which would seem to indicate a physical basis for the difference in permeability of

bovine and human placentas. In analyzing the literature from this point of view, we found a striking conformity in results when cows, horses, goats and sheep were the experimental animals. These animals gave negative results while the work on human beings, rabbits, guinea pigs, and mice all gave correspondingly positive results.

The only apparent discrepancies that we could find to militate against this hypothesis were the reports of Gengou (36), Chauveau (45), Arloing et al. (46) and Ransom (58). However, in analyzing these instances, we find that Gengou, in working with a still-born kid, showed a slight presence of anthrax agglutinins in the kid's blood (1–10) but this was less than that often found in the blood of a normal goat; that Chauveau and Arloing and his collaborators studied the new-born ruminants one to weeks after birth, thus not excluding the influence of colostrum; that Ransom actively immunized the mare during pregnancy and that the foal may have been actively immunized in utero. Therefore, in spite of these apparent exceptions, we believe that our premise is still valid, i.e., that the difference in placental construction accounts for the difference in the permeability of the ruminant placenta from that of other species.

There can be no more forceful example of the fact that the bovine species has an impermeable placenta—at least to agglutinins—than in the work of Little and Orcutt (44). This is strengthened by the demonstration of Smith and Little (68) that a calf deprived of colostrum can be saved from a septicemia resulting from a *B. coli* invasion by the injection and feeding of adult cow's serum immediately after birth. This shows beyond doubt that were the placental partition not a barrier, there would have been an interchange of these necessary immune substances between the maternal and fetal circulations.

To summarize, it seems very likely to us, in accord with Kuttner and Ratner, who first voiced this opinion, that histologic differences in the structure of the placentas of the various species might sufficiently explain the discordant results obtained by the previous investigators.

CONCLUSIONS

1. The passage of heterologous substances through the placenta is a physiologic function and not a pathologic one.

2. The placenta is permeable to antitoxins, precipitins, bacteriolysins, heterologous proteins, protein sensitizing antibodies, etc., in man, guinea pigs, and rabbits.

3. The placenta is not permeable to these substances in cows, goats, and sheep.

4. A histologic difference in the placenta in the various species is offered to explain this difference in permeability. In man and rodentia there is a single cell membrane separating the maternal from fetal circulation, and in ruminants there are three cell layers separating these circulations.

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