

REVIEW ARTICLE

PLACENTAL TRANSFER AND DRUGS USED IN ANESTHESIA

GERTIE F. MARX, M.D.

FUNCTIONALLY, the placenta constitutes the regions through which exchanges take place between the maternal and fetal organisms. Oxygen, nutrients, water, electrolytes, vitamins, and antibodies are transported to the fetus; carbon dioxide and excretory substances are transferred to the mother. In addition to this role as an essential link between mother and fetus, the placenta has a wide range of enzymatic activities, and also serves to produce certain hormones and to inactivate and degrade others. With respect to the number of actions it performs, the placenta is unique, being at once lung, intestine, liver, kidney, and endocrine gland.

The following report deals with those aspects of placental transfer which are of importance to the anesthesiologist.

PLACENTAL BARRIER

The barrier which separates maternal and fetal blood at the villous-intervillous space site consists, in the mature human placenta, of three layers of fetal tissue: (1) the trophoblastic epithelium or syncytium (covering of the villi), (2) the chorionic connective tissue, and (3) the capillary endothelium (lining of the capillary wall).¹ In the terminal villi, however, many fetal capillaries lie immediately subjacent to the syncytium so that the barrier is thinned to two delicate unicellular membranes.² Prior to the sixth month of pregnancy, an additional layer consisting of cytotrophoblasts (Langhans cells) is found beneath the syncytium. These cytotrophoblasts disappear gradually and at full term only remnants or occasional cells are present.³

The syncytial cells constitute the parenchyma of the placenta. They are engaged in the active enzymatic transfer of selected

substances and in the secretion of placental steroid hormones.⁴ They carry out a wide spectrum of synthetic and catabolic reactions.⁵ In certain areas of the syncytium the cells have a brush border, whereas in other regions the brush border is absent. It is not known whether only selected cells possess a brush border or whether all syncytial cells have a brush border which waxes and wanes at different times.⁶ The brush border is made up of large numbers of microvilli which are capable of engulfing macromolecules or droplets of plasma and transferring them to the fetal capillaries by pinocytosis.⁴

As gestation progresses, two morphological processes of "aging" go on simultaneously. One is the loss of the cytotrophoblast; this causes thinning which may facilitate the transport mechanism. The other is a break in the covering of the villous space leading to deposition of fibrin; this may actually make the exchange less efficient.^{3,7} Indeed, the morphological changes are accompanied by both decreased rates of some placental functions and increased rates of others. However, neither the changes in composition nor the alterations in function take place in a fixed sequence. As Villee stated, "There is no regular change in the efficiency of placental transfer and no general senescence at term."⁵

The number of tissue layers interspersed between the maternal and fetal circulations varies with different species. In pigs and horses, the placental barrier consists of 6 layers, in sheep, goats and cows of 5, in dogs and cats of 4, in man, monkeys and primates of 3, and in the rabbit of only 1 layer.⁸

TRANSPORT MECHANISMS

There are separate routes for the passage of different compounds, namely: (1) diffusion, unimpeded or limited by the barrier,

Dr. Marx is Associate Professor of Anesthesiology, Albert Einstein College of Medicine, Yeshiva University, New York 61, N. Y.

(2) Starling-Landis filtration,* (3) active transport processes, (4) leakage through porous defects in the barrier, (5) pinocytosis, and (6) various combinations thereof.^{1, 4, 9} Histiotrophic activity plays a role in the transport during the early stages of development when chorionic giant cells are implicated in phagocytosis and other transfer processes.¹⁰

The possibility of absorption across paraplacental membranes has recently been entertained. So far no proof of vascularization of amnion or chorion has been found.¹¹ The amniotic fluid, on the other hand, takes part in the transport mechanism, especially in the transfer of water and electrolytes. Plentl studied the dynamics of amniotic fluid by transabdominal catheterization of this compartment and injection of tracer substances into it. He concluded from the resultant "ratio of the transfer rates of water, sodium and potassium" that amniotic fluid is not an ultrafiltrate of serum, but a pool of various components each of which is in equilibrium with the maternal organism and probably the fetus.¹² The first drug which, to my knowledge, was ever reported to pass from mother to fetus was discovered in the amniotic fluid. Schauenstein and Spaeth, as quoted by Preyer,¹³ observed in 1858 that potassium iodide, given to syphilitic pregnant women near term, could be found in amniotic fluid and in meconium.

In general, the relative rate of passage of a transferable substance is dependent upon its size, shape, and electrical charge, and upon the concentration gradient across the barrier. All substances with a molecular weight below 350 to 450 can diffuse across the human placenta freely in both directions.⁹ Active transport is performed by "carriers" visualized as rapidly oscillating back and forth between the two surfaces and being able to select certain substances or reject others.¹⁴ The concentration of transferred materials may be equal or unequal on either side of the membrane. Inequality of the distribution of diffusible substances may ensue from destruc-

tion by the placenta or from difference in the rate of removal and/or different dissociation constants of the complexes formed. Destruction during passage is evidenced in the fate of serotonin, histamine and epinephrine. These substances are capable of easily traversing the placenta, but ordinary amounts are deaminated in transit by the high content of monoamine oxidase present in the placenta. Different rates of removal may be caused by dilution in the mother, by excretion via her kidneys, or by difference in the respective rates of metabolism. Different dissociation constants may occur when substances form a complex with other molecules; an example of this is found in oxygen combining with maternal versus fetal hemoglobin. With regard to the actively transported substances, unequal distribution may result from the carrier system operating against a concentration gradient or from molecular alterations taking place during the process of transmission. The former explains the higher concentration of essential amino acids in fetal plasma as compared to maternal plasma; the latter accounts for the transfer mechanisms of iron, calcium, magnesium, the vitamins as well as the phospholipids and most fatty acids.⁹

