Transmission of Drugs Across the Placenta.*

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KNOWLEDGE REGARDING the transmission of substances across the human placenta to the fetus has been gained in several ways. Clinical impressions constitute by far the largest group of observations and have only a limited value because of their purely qualitative nature. The estimation of depression of the newborn infant after various sedatives, analgesic and anesthetic agents have been administered to the mother varies considerably with the interpreter. The exact meaning of "breathing time" and "crying time" is indefinite although variations in interpretation are minimized by having only one or two observers.

Reliance upon clinical impressions alone has accounted for the unhappy life history of many new drugs and techniques used in obstetric analgesia. The cycle of enthusiastic introduction and subsequent optimistic reports, followed by a quiet disappearance of such papers from the literature, and finally a slow death of the new method because of adverse experiences spread by word of mouth rather than the printed page, is all too familiar.

The need for resuscitation of the newborn infant has been used as a method of evaluation of transplacental passage of potent analgesic drugs and anesthetic agents.[1] However, the quality of the administration of anesthesia, familiarity with resuscitative measures and the availability of appropriate equipment often are limiting factors which may vitiate attempts at quantitative interpretation of the effects of anesthetic agents on the newborn.

In a clinical sense, a long range program of follow-up visits of severely depressed babies, as well as healthy active infants, alone can determine the extent of cerebral and other organic damage. Beginnings in this direction have been made.[2]

Observation of the fetus in utero is a method applicable to animal experimentation and has been used extensively by Barcroft[3] and by Snyder and Rosenfeld.[4] Abnormal factors, however, are always introduced, such as a transected cord, administration of labor-arresting drugs, and opening of the abdominal cavity and uterus in a saline bath. Despite these difficulties, valuable information can be gained concerning the effect upon the fetus of analgesic and anesthetic drugs.

Chemical analysis of specific substances in the maternal blood and placental blood simultaneously may also yield knowledge of the mechanisms of placental transmission as well as the production and

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circulation of amniotic fluid. Several pitfalls exist in the collection of fetal blood for analysis. Eastman[5] in 1930 used twelve-inch lengths of umbilical cord, doubly clamped at the vulva and at the umbilicus, and took samples from the umbilical arteries and vein by direct puncture. He assumed that no essential change in oxygen or carbon dioxide tensions took place over several hours. This assumption of the chemical stability of cord blood may be questionable since Smith[1] found a definite loss of ether from blood samples drawn from the isolated cord in one, two and three hours. He calculated the loss and devised a mathematical constant to correct for the gradual loss of ether. The physical state of the blood in such isolated cords can change over a period of hours. Changes in viscosity, clotting, and development of a tendency to sludge may interfere with chemical analysis. Barcroft has written a masterly description[6] of the difficulties encountered in obtaining blood from the umbilical vessels of the intact sheep cord. The vessels showed immediate "resentment" by going into spasm whenever they were touched with a needle, which surely interfered with the normal rate of exchange of gases and nonvolatile compounds.

The method of catheterization of the umbilical vein to obtain blood samples in the newborn infant probably provides the least abnormal values. This method has been popularized by its use for exchange transfusions in infants with hemolytic disease, and has been used for blood sampling by Hellman et al.[7]

Analysis of the organs of the mother, fetus, placenta and amniotic fluid has been used in animal studies for determining quantitatively the presence of nonvolatile drugs, such as barbital and amytal.[8]

In 2 human full-term cases of fatal self-administered overdosage with barbiturates, Martland and Martland[9] studied brain samples of equal weight from the mother and the fetus and combined equivalent samples of kidney, liver and spleen of each to determine the relative content of barbituric acid ester. In both cases fetal tissues contained one and one-half times the barbiturate contents of maternal tissues.

Isotopic tracers have been employed recently in studies of placental transmission of water and electrolytes, the rate of extraction of substances by the fetus from the maternal circulation, the relation of such rates to growth of the fetus, and formation and circulation of amniotic fluid. Flexner and Gelhorn,[10] Vosburgh[11] and others have reported studies of the rate of exchange of amniotic fluid and placental permeability to water, with the aid of heavy water and sodium 24. They found in the guinea pig that the water of the amniotic fluid was changed 33 per cent in an hour and the sodium content at one-fifth that rate.

