THE PATHOGENESIS OF ERYTHROBLASTOSIS FETALIS

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MICROSCOPIC examination of numerous sections of the placenta of an 8½ month pregnancy in a case of erythroblastosis fetalis, in which the baby lived 33 minutes, and of the placenta of a 7½ month pregnancy in a similar case in which the baby lived 25 minutes, showed occlusion of peripheral blood vessels of many villi and trunks by agglutinated red blood cells and fibrin. Associated with the vascular thromboses, there were, in places, necrosis of the walls and of regional tissues with rupture and hemorrhage of fetal blood, containing numerous intact nucleated red blood cells, into regional intervillous spaces. Through the broken surfaces, adjacent maternal blood was in contact with the fetal circulation.

These observations indicate the mechanism of transfer to the mother of incompatible fetal red blood cells in cases of erythroblastosis fetalis and of the transfer to the fetus of the maternal antibody that produces the anemia.

The two placentas showed, in addition to hemorrhages that apparently occurred at or very shortly before the time of expulsion, others somewhat older, with abundant fibrin and red blood cells, some with degenerating nuclei, covering the ruptured surfaces of villi and trunks, indicating that the intermingling of fetal and maternal bloods had been stopped by the clotting of fetal blood at the sites of hemorrhage.

Vascular thromboses with necrosis and rupture of peripheral tissues of many villi and trunks and hemorrhage of fetal blood into regional intervillous spaces was observed in the placenta of all 13 additional cases of erythroblastosis fetalis and of all 213 cases in the last half of normal pregnancy examined and reported previously. Although the changes in the 213 placentas of the last half of normal pregnancy observed microscopically are the same as those in the two cases of erythroblastosis fetalis described above, it is doubtful if the fetal hemorrhages into intervillous spaces would have been recognized as such, without the previous identification of unquestionable fetal hemorrhages with nucleated red blood cells into intervillous spaces in the two placentas here reported.

Since the first report, by Levine and Stetson, of transplacental transfer of an immunizing blood factor inherited from the father, various explanations of the mechanism concerned have been offered.

The permeability of the placenta of mammals has been found to increase progressively to the end of pregnancy as the layers of tissue between maternal sinuses and fetal circulation diminish (Flexner and Gellhorn). Levine has assumed that the thinning of the placental barrier and the pressure in the fetal circulation, greater than in the local maternal sinuses, afford ample opportunity for the escape into the sinuses of a minute number of fetal red blood cells in one or another form.

Haldane is of the opinion that the abnormal permeability of the placenta

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to the passage of an antigen from the fetus to the mother is at least often genetically determined. Burnham\(^6\) has suggested that subclinical deficiency of vitamin C in the mother might be sufficient to permit a break in the integrity of the capillaries of the chorion with escape of Rh positive fetal blood, thus leading to isoimmunization of the Rh negative mother. Naeslund and Arén\(^7\) have recently reported a case of toxemia of pregnancy in which the full term placenta showed multiple gross hematomas and microscopically in these areas, gaps in the epithelium of villi and in the walls of their blood vessels. The photomicrographs show

marked vascular engorgement suggesting that the regional fetal hemorrhage was due to rupture following obstruction to the return of venous blood at or very shortly before the expulsion of the placenta.

Javert\(^4\) has reported the finding of gross hematomas in the placenta of 8 of 34 cases of erythroblastosis neonatorum and in 7 of 10 examined microscopically, nucleated fetal red blood cells were found.

The observations especially in the two cases reported here and also in all the additional 13 cases of erythroblastosis fetalis and in all the 213 cases in the last half of normal pregnancy studied, indicate that hemorrhage of fetal blood from many villi and trunks into the regional intervillous spaces occurs in the last half of all pregnancies as a result of occlusion of the involved peripheral blood
FIG. 2.—Placenta 82243 of 71/2 month pregnancy. Case of erythroblastosis fetalis. (Magnification about 150 X.) (Middle, lower area.) Very recent hemorrhage from villus into regional intervillous spaces. (Many of the fetal red blood cells are nucleated.)

FIG. 3.—Placenta 82243. (Magnification about 100 X.) (Center) Recent hemorrhage from villus into regional intervillous spaces showing early formation and molding of clot. (Some of the fetal red blood cells are nucleated.)
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Fig. 4.—Placenta $1979. (Magnification about 350 X.) (Left and upper.) Recent clot containing numerous intact and degenerating nucleated fetal red blood cells (especially upper right) following hemorrhage from villus. (Reprinted by permission of the American Journal of Obstetrics and Gynecology.)

Fig. 5. Placenta $1979. (Magnification about 350 X.) (Center and right.) Clot containing intact and degenerating nucleated fetal red blood cells following hemorrhage from villus.
Fig. 6.—Placenta # 1979. (Magnification about 200 X.) (Left lower and center, right upper.) Fetal hemorrhage from peripheral vessels of trunk with recent blood clot formation.

Fig. 7.—Placenta # 2330 of a 9 month pregnancy. Case of erythroblastosis fetalis. (Magnification about 400 X.) Villi with double epithelial lining, and thick stroma.
vessels by agglutinated red blood cells and fibrin and necrosis and rupture of the walls and of the regional fetal tissues. It is possible that the primary damage is due to the excretion of waste products of metabolism.

The placenta in every one of the 228 cases reported showed, in addition to recent fetal hemorrhages, older ones with the clots composed mostly of fibrin stained by hemoglobin of laked fetal red blood cells, and degenerating and degenerated fetal red blood cells. Fetal blood clots, apparently still older, consisting of little more than fibrin are the most conspicuous finding in all placentas after mid-pregnancy. The oldest clots were observed in various stages of organization.

In the placenta of 8 of the 15 cases of erythroblastosis fetalis, the villi showed the changes characteristic of the disease. They were much thicker than normal and some were edematous. The surface epithelium was thickened and in places double. The stroma was thicker than average and compact where not edematous. Many of the central vessels of villi and trunks showed degenerative changes and shrinkage, in places complete obliteration. Some showed thickened endothelium and prominent perivascular fibrosis.

The villi of erythroblastosis fetalis, with thick double epithelial covering and thick stroma, resembled those of the first few months of normal pregnancy. The thickening and the doubling of the epithelial covering, the thickening of the stroma and the other changes may well have been a response to their constant exposure to the harmful fetal red blood cell antibody of the maternal blood.

Since it is now known that the erythroblastosis is a secondary manifestation, the designation “erythroblastosis fetalis” for the disease, is by no means satisfactory and appears to be no longer justified. Furthermore, since it has been found that destruction of the incompatible fetal red blood cells in the disorder may occur in part by phagocytosis (references given in a previous article), the term “hemolytic disease of the newborn” is not entirely accurate. A more fundamental designation in keeping with the author’s concepts would be “transplacental erythrocytotoxic anemia.”

SUMMARY

The mechanism of transfer, in cases of erythroblastosis fetalis, of incompatible fetal red blood cells to the mother and of maternal blood with antibody to the fetus, was observed especially well in 2 cases in which the infants were born alive.

The two placentas showed occlusion of peripheral blood vessels of many villi and trunks by agglutinated red blood cells and fibrin. Associated with the vascular thromboses, there were, in places, necrosis of the walls and of regional tissues with rupture and hemorrhage of fetal blood, containing numerous intact nucleated red blood cells, into regional intervillous spaces. Through the broken surfaces, adjacent maternal blood was in contact with the fetal circulation.

A more accurate designation for “erythroblastosis fetalis” would be “transplacental erythrocytotoxic anemia.”
REFERENCES

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