Page has proposed a classification of transport mechanisms across the human placenta based primarily on the factors of physiological significance of the substance and on the route and rate of its transfer.⁹ His scheme consists of the following four groups: (1) substances concerned with the maintenance of biochemical homeostasis or protection against sudden fetal death are transferred by rapid diffusion (oxygen, carbon dioxide, water, electrolytes, urea, etc.); (2) substances concerned with fetal nutrition are transported by active mechanisms with or without diffusion (glucose, amino acids, vitamins, etc.); (3) substances concerned primarily with modification of fetal growth and the maintenance of pregnancy are transmitted predominantly by slow diffusion (steroid and protein hormones), and, (4) substances of immunological importance are transported by leakage through large pores (red blood cells—Rh sensitization) or possibly by pinocytosis (plasma proteins—protein sensitization).

Analyses of the contents or tensions of

* Starling-Landis theory: the exchange of fluids between the tissue spaces and the blood stream is regulated by a balance between two opposing forces, the hydrostatic pressure in capillaries and the partial osmotic pressure of the plasma colloids.

substances transmitted across the placental barrier are complicated by many factors. The organization of the barrier and the characteristics of maternal and fetal bloods vary so markedly in different species that the data obtained from one animal are not easily applicable to another. Similar difficulties limit the usefulness of results gathered at different stages of gestation. Gas exchange data are altered by the fact that both the placental barrier and the uterine musculature extract oxygen from the current of maternal blood flowing through the intervillous spaces and add carbon dioxide to it.¹⁵

Circulation through the placenta varies in different regions, with changes in the position of the pregnant woman and with the tonus of the uterus. Romney injected intact uteroplacental sites with a radiopaque material and found that in some areas blood was present in slowly moving pools whereas in others it flowed rather rapidly through distinct vascular channels.¹⁶ Ramsey observed blood from the maternal circulation to enter in spurts with only certain arterioles permitting passage at a given moment. In addition, she noticed the frequent presence of fibrin clots in the intervillous lakes indicating stasis for longer periods of time.¹⁷ Prystowsky aspirated two different regions of the intervillous spaces at the same time; the two samples of blood had significant differences in their oxygen content.¹⁸

The influence of the mother's position on placental circulation is explained by the relationship of the uterus to the great veins. In the supine position, and with the myometrium relaxed, the enlarged uterus compresses the inferior vena cava, causing a rise in venous pressure cuudad and a decrease in right auricular pressure. The pressure gradient between uterine artery and vein is reduced.¹⁹ The contracted uterus does not exert pressure posteriorly upon the veins in any position.²⁰ The pressure in the intervillous space has been recorded at 7–10 mm. of mercury when the pregnant woman near term is supine, and at over 30 mm. of mercury when she sits or stands. The pressure in fetal capillaries remains constant at slightly over 20 mm. of mercury. Consequently, the direction of the pressure gradient between maternal and fetal

blood streams shifts with different postures of the mother.⁴

Uterine contractions are associated with a reduction in effective blood flow in both animal and man. Assali and his colleagues measured uterine circulation during labor in unanesthetized pregnant sheep and dogs by means of a chronically implanted electromagnetic flow meter. In either spontaneous or oxytocin induced labor, myometrial contractions were accompanied by decreases in blood flow and myometrial relaxations by a return of the flow to control values. The degree of ischemia was dependent upon the intensity and duration of uterine contractions.²¹ Wright and her group studied the effective uterine circulation in 20 women during the early first stage of labor and in 26 during the later first stage by determining uterine clearance times following injection of Na¹⁴Cl into the uterine muscle. In the early stage, blood flow was within normal resting limits in all but 3 instances, but in the late stage, 16 or more than half showed diminished uterine circulation.²²

On the maternal side, blood samples are available from systemic arteries and veins, from the intervillous spaces by transabdominal or transuterine aspiration, and during Cesarean section from the uterine vessels. On the fetal side, samples can be taken only from the umbilical cord vessels at the time of delivery. These, however, do not give a true picture of the normal intrauterine conditions.

RESPIRATORY GAS EXCHANGE

The movement of respiratory gases through the placental barrier occurs in the same manner as their exchange across the alveolar-capillary membrane, namely by the process of diffusion.^{9, 15} The rate of diffusion is a direct function of the pressure gradient and of the area available for exchange, and is an inverse function of the thickness of the barrier.