There are many factors concerned with the transport of substances to and from the placenta. Circulatory changes are important, although exceedingly difficult to measure, especially in the human

patient. Effective placental blood pressure has been estimated to be the difference between the systemic arterial pressure and the intrauterine pressure. In the unmedicated human patient the pressure in the resting uterus at term is in the range of 5 to 20 mm. Hg. During uterine contractions, the intrauterine pressure rises to 60 or 70 mm. Hg, while during the active bearing down phase, the added work of the abdominal muscles brings the total intrauterine pressure to 160 mm. Hg.[12] Since the systemic blood pressure rise is considerably less pronounced, there are periods, especially early in labor, during which the effective placental blood pressure is low. The fetus, at these times, experiences temporary interruption in the transfer of all substances in both directions. Clinically, this is often evidenced by fetal bradycardia or other cardiac arrhythmias.

It is unlikely that all the placental blood, estimated to be 1000 cc. at term, is squeezed out of the placenta with each contraction, since the subsequent rise in maternal venous pressure is not enough to account for an autotransfusion of that size. From the anatomical studies of Grosser,[13] Spanner[14] and Falkiner,[15] it is evident that intervillous blood drains into peripherally placed marginal sinusoids and thence into marginal veins which empty into the uterine veins. As the intrauterine pressure rises to 20 or 30 mm. Hg, these sinusoids are compressed completely so that no further emptying of placental blood can occur. The fetus is thus left in contact with much of the placental blood even during a contraction.

It is possible to separate the contributions of the uterine musculature and the abdominal muscles to total intrauterine pressure with the aid of a differential manometer recording from intragastric (intraperitoneal) and intrauterine balloons. Woodbury, Hamilton and Torpin[12] found that all anesthetic agents and pentobarbital and morphine depressed the power of the abdominal muscles to contract. These compounds, except for ether and chloroform, had no significant effect on uterine contractions. The various regional methods of anesthesia were not studied. Because the depression caused by anesthetic agents affects the abdominal muscles predominantly, the effective placental blood pressure is actually improved, for the total intrauterine pressure is lessened. More blood remains in the placenta during contractions. The ultimate survival of the fetus during labor, however, is dependent upon many other factors and not upon the effective placental blood pressure alone. These must also be evaluated in the attempt to understand fetal physiology in the birth process.

The only substances which regularly increase the uterine component of intrauterine pressure are the oxytoxic drugs and norepinephrine. A negative effective placental blood pressure was not infrequently registered. From these facts one would expect a higher incidence of intrapartum fetal death from interference with oxygen transfer when oxytocic drugs are administered. Clinically this does not seem to be the case, as evidenced by over 2,500 pitocin infusions

given at the Sloane Hospital for Women, with an actual diminution in the stillbirth and neonatal death rates.[16]

The blood flow through the uterus has intrigued many workers and remains difficult to study in the human subject. The changes in flow during various periods of gestation in the rabbit have been satisfactorily outlined.[17] In the middle of the gestation period, the uterus contains 8 cc. of blood with a flow of 5 cc. per minute. By the beginning of the third trimester, the volume has doubled to 16 cc. and the flow increased decidedly to 29 cc. per minute. Then follows a reduction in flow to 19 cc. per minute, and a final increase back to 29 cc. per minute with a volume of 32 cc. The decrease in flow coincides with the slowing of uterine growth and the increase in fetal growth.

While studying the oxygenation of the umbilical venous blood in the human newborn whose mothers received ether, nitrous oxide or cyclopropane, Smith noted a small peripheral arterial-venous oxygen difference in the mothers who received cyclopropane and implied that the high oxygen venous content was due to increased blood flow. It was assumed further that this increased blood flow was present in the placental as well as the peripheral circulation.

The placenta structurally is comparable to a large arterio-venous fistula. The blood in the intervillous spaces is both arterial and venous in composition. The surface area of the villi which is exposed to this blood has been estimated to be between 9 and 16 square meters. Eastman has stated graphically that this surface is at least as large as a 9x12 foot living room rug.[18] Mossman[19] was the first to conclude that the direction of flow of blood in the intervillous space was opposite in direction from that in the fetal villi. The umbilical arteries bring blood from the fetus to the more venous end of the intervillous space, where metabolic products are discharged, and the umbilical vein carries blood back to the fetus from the more arterial end of this arteriovenous fistula. As much oxygen as the placental blood has to offer is thus carried to the fetus. At best, the placental blood has a relatively low oxygen content. From umbilical vein determinations, Eastman estimated that the highest oxygen tension in the intervillous spaces is only 40 mm. Hg, as compared with the normal peripheral arterial tension of 100 mm. Hg.[5] Because of the high capacity of fetal blood for oxygen, it is probable that the infant is normally cyanotic in utero, for the saturation of oxygen is about 50 per cent. Fortunately, the oxygen dissociation curve characteristics of fetal blood favors relatively great increases in oxygen saturation with smaller changes in tension. If the placental blood oxygen tension is lower than 40 mm. Hg, the administration of oxygen to the mother can be expected to provide improvement. At the same time the fetal blood saturation will profit more by a small increase in oxygen tension than the maternal blood would under similar conditions of desaturation. These facts are of great importance in situations where effective placental blood pressure is probably low, such as peripheral

hypotension from spinal or epidural anesthesia, a tonic contraction of the uterus from unwise administration of pitocin, or the presence of severe anemia in the mother.

Quantitative estimations of drug levels in the human mother and newborn infant taken simultaneously are few in number. In 1930, Eastman deplored the lack of definite information about the transfer of oxygen and carbon dioxide between mother and child.[5] A series of studies was initiated and extended by Eastman and his students[5 20 21 11] to include the effect of anesthetic agents on the oxygenation of the baby, the placental transmission of thiopental, and the exchange of body water and sodium. In 1939, Smith became interested in the effect of anesthetic agents on oxygenation of the newborn infant and performed quantitative studies with cyclopropane, ether and nitrous oxide.[1 22] In 1940, Gardner, Levine and Bodansky analyzed the blood of the mother and newborn infant for paraldehyde levels after oral and rectal administration for amnesic and analgesic purposes.[23] Studies on the transmission of meperidine (demerol) across the placenta are in progress with the aid of a specific quantitative method of analysis devised by Brodie and Burns.[24] Lack of suitable methods of analysis for morphine, heroin and curare have delayed the study of the behavior of these compounds with respect to the placenta and relative maternal and fetal distributions.

The information obtained from the studies described above will be summarized briefly.

Oxygen Transfer: (16 cases) The oxygen capacity of infant's blood at birth is distinctly greater than that of the mother's blood, averaging 20.8 volumes per cent compared with the maternal capacity of 15.4 volumes per cent.[5] The oxygen saturation of fetal arterial blood in utero (cesarean section—local anesthesia) was 63 per cent in one subject and 50 per cent at birth, while the mother's venous saturation was 71 per cent with an estimated arterial saturation of 95 per cent. The oxygen content of the baby's arterial blood at birth is 10.5 volumes per cent and the maternal arterial content 14.7 volumes per cent. The oxygen capacity and content of the blood of the pregnant female are less than those of the nongravid female because of an increased blood volume and proportionately larger increase in plasma volume during pregnancy. Apparently the red cell mass is stationary. Eastman found that the oxygen capacity of 18 nonpregnant women averaged 18.9 volumes per cent while that of 16 pregnant women was 15.4 volumes per cent. He also studied the effect of various anesthetic methods on the oxygen saturation of the fetus at the time of birth. With 15 infants as controls, he described 40 newborn infants whose mothers had been anesthetized with chloroform (4 cases) ether (8 cases) and nitrous oxide and oxygen (28 cases). Inhaled gas concentrations were estimated from the flow of gases as registered on the flowmeter of the anesthetic machine, a method which is subject to error and considerable variation.[23] In all cases the oxygen content of newborn blood was lower than expected. There was no

lowering of oxygen saturation of arterial or venous blood of the infant with chloroform, little change with ether, more with 80 per cent nitrous oxide and 20 per cent oxygen, and a decided drop with 90 per cent nitrous oxide and 10 per cent oxygen mixture. No analysis of the concentration of the anesthetic agent in the blood stream was reported.