In addition to the driving force of the pressure gradient (maternal arterial blood P_{O_2} of 100–110 mm. of mercury²³—umbilical venous blood P_{O_2} of 22.4 mm. of mercury²³ to 30 mm. of mercury²⁴), the transfer of oxygen and carbon dioxide across the placenta is

aided by dissimilarities in the oxygen-hemoglobin relationship and in the pH values between the two blood streams.^{23, 25} Fetal blood becomes oxygenated at lower oxygen tensions than maternal blood or, at the same tension, fetal blood attains a higher percentage of saturation as compared to maternal blood.²⁵ This may be due to a greater affinity of fetal hemoglobin for oxygen,^{9, 25} or to a possible difference in the chemical environment of the adult and fetal red cell.²⁶ The concurrent transfer of carbon dioxide and fixed acids from fetal into maternal blood increases the fetal pH, moving the oxygen dissociation curve to the left; this promotes the uptake of oxygen into fetal blood. Simultaneously, the maternal blood is acidified, and the maternal oxygen dissociation curve is deviated to the right; this increases the release of oxygen from maternal blood.²³ At the same pH, the oxygen dissociation

curves of pregnant women fall within the range of normal nonpregnant individuals (fig. 1).^{23, 26}

Carbon dioxide exchange is favorably influenced by the synchronous oxygenation of the fetal and deoxygenation of the maternal blood.²³ The carbon dioxide dissociation curves of both the fetus and the mother are displaced to the right, the fetal about twice as much as the maternal (fig. 2).^{23, 27} Therefore, blood of the fetus gives off carbon dioxide more readily than blood of the mother. "From the viewpoint of placental interchange, the dissociation relationships of the two bloods are, thus, ideal."²⁷

Prystowsky developed a new approach to the study of oxygen pressure gradients between maternal and fetal blood. He compared blood from the intervillous space with samples from the umbilical vessels in 14 patients. In 6 normal vaginal deliveries, accom-

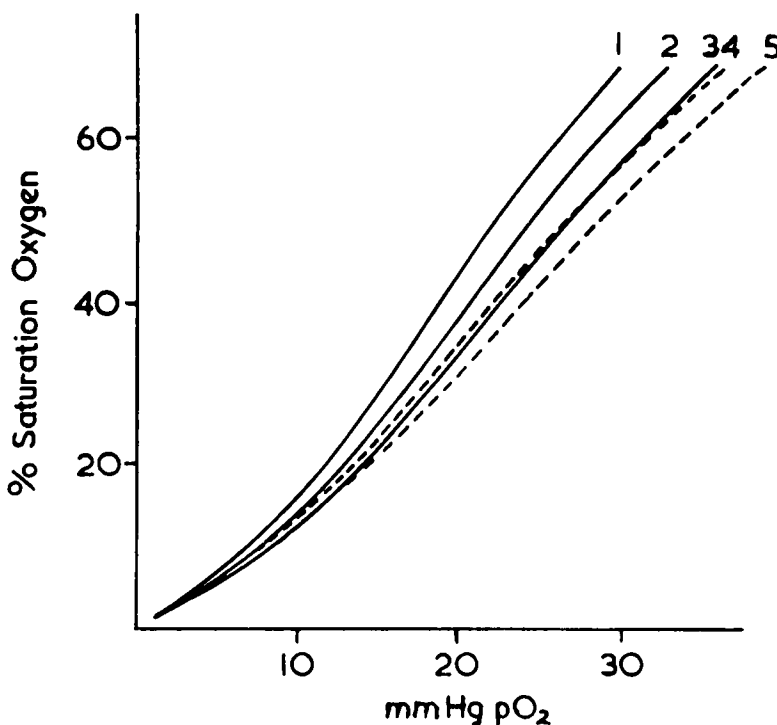


FIG. 1. Fetal (curves 1-3) and maternal (curves 4-5) oxygen dissociation curves. Ordinate: O₂ saturation in per cent. Abscissa: O₂ tension in mm. of mercury. Curves 1 and 4 at pH 7.40. Curve 2 at pH 7.32 (pH of umbilical vein). Curve 3 at pH 7.24 (pH of umbilical artery). Curve 5 at pH 7.33 (calculated pH of ideal mixed venous intervillous blood). (Reproduced from Bartels²⁸ with the permission of Dr. Heinz Bartels, Tübingen, Germany, and Blackwell Scientific Publications, Oxford, England.)