In a recent study at the Sloane Hospital for Women the oxygen content of heel blood taken one to five minutes after birth in 239 infants averaged 8.0 volumes per cent, with a range of 1.1 per cent to 15.5 volumes per cent.[26] No correlation was made with the type of anesthetic agent used or with the maternal blood contents.

Large volumes of water traverse the placenta as determined by the use of deuterium oxide.[11] From the fourteenth to the fortieth week, there is a five-fold increase in transfer of water per unit of weight of placenta. At the fourteenth week, the human fetus receives 700 times as much water as is incorporated into his tissues, and at thirty-one weeks he receives 3800 times more than he retains. Hellman defined the excess of a substance delivered to the fetus and not retained by it but returned to the mother as the "safety factor."[7] The placenta of the guinea pig is twice as permeable to water as the human placenta, though they are of the same anatomic type (hemochorial). The peak in water transfer occurs at thirty-six weeks, with a pronounced fall until birth at the fortieth week.

By injecting deuterium oxide intravenously into a maternal vein and sampling amniotic fluid for the appearance of the isotope, the rate of renewal of the water of amniotic fluid was found to be 34.5 per cent per hour, with a range of 17 to 74 per cent in five subjects. If the amniotic fluid is present in usual amounts, averaging 1000 cc., this finding indicates that the entire water content changes every three hours. From the experimental work of Davis and Potter,[27] who injected thorotrast into the amniotic sac of the mother at varying times in gestation with resulting x-ray visualization of the fetus's lungs and intestinal tract, it is possible that one major route for removal of this volume of amniotic fluid is by reabsorption into the fetus by way of his respiratory and intestinal tracts.

The transfer of sodium in amniotic fluid is less rapid. Using radioactive sodium, the rate of transfer per hour was determined in 20 patients. It was found that 6.9 per cent of sodium was renewed each hour.[28]

Lactic acid determinations of maternal and fetal blood were made by Bell in 1928.[29] He found the highest values in fetal venous blood, while even the fetal arterial blood contained almost twice as much as the maternal arterial or venous blood. Wilson recently[30] has summarized the latest data on acid-base balance in the newborn infant and corroborates the presence of a mechanism of anaerobic oxidation at birth and for several days of life. An uncompensated acidosis of mild degree apparently is normal for the newborn infant, especially a

premature infant. A low blood hydrogen ion concentration, low total carbon dioxide content and tension, and end products of metabolism other than carbonic acid, such as lactic and pyruvic acid, all indicate the presence of this accessory mechanism of oxidation.

The transmission of thiopental has been determined in 7 cases.[21] Before seven minutes and after twelve minutes, minimal amounts of thiopental were found in the blood of the newborn infant. Between these two intervals, the fetal level was 50 per cent or more of the maternal level. The physiologic fate of thiopental or its distribution in the newborn infant have not yet been studied.

Ten patients at term were given paraldehyde by nasal gastric tube and 10 by the rectal route, and blood levels for paraldehyde were determined.[23] Thirteen cord blood determinations were made also. The oral route produced higher blood levels three hours after administration. At the time of delivery, several hours after the initial dose, the cord blood samples averaged 15.5 mg. per cent, while the maternal average was 16.6 per cent. In several cases the fetal level was higher than the maternal. There was no correlation between onset of respiration and the fetal blood level of paraldehyde. The 3 infants with the highest levels all cried lustily, while the 3 apneic babies, 2 of whom were premature, had levels well below the average. One of the mothers of the 3 infants had received a small amount of nitrous oxide, while the other 2 had only local anesthesia for episiotomy.

During his study of blood oxygen in the infant, Smith made many determinations for nitrous oxide, cyclopropane and ether in maternal and fetal arterial and venous blood.[1 22] Cyclopropane and ether traversed the placenta almost quantitatively, while only 60 per cent of the nitrous oxide in maternal blood reached the fetus. When the infants were classified as to promptness of respiration, there was no correlation with the oxygen content of fetal arterial blood, but with the 66 ether cases, there was a direct correlation of ether levels with the depression of respiration.

Meperidine is transmitted by the placenta to the fetus. Plasma levels in the mother and infant taken simultaneously show that 60 to 70 per cent of the maternal blood concentration is present in the blood of the newborn infant.[31] Comparison of maternal and newborn infant urinary excretion of meperidine after one or two doses of 100 mg. of drug given intramuscularly to 9 mothers showed that at the most 1 per cent of the drug was recovered in the infant's urine, while 10 per cent was found in maternal urine.[34]

The clinical impression exists and is growing that d-tubocurarine does not pass the placental barrier. Reports of its use, along with light general anesthesia for both cesarean section[32] and for vaginal deliveries,[33 35] suggest that respiration of the infant is not unfavorably influenced. Quantitative proof of these clinical observations has not been presented in human subjects. Brodie[42] suggests that the

rapid binding of curare with maternal proteins may be a possible explanation for this phenomenon.

Harroun and Fisher studied the problem of placental transfer of curare in 10 pregnant dogs.[36] The animals were made apneic with d-tubocurarine. Artificial respiration was carried out with oxygen through an endotracheal airway by manual pressure on the breathing bag. General anesthesia was induced and the litters of pups delivered by cesarean section. All 67 pups were lively, active and breathed well. One pup was subsequently given curare intravenously and promptly became apneic. The authors concluded that curare did not traverse the placenta of the pregnant dog.

Observations on transmission of decamethonium iodide (C 10) have been made by Young[44] in the guinea pig and the rabbit. She found the fetal circulatory and respiratory responses were normal after intravenous injection of the drug into the mother, and conversely, injection of the drug into the umbilical arteries of the fetus while still in utero produced no changes in the mother. Scurr[45] from clinical observations on human patients concurs that the drug does not pass into the placental circulation.

In 1949, Helliwell and Hutton[43] performed quantitative estimations of trichlorethylene on the fetuses of the ewe and the goat. They found that the drug appeared almost immediately after its administration to the mother. *In vitro,* fetal blood of the ewe had a higher capacity for trichlorethylene than did the maternal blood.

Dillie[8 37] studied the effect of small and large doses of barbiturates on the rabbit embryo when administered to the mother. Pregnant rabbits were given spinal anesthesia with spinocain, and placed in the supine position. Barbital 75 to 100 mg./kg. were then given intravenously. Portions of the uterus were delivered and a fetus removed without disturbing the rest of the uterus which was returned to the abdominal cavity. Fetuses were removed at varying intervals after the barbital injection. The amniotic fluid, the placenta, and the fetus were analyzed separately for barbital content.

After five minutes, the drug was identified in all three materials. All animals breathed spontaneously and reacted to stimuli but barbital content of the fetus suggests that some central nervous system depression was present.

With large single doses in 9 rabbits, 1 guinea pig and 1 cat, the placental transmission of amytal and barbital was proved. Large anesthetic doses administered intravenously could be detected in the amniotic fluid, placenta and in fetal organs within fifteen minutes. Repeated daily doses of barbital for 5 to 32 days in 7 dogs resulted in abortion or resorption of the fetuses. In a single animal, which received barbital for five days before delivery, the drug level in blood and liver of the mother and the newborn pups was the same.

The following substances are known to traverse the placenta: oxygen, carbon dioxide, all anesthetic gases and vapors, morphine, meperidine, barbiturates, bismuth, iron, sodium chloride, magnesium, water, urea, uric acid, creatine, creatinine, phosphorus, calcium, free ammonia nitrogen, nucleic acid, sulphanilamide, penicillin, streptomycin, thiamine, vitamin C, lipoids, glucose, fructose, cholestrol, estrogens, copper, thyroxin, epinephrine, progesterone and certain antibodies which are gamma globulins of molecular weights of approximately 103,000.[18 41] Vitamins A and K traverse slowly, if at all. Carbon monoxide, parathyroid hormone, polypeptides, plasma proteins, phospholipids, gonadotropins and the virus of poliomyelitis apparently do not cross the placental barrier. It remains to be shown whether curare and procaine and related local anesthetic agents are present in fetal blood.