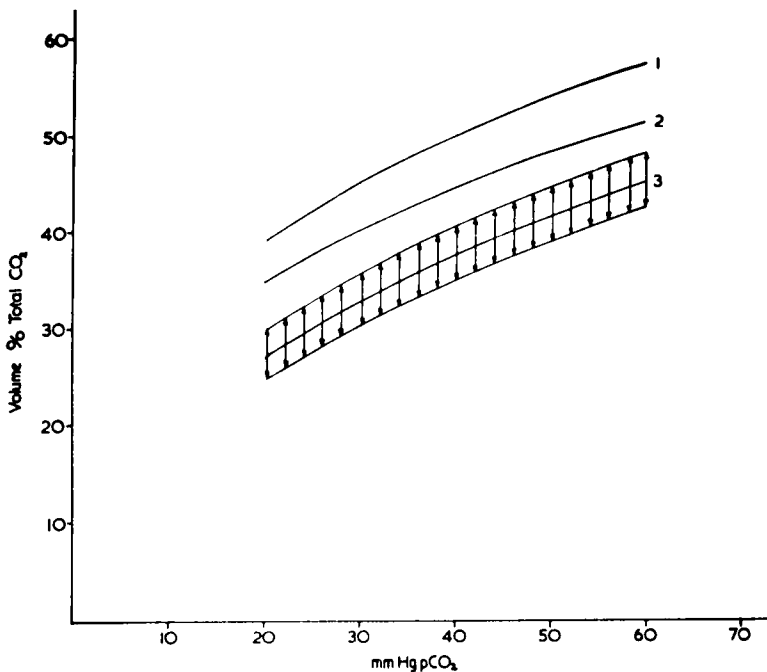


FIG. 2. Carbon dioxide dissociation curve of fetal blood (3) with standard deviation. Curve 1 is the average curve for nonpregnant women after Bartels *et al.* (1955) and curve 2 an average curve for pregnant women after Rossier and Hotz (1953). (Reproduced from Bartels²³ with the permission of Dr. Heinz Bartels, Tübingen, Germany, and Blackwell Scientific Publications, Oxford, England.)

plished without anesthesia, the intervillous blood was sampled just prior to the birth of the infant. In 2 normal patients during Cesarean section, the peritoneal cavity was opened under infiltration anesthesia and the intervillous blood aspirated by the trans-uterine approach. The remaining 6 patients had abnormal pregnancies (preeclampsia, abruptio placentae and one case of "spinal hypotension"). In all blood samples, oxygen capacity and oxygen contents were determined (method of Van Slyke and Neill), and the percentage saturation was calculated. The partial pressure of oxygen was estimated from the oxygen dissociation curves. In normal patients, P_{O_2} in the intervillous spaces averaged 37.5 mm. of mercury, and in the umbilical vein 19.5 mm. of mercury. In the 6 clinically abnormal patients, the intervillous P_{O_2} averaged 15.8 mm. of mercury and the umbilical venous P_{O_2} 13.1 mm. of mercury. The major difference demonstrated by these data seems to be the low partial pressure of oxygen in intervillous blood during abnormal

pregnancy. Whereas the mean difference in the partial pressure of oxygen between maternal and fetal circulations was approximately 20 mm. of mercury in the normal patients, it fell to 3.5 mm. of mercury in the abnormal cases.²⁸

In 1955, Eastman reported that it is possible to elevate the oxygen saturation of umbilical blood by the administration of oxygen to the mother. Alternate patients inhaled oxygen for 5, 10, or 15 minutes prior to vaginal delivery under pudendal block. Oxygen determinations in the umbilical vein blood revealed an average of 75 per cent saturation in the study group as compared to 65 per cent in the control group.²⁹ This finding has been substantiated by several investigators.³⁰⁻³⁶ One of the few dissenters is James who compared a group of 40 infants delivered with the mothers breathing air to a group of 40 infants whose mothers were given oxygen for up to one hour before parturition. There appeared to be no significant difference in the oxygen saturation of the infants.³⁷ In

TABLE 1
AVERAGE UMBILICAL VEIN P_{O_2}

Number of Patients	Inspired Gas	Time in Minutes	Umbilical Vein P_{O_2} (mm. Hg)
45	Air		28.5
51	Oxygen	10 or less	31.0
51	Oxygen	11-15	34.4
18	Oxygen	16 or more	40.4

From McClure and James.³¹

contrast, McClure observed definite increases in the partial pressure of oxygen (modification of method of Riley) in the umbilical vein blood of 95 newborns whose mothers had inhaled 10 liters/minute of oxygen through a BLB mask for various durations preceding delivery by pudendal block or without anesthesia. Sixty-four other babies served as controls. The data of his second report, which are depicted in table 1, indicate that inhalation of oxygen for more than 10 minutes resulted in significant increases in umbilical P_{O_2} (21 per cent above controls after 11-15 minutes of inhalation and 40 per cent above controls after inhalation for more than 15 minutes).^{30, 31} In order to evaluate the rationale of prophylactic oxygen inhalation, Prystowsky determined the oxygen pressure gradient between maternal and fetal bloods in 5 normal and 3 abnormal cases of pregnancy following administration of oxygen by mask for 5 to 15 minutes prior to delivery. He employed the same method as described and compared the data to those obtained from 19 controls. In the normal parturient, the average difference in oxygen tension between intervillous space blood and umbilical vein blood was 19.5 mm. of mercury (maternal 37.5 mm.—fetal 18.0 mm.) without prophylactic oxygen and 33.3 mm. of mercury (maternal 65.0 mm.—fetal 31.7 mm.) following oxygen inhalation. In the abnormal patient, the difference amounted to 2.7 mm. of mercury (maternal 15.8 mm.—fetal 13.1 mm.) without prophylactic oxygen and to 30.3 mm. of mercury (maternal 59.2 mm.—fetal 28.9 mm.) when oxygen was inhaled. The coefficient of oxygen utilization † across the

† = $\frac{O_2 \text{ content umbilical vein} - O_2 \text{ content umbilical artery}}{O_2 \text{ content umbilical vein}} \times 100$.