Amniotic fluid as a vehicle for transmission of many substances, including drugs, to the fetus is probably more important than was previously realized. Heretofore, the umbilical vein has been considered the only route of transfer. The origin of the large volume of amniotic fluid, from 600 to 2500 cc., is still mysterious. Although fetal urine contributes some volume, it is indeed small. Vosburgh and his associates have recently proved that the entire water content of the amniotic fluid changes at the rate of 350 cc. per hour, so that an average volume of 1000 cc. is changed every three hours.[11] Whether its source is partially secretory from the cells of the amnion, as described by Polano in 1905,[38] or wholly a transudation from the mother is unknown. It is likely that increased plasma volume of the mother would allow enough volume for such transudation but this thesis has not been proved. Transudation through the cord itself is another possibility but would not account for such a rapid production of fluid. What becomes of the 350 cc. per hour? Davis and Potter have demonstrated that the gastrointestinal tract and the lungs of the human fetus, after the age of 4 months at least, normally contain large amounts of amniotic fluid.[27] If a radiopaque medium is introduced into the amniotic sac and left there over one hour, an excellent radiograph is obtained of the respiratory and gastrointestinal tracts, including the rectum. It is possible that deglutition and respiration *in utero* account at least partially for the rapid turnover of amniotic fluid. Obviously, this also affords another route for absorption of drugs into the fetus, in addition to blood coming via the umbilical cord.

Dillie, in his work on barbital and amytal in rabbits, guinea pigs and cats, analyzed fetal blood, amniotic fluid and the placentas separately. In over half the experiments which included amniotic fluid determinations, the level of barbituric acid esters was higher in this fluid than in the fetal blood or the placenta.

Further evidence of the removal of amniotic fluid by way of the fetus and thence back to the mother was adduced by Lell, Liber and Snyder.[40] They injected phenolsulfonphthalein into the muscles of the

back of rabbit fetuses and analyzed the maternal urine for the presence of dye. In another experiment the dye was placed in amniotic fluid rather than into the fetus itself. At term, 40 per cent of the dye was found in maternal urine when it had been placed in amniotic fluid, while only 13 per cent was recovered when it had been injected into the paraspinal muscles.

The citing of 2 cases of hydramnios in which the infants had duodenal atresia, one proved at autopsy, the other at operation, suggests that the gastrointestinal route of absorption of amniotic fluid is more important than the respiratory route.[32] No cases of hydramnios accompanying complete laryngeal stenosis have been reported to our knowledge.

The surprisingly frequent association of anencephaly and hydramnios suggests that deficient innervation may prevent intrauterine fetal deglutition and respiration so that the circulation of amniotic fluid is seriously obstructed.

Whether or not the fetus excretes drugs or metabolic products into amniotic fluid, other than by the urinary route, remains to be demonstrated.

In future experimental work with transmission of drugs across the placenta, it would seem advisable to take samples from amniotic fluid, as well as from the umbilical vein, for both routes transport substances to the fetus.

Summary

INFORMATION REGARDING transmission of drugs across the placenta has been gained in various ways; by rough clinical estimates of the condition of the infant and its need for resuscitation; by observation of the animal fetus in utero and observing the effect of drugs administered to the mother on fetal respiration; by analyses of maternal and fetal brain, liver, kidneys and spleen for drug content; and by quantitative simultaneous chemical analyses of maternal and fetal blood. The new method of using isotopic tracer substances should be as applicable to studies of drug transmission as it is to studies on transfer of water and electrolytes. Anesthetic gases, vapors, barbital, amytal, thiopental, paraldehyde and meperidine have been shown by quantative studies to pass through the placenta. It is probable that d-tubocurarine and similar relaxants and drugs used for regional anesthesia are not transmitted.