fetal circulation averaged 43.1 per cent when the mothers had received no oxygen prior to delivery, and rose to a mean of 72.1 per cent when oxygen had been given prophylactically. The mechanisms by which the gradient is steepened was assumed to result from an increased intervillous P_{O_2} and an increased coefficient of utilization across the fetal circulation.³² Similar results were reported by Vasicka, Quilligan and their associates who measured oxygen tension (polarographic method) serially in simultaneous samples of amniotic fluid, of maternal arterial blood, intervillous space blood and fetal blood in 31 normal pregnant women breathing air and prophylactic oxygen. After 100 per cent oxygen was inhaled for 5 minutes, the oxygen tension was increased in all four media.³³ In another study by the same authors, intervillous space and umbilical vein blood P_{O_2} were determined in 4 patients undergoing Cesarean section under spinal anesthesia. Samples were taken before and after 5 minutes' inhalation of 5 liters/minute of oxygen. The partial pressure of oxygen in the intervillous space blood rose from a mean of 23.3 mm. of mercury to an average of 39.2 mm. of mercury, while the pressure in the umbilical venous blood increased from 16.8 mm. to 26.1 mm. of mercury.³⁴ In very recent experiments, Rudolph and his co-workers attempted to obtain physiological information on the fetus in utero in a relatively undisturbed state. Small soft polyethylene catheters were inserted into the umbilical artery and vein in fetal puppies and a fetal goat. The catheters did not appear to disturb the fetus. With the maternal animal breathing room air, umbilical venous oxygen saturation

TABLE 2
OXYGEN SATURATION IN MATERNAL ARTERIAL AND UMBILICAL ARTERIAL BLOODS WITH MATERNAL DOG BREATHING VARIOUS CONCENTRATIONS OF OXYGEN

Inspired Gas	Oxygen Saturation	
	Maternal Artery (Per Cent)	Umbilical Artery (Per Cent)
Room Air	85	40
100 Per cent oxygen	96	60
8 Per cent oxygen	58	19

From Rudolph³⁵

(spectrophotometric method) ranged from 40 to 60 per cent, and umbilical arterial oxygen saturation from 20 to 50 per cent. Administration of high oxygen mixtures to the mother increased both umbilical venous and arterial saturations with a maximal venous saturation of 72 per cent.³⁵ Detailed results obtained in one dog are shown in table 2.³⁶

Although the absolute values of oxygen tension or saturation vary in the different reports quoted, possibly due to the different experimental techniques, there appears to be no doubt that the administration of supplemental oxygen enhances the transfer of oxygen from mother to infant. Prophylactic oxygen is, therefore, warranted in all pathological conditions which would otherwise lead to decreased fetal oxygenation. This should include all Cesarean sections. The "unphysiological" supine position of the mother during this operation may be one of the reasons for the increased evidence of fetal distress.

TRANSFER OF ANESTHETIC VAPORS AND GASES

A review of the laboratory data on placental transfer of the commonly used anesthetic vapors and gases illustrates their rapid passage across the placenta. Physical factors influencing their transfer are the partial pressure, the rate of diffusion, the solubility coefficient, and the possible formation of combinations.

CHLOROFORM: As early as 1874, Zweifel (quoted by Preyer)¹³ proved by chemical analysis (Hofmann's method) that chloroform passed promptly from blood of the pregnant woman to blood in the umbilical cord. In 1912, Whipple studied the effects of this vapor in bitches and their pups. He found that "the placenta contained about one half as much of the drug as did the maternal blood, and the fetus about one eighth as much by weight as present in the maternal blood" (Ragsky process). "This indicated the same concentration in maternal, placental, and fetal blood." Whipple stated that objections may be raised to the application of conclusions derived from experiments on dogs to human patients, but that the similarity of the effects of the drug in man and dog surely afford a sound basis for comparison.³⁸

NITROUS OXIDE: In 1939, Smith began a series of investigations on the effect of obstetrical anesthesia on the fetus. He determined the concentration of nitrous oxide (method of Orcutt and Waters) in 21 cases anesthetized with nitrous oxide-oxygen and in 28 cases with nitrous oxide-oxygen-ether. The anesthetics were administered in the usual manner with at least 20 per cent oxygen. Duration of anesthesia, mode of delivery, and sedation during labor varied from patient to patient. The average volume per cent of nitrous oxide detected at the time of delivery was 28.0 in the maternal arterial blood, 21.7 in the maternal venous blood, 13.5 in the fetal arterial blood, and 9.8 in the fetal venous blood. These figures disclose that only about half as much nitrous oxide was present in the infant's blood as compared to the mother's. Neonates born during nitrous oxide-oxygen-ether anesthesia had as much nitrous oxide in their blood as did those born during nitrous oxide-oxygen alone, although the gas was found in lower concentrations in the maternal blood of the former group.^{39, 40} The transmission of nitrous oxide across the human placenta was also demonstrated by Cohen, Paulson, Wall and Elert in their studies on "Thiopental, Curare and Nitrous Oxide Anesthesia for Cesarean Section." Simultaneous samples of maternal venous blood and blood obtained from the placental side of the clamped cord in 9 cases revealed mean values of 13.6 volumes per cent for the mother and 7.8 volumes per cent for the infant (method of Van Slyke and Neill). Nitrous oxide had been administered in a 2 liter/minute flow with 1 liter/minute of oxygen for 4 to 19 minutes (average 13½ minutes).⁴¹