The amount of information regarding many physiologic factors related to maternal uterine circulation is growing slowly. The net effective placental blood pressure has been studied during various periods of gestation and during the course of labor. It has shown improvement during light planes of general anesthesia, and diminution to dangerous levels following the use of oxytocics during the ante-partum period. A recent clinical series of pitocin infusions, how-

ever, was not accompanied by any increased stillbirth or neonatal mortality.

The tension of oxygen offered to the fetus in the uterus at term is less than half the maternal arterial level. The maternal decreased oxygen capacity, probably related to an increased plasma volume, necessitates more frequent administration of oxygen to the mother during periods of hypotension, or of uterine hypertonicity. Fetal factors which tend to make efficient use of the low oxygen tensions offered to it in the intervillous spaces are the direction of flow of blood in the villi which is opposite to that of the mother's, a high oxygen capacity, a shift to the left of the oxygen dissociation curve, and the existence of a reserve mechanism for anaerobic oxidation. Further understanding of transmission of water, electrolytes and metabolic products will aid in the study of drug transmission, distribution and metabolism.

The circulation of amniotic fluid is becoming clarified, except for its origin. Its rate of change is approximately 350 cc. per hour and its route of removal is related to fetal deglutition and respiration. Amniotic fluid as well as the umbilical vein should be considered a route for drug transmission from mother to fetus. Its relative importance remains to be determined.

References

1. Smith, C. A. and Barker, R. H.: Ether in Blood of Newborn Infants, *Am. J. Obst. & Gynec.* 43:763-744, 1942.
2. Babies Hospital, New York City, Personal communication.
3. Barcroft, J.: Researches on Prenatal Life, Springfield, Ill., C. C. Thomas, 1947.
4. Snyder, F. F.: Obstetrical Analgesia and Anesthesia, Philadelphia, Pa., W. B. Saunders Co., 1949.
5. Eastman, N. J.: Foetal Blood Studies: I. The Oxygen Relationships of Umbilical Cord Blood at Birth, *Bull. Johns Hopkins Hosp.* 47:221-230, 1930.
6. Barcroft, J.: Researches on Prenatal Life, Springfield, Ill., C. C. Thomas, 1947, p. 192.
7. Hellman, L. M. et al.: Permeability of the Placenta to Water and the Supply of Water to the Human Fetus as Determined by Deuterium Oxide, *Am. J. Obst. & Gynec.* 56:861-868, 1948.
8. Dillie, J. M.: Studies on Barbiturates: IX. Effect of Barbiturate on Embryo and on Pregnancy, *J. Pharmacol. & Exper. Therap.* 52:129-136, 1934.
9. Martland, H. S. and Martland, H. S., Jr.: Placental Barrier in Carbon Monoxide, Barbiturate and Radium Poisoning: Original Observation on Humans, *Am. J. Surg.* 80:270-279, 1950.
10. Flexner, L. B. and Gelhorn, A.: The Comparative Physiology of Placental Transfer, *Am. J. Obst. & Gynec.* 43:965-974, 1942.
11. Vosburg, G. J. et al.: Rate of Renewal of Water and Sodium in Amniotic Fluid as Determined by Tracer Technics, *Am. J. Obst. & Gynec.* 56:1156-1159, 1948.
12. Woodbury, R. A., Hamilton, W. F. and Torpin, R.: Relationship Between Abdominal Uterine and Arterial Pressures During Labor, *Am. J. Physiol.* 121:640-649, 1938.
13. Grosser, O.: Fruhentwicklung, Eihautbilding und plazentation des menschen und der saugetiere, München, 1927.
14. Spanner, R.: Mutterlicher und kindlicher Kreislauf der menschlichen placenta und seine Strombahnen, *Zeit. Anat. Entw. gesch.* 105:(ii) 163, 1935.
15. Falkiner, N. McI.: Placental Circulation, *Proc. Royal Soc. Med.* 37:417-425, 1943-1944.
16. Sloane Hospital for Women, New York City, Personal communication.
17. Reynolds, S. R. M.: The Physiology of the Uterus, New York, Hoeber, ed. 2, 1949.
18. Eastman, N. J.: William's Obstetrics, New York, Appleton, Century Crafts, ed. 10, p. 185, 1950.
19. Mossman, H. W.: The Rabbit Placenta and the Problem of Placental Transmission, *Am. J. Anat.* 37:433-497, 1926.
20. Eastman, N. J.: Foetal Blood Studies, 5. Role of Anesthesia in Producing Asphyxia Neonatorum, *Am. J. Obst. & Gynec.* 31:563-572, 1936.
21. Hellman, L. M., Shettles, L. B., Managan, C. P. and Eastman, N. J.: Sodium Pentothal in Obstetrics, *Am. J. Obst. & Gynec.* 48:851-860, 1944.
22. Smith, C. A.: Cyclopropane in Obstetrics, *Surg., Gynec. & Obst.* 69:584-593, 1939.
23. Gardner, H. L., Levine, H. and Bodansky, M.: Concentration of Paraldehyde in Blood After Administration During Labor, *Am. J. Obst. & Gynec.* 40:435-439, 1940.
24. Brodie, B. B. and Burns, J. R.: Personal communication.
25. Department of Anesthesiology, Presbyterian Hospital, New York: Personal communication.