In both studies, the concentration of nitrous oxide in the infant's blood was considerably below that determined in the mother's blood. The reason for this is not clear. Romney *et al.* postulate that vasoconstriction of the cord vessels may be present during nitrous oxide anesthesia.⁴²

CYCLOPROPANE: Smith must also be credited with being the first investigator to quantitate cyclopropane in obstetrical narcosis (1939). In 19 patients receiving approximately 15 per cent cyclopropane in a closed system at the time of actual delivery, the

TABLE 3
CYCLOPROPANE CONTENT OF MATERNAL ARTERIAL
AND FETAL ARTERIAL BLOODS IN MG./100 ML

Type of Delivery	No. Patients	Maternal Arterial Blood (mg./100 ml.)	Fetal Arterial Blood (mg./100 ml.)
Normal	6	5-12	2-8
Forceps	12	14	12
Cesarean section	18	15	13

From Rovenstine, Adriani and Studdiford.⁴³

following average volumes per cent of anesthetic were recorded: maternal arterial blood 7.5, maternal venous blood 6.7, fetal arterial blood 6.0, and fetal venous blood 5.1.³⁹ Rovenstine, Adriani and Studdiford examined the gas exchange in maternal and fetal blood during cyclopropane anesthesia. Narcosis was started with 25 per cent cyclopropane and maintained in the second stage of third plane; no premedication was used. The cyclopropane content of the fetal arterial blood was considerably lower in babies with low oxygen saturation, but there was no direct correlation between the oxygen or cyclopropane saturation of fetal blood and the initiation of respiratory activity. The mean values determined are shown in table 3.⁴³ Hingson and Hellman measured maternal and fetal blood cyclopropane levels during anesthetics induced with 50 per cent cyclopropane and maintained with 25 per cent. The level in the mother's blood † reached 16-20 mg. per cent in 10 minutes. The simultaneously sampled cord bloods † showed levels of 13-16 mg. per cent. In one second twin, the blood value was 22 mg. per cent after 23 minutes of maternal anesthesia.⁴⁴ Apgar and her group investigated the transplacental passage of cyclopropane in 25 patients (7 cesarian sections, 18 vaginal deliveries) by manometric analysis of simultaneously drawn samples of maternal and fetal blood at the time of delivery.⁴⁵ The blood of most infants delivered of mothers receiving only cyclopropane during the second stage of labor contained the gas in demonstrable quantities.

† Not indicated whether arterial or venous blood.

The amount of cyclopropane in the umbilical cord was usually less than, but proportionate to, the amount in the maternal extremity blood. The mean cyclopropane levels after 1½ to 17 minutes of anesthesia were as follows: maternal artery 8.5 volumes per cent, maternal vein 3.1 volumes per cent, umbilical vein 1.8 volumes per cent. There was no obvious correlation between the concentration of cyclopropane in the umbilical cord blood and the response of the infant as judged by the "Apgar" score. There also was no biochemical evidence that cyclopropane depresses placental function so that any effect of the gas on the fetus must be due to a direct narcotic action.⁴⁵

The four laboratory investigations on cyclopropane indicate that the fetal blood levels of this gas approach those of the mother rapidly, but that equilibrium is not reached in clinical practice.

ETHER: The concentrations of ether in maternal and fetal blood were analyzed by Smith and Barker (method of Shaffer and Ronzoni).⁴⁶ The relationship between maternal and fetal ether levels was found to be generally, although not always individually, a directly proportional one. In a series of 58 deliveries, the concentration of ether in the maternal venous blood averaged 71.3 mg./100 ml., while the umbilical venous blood had a mean level of 68.1 mg./100 ml. These cases included administration of ether by rectum, by open drop, and by closed system; duration of anesthesia ranged from 8 to 50 minutes. The incidence of delayed respiration and the need for resuscitation were directly related to the ether concentration in the fetal and/or maternal bloods (table 4).⁴⁶ Dotzauer compared the ether content of cord blood with

TABLE 4
AMOUNT OF ETHER IN MG. PER CENT TO
ONSET OF RESPIRATION

	Breathed at Once	Breathing Delayed	Resuscitation Needed
Maternal vein	68.4 mg. (40)*	78.9 (17)	101.5 (7)
Umbilical vein	64.3 mg. (50)	79.3 (18)	102.8 (8)
Umbilical artery	38.7 mg. (23)	24.3 (9)	42.2 (2)

* Figures in parentheses represent number of samples.
From Smith and Barker.⁴⁶

that of the retroplacental blood following 33 anesthetics administered for cesarian section or forceps delivery (microdistillation method of Widmark). Maternal circulating blood was not sampled. In 17 of the cases, the ether content was slightly higher in the cord blood than in the retroplacental blood (table 5).⁴⁷ Dybing and Stormorken measured the ether concentration in mothers and fetuses in rats, mice and guinea-pigs.⁴⁸ A 10 per cent mixture was administered for up to 60 minutes. Ether concentrations in all three species were almost the same in the brain and liver of the fetus and in the placenta. Considerably higher values were found in the arterial blood and brain of the mother. In the fetus, the ether concentration rose at approximately the same rate as in the maternal muscles.⁴⁸

In two of the studies, higher ether levels were found in fetal blood than in maternal venous or mixed blood. One may conclude that the infant's arterial blood levels of ether approach those of the mother's arterial blood within a short time.

TRICHLORETHYLENE: Laboratory evidence of placental transmission of trichlorethylene was demonstrated by Helliwell and Hutton in experiments on sheep and goats (1949). In both animals, the agent appeared in the fetal circulation almost immediately after being administered to the mother.⁴⁹

HALOTHANE: Sheridan and Robson reported on a large series of halothane anesthetics administered for vaginal deliveries. Blood concentrations of the agent in mother (hand vein) and infant (segment of cord) at the time of delivery were determined in 6 cases (modified method of Duncan). The results

TABLE 5
ETHER CONTENT IN CORD BLOOD AND RETROPLACENTAL BLOOD IN MG. PER CENT WITH INCREASING DURATIONS OF ANESTHESIA

Time in Minutes Between Start of Anesthesia and Sampling	Average Cord Blood Ether Values	Average Retro- placental Blood Ether Values
0-10	47	—
11-15	56	61
16-18	54	64
19-21	43	37
22-25	57	47
26-40	—	50

From Dotzauer⁴⁷

TABLE 6
MATERNAL AND FETAL BLOOD HALOTHANE LEVELS
IN MG. PER CENT WITH INCREASING
DURATIONS OF ANESTHESIA

Duration of Anesthesia (minutes)	Average Concen- tration of Halothane Administered (%)	Blood Halothane	
		Maternal	Fetal
		(Mg. Per Cent)	
2	3.0	7.8	5.6
3	1.5	8.0	4.2
5	2.0	5.7	2.2
6	2.0	4.0	0
9	1.5	3.6	2.8
9	2.0	10.5	4.2

Adapted from Sheridan and Robson.⁵⁰

(table 6) indicate that halothane may be demonstrable in umbilical blood after only 2 minutes of inhalation by the mother.⁵⁰

TRANSFER OF ANESTHETIC AND
ADJUVANT DRUGS

NARCOTICS: Concern about the transmission of a narcotic drug from mother to infant dates back to 1885. Preyer described a case of fetal bradycardia and arrhythmia following injection of morphine into the mother.¹³ Since then, a variety of clinical observations have substantiated Preyer's finding. Pinpoint pupils have been reported in infants who exhibited "narcosis" subsequent to the administration of morphine to the mother.⁵¹ Withdrawal symptoms have been diagnosed in the offspring of mothers addicted to morphine, heroin, and meperidine.^{52, 53, 54} The symptoms can occur in the fetus *in utero* as well as in the neonate, and their severity has been directly correlated to the maternal drug dosage.⁵⁴ Delayed or depressed respirations in the newborn became apparent soon after the beginning of the "twilight sleep" era. Snyder, observing rabbit fetuses in the unopened uterus, noted that depression or abolition of fetal respiratory movements followed administration of morphine to the maternal animal. Large doses of morphine were given to pregnant rabbits with the fetuses delivered by hysterotomy at intervals from 12 minutes to 15 hours after the administration of the

drug. In litters delivered less than one hour following injection, the fetuses showed signs of marked narcosis. Body movements were sluggish, response to stimulation was retarded, and respiratory activity was depressed. Litters delivered 12 to 15 hours after morphine were undistinguishable from the untreated controls.⁵⁵ Shute and Davis⁵¹ and McNab⁵⁶ reported that in the human the time interval between injection of morphine and delivery was more important than the size of the dose; the incidence of neonatal depression in their infants became progressively greater in the second and third hours after administration of the drug to the mother. Similar observations were made following the use of heroin,⁵⁷ meperidine,⁵⁸ alphaprodine,^{59, 60} methadone,⁶¹ and dihydrocodeine.⁶² Little and Tovell quoted delayed neonatal respirations in 21.8 per cent of 2,195 patients sedated with morphine or its derivatives during labor, and in 11.9 per cent of 2,649 patients sedated with meperidine; resuscitation was required in 10.7 per cent of the newborns in the first group and in 6.1 per cent of the infants in the second group. In contrast, in the neonates of 15,167 mothers managed with continuous block caudal anesthesia without narcotics, resuscitation became necessary in only 0.8 per cent.⁶³

Three of the narcotic drugs, morphine, meperidine, and methadone, have been studied in the laboratory. Shute and Davis administered 15 mg. doses of morphine to different mothers, 2, 3, 4, 5, and 6 minutes, respectively, before the child was delivered. The stools of the neonates were examined for narcotic daily by two different methods (Marquis and Wasicky). All babies gave positive results in their stools; the levels were highest from the fourth to the seventh day after birth. Two placentae of mothers who had received a total of 61 mg. of morphine were also examined; quantitative tests on the pulp were negative. This would indicate that the placenta does not retain morphine and is not an important barrier to its passage.⁵¹ Apgar and her group determined plasma levels of meperidine in 9 infants and their mothers following administration of from 50 to 300 mg. of the drug during labor. The concentration in infant blood varied from 45 to 106 per cent (average 77 per cent) of the

levels measured simultaneously in maternal blood.⁶⁴ Eisenbrandt and his coworkers, investigating the role of the gastro-intestinal tract in the excretion of C¹⁴-labeled methadone in rats, found on autopsy that one of the animals was pregnant. Analysis revealed considerable amounts of radioactivity in the two fetuses and in the placenta.⁶⁵