26. Apgar, V.: Oxygen as a Supportive Therapy in Fetal Anoxia, *Bull. N. Y. Acad. Med.* 26:474-478, 1950.
27. Davis, M. E. and Potter, E. L.: Intrauterine Respiration, *J. A. M. A.* 131:1194-1201, 1946.
28. Flexner, L. B. et al.: Permeability of Human Placenta to Sodium in Normal and Abnormal Pregnancies and Supply of Sodium to Human Fetus as Determined by Radioactive Sodium, *Am. J. Obst. & Gynec.* 55:469-480, 1948.
29. Bell, W. B. et al.: Metabolism and Acidity of Fetal Tissues and Fluids, *Brit. M. J.* 1:126-131, 1928.
30. Wilson, J. L., Reardon, H. S. and Murayana, M.: Anaerobic Metabolism in the Newborn Infant, *Pediatrics* 1:581-592, 1948.
31. Department of Anesthesiology, Presbyterian Hospital, New York: Personal communication.
32. Gray, T. Cecil: d-Tubocurarine in Cesarean Sections; *Brit. M. J.* 1:444-445, 1947.
33. McMann, W.: Curare and General Anesthesia in Vaginal Deliveries, *Am. J. Obst. & Gynec.* 60:1366-1368, 1950.
34. Way, E. L. et al.: The Absorption, Distribution and Excretion of Isonipecaine, *J. Pharmacol. & Exper. Therap.* 96:477-484, 1949.
35. Austin, B. and Mering, T. W.: Use of Muscle Relaxing Drugs in Complicated Deliveries, *Am. J. Obst. & Gynec.* 62:143-149, 1951.
36. Harroun, P. and Fisher, C. W.: The Physiological Effects of Curare, *Surg., Gynec. & Obst.* 89:73-75, 1949.
37. Dillie, J. M.: Placental Transmission of Nonanesthetic Doses of Barbital, *Am. J. Obst. & Gynec.* 32:328-330, 1936.
38. Polano, O.: Experimentelle beitrag zur Biologie der Schwangerschaft: Habilitationscrift, Wurzburg, Sturtz, 1904.
39. Mengert, W. F. and Bourland, J. W.: The Circulation of Amniotic Fluid, *Am. J. Obst. & Gynec.* 50:79-83, 1945.
40. Lell, W. A., Liber, K. E. and Snyder, F. F.: Quantitative Study of Placental Transmission, *Am. J. Physiol.* 100:21-31, 1932.
41. Needham, J: Chemical Embryology, Vol. 3, Cambridge Univ. Press, 1930.
42. Brodie, B. B.: Personal communication.
43. Helliwell, P. J. and Hutton, A. M.: Analgesia in Obstetrics, *Anaesthesia* 4:18-21, 1949.
44. Young, I. M.: Abdominal Relaxation with Decamethonium Iodide During Caesarian Section, *Lancet* 1:1052-1053, 1949.
45. Scurr, C. F.: Comparative Review of Relaxants, *Brit. J. Anaes.* 23:102-116, 1951.