The competitive antagonists have been shown to reverse the depressant effects of narcotics on the infant. Their equally prompt action, regardless of whether injected into the umbilical vein or given to the mother shortly before delivery, proves that they, too, transverse the placenta readily.^{66, 67, 68}

Although the placenta does not present a barrier to the passage of the narcotic drugs, their status as analgesics during labor has been reversed by the advent of the antagonists. Once considered the most dangerous pain relieving drugs from the point of view of neonatal morbidity and mortality, they may now be adjudged safer than other categories of agents which cannot be specifically antagonized.

BARBITURATES: In 1934, Dille stated that anesthetic doses of barbituric acid derivatives cross the placenta.⁶⁹

Long and Intermediate Acting Barbiturates. Dille injected sodium barbital (75 mg./kg. and 100 mg./kg.) into the ear vein of pregnant rabbits and determined the barbiturate content separately in fetuses, placentae, and amniotic fluids. Positive results were obtained in fetus and placenta from 1 minute to 60 minutes after injection, and in both, the amount of barbiturate accumulated steadily within the first hour. Most amniotic fluids also revealed the presence of the drug.⁶⁹ Flowers studied sodium barbital in 23 mothers and their infants. Within 2 to 3 minutes, the drug began to achieve equilibrium in fetal and maternal blood; comparable blood levels were maintained for as long as 15 hours. There were some wide differences between fetal and maternal blood levels when the interval between injection and delivery was very short. The author explained these as being due to variations in volume distribution of the barbiturate in both mother and fetus and to variations in placental circulation.⁷⁰ Ploman and Persson gave amobarbital, pheno-

barbital, and barbital to 35 pregnant women 30 minutes to 50 hours prior to legal abortions. All three drugs were found to reach the fetuses, accumulating mostly in brain, liver, and placental tissues.⁷¹ Nyberg and his associates evaluated vinbarbital sodium clinically and, in 14 cases, did chemical determinations of the barbiturate levels in maternal venous and infant cord bloods. The cord blood levels of barbiturate were quickly established at or near the maternal level. However, little or no correlation was noted between the levels and the degree of neonatal depression.⁷²

Short Acting Barbiturates. Lovitt and his coworkers analyzed maternal and umbilical cord blood in 12 patients who had received secobarbital during labor. The doses ranged between 100 mg. to 300 mg. administered orally $3\frac{1}{2}$ to $4\frac{1}{2}$ hours before delivery, and 100 mg. to 200 mg. injected intravenously at intervals from $\frac{1}{2}$ to 8 hours before delivery. The analytical method was sensitive enough to detect 0.2 mg. per cent of barbiturate. In only one mother and in none of the cord blood samples was the barbiturate concentration above the minimum at the time of birth.⁷³ Fealy studied the placental transmission of pentobarbital sodium. One hundred mothers were given the drug intravenously during the first stage of labor. Eighty of these received a single injection of 250 mg. one to 185 minutes prior to parturition, and the remaining 20 received multiple doses. Newborn blood barbiturate levels were present almost immediately after maternal intravenous injection. There were three patients with a time interval of one minute between administration and delivery. The barbiturate level was 8.0 mg./ml. in one mother and 7.0 mg./ml. in her infant; in the other two mothers the concentration was 6.5 mg./ml. as compared to 5.0 mg./ml. in the neonates. The average blood levels in the newborn were about 74 per cent of the maternal blood levels and persisted at about the same distribution for at least 185 minutes.⁷⁴

Ultrashort Acting Barbiturates. The first investigation on thiopental was accomplished by Dreisbach and Snyder who carried out a series of observations to determine the effect

of various doses upon the full term rabbit. In 8 normal litters, a single injection of 10 mg./kg. into the maternal ear vein decreased fetal respiratory activity promptly to one-third the initial rate; recovery required 5 to 10 minutes. With more than 15 mg./kg., apnea occurred in the fetus almost immediately although the mother continued to breathe regularly.⁷⁵ Hellman and his group applied ultraviolet spectrometric methods to measure acid thiopental levels, and established evidence of transplacental passage of the drug in 7 patients.⁷⁶ McAllister and Flowers,⁷⁷ in 21 patients, and McKechnie and Converse,⁷⁸ in 15 patients, detected thiopental in fewer than 45 seconds in the fetal circulation, but could find no relationship between maternal depth of anesthesia, fetal responsiveness, and the thiopental concentration in neonatal or maternal blood. Investigation by Crawford in 41 cases revealed that, following administration of 250 mg. of drug, the neonatal thiopental blood levels were highest for the shortest intervals between injection and delivery, and that they fell exponentially with the increase of time before delivery.⁷⁹ Thiamylal was studied by Kahn and his coworkers in 20 patients who received an average dose of 4.85 mg./kg. The cord blood concentration reached that of the maternal blood in 4 to 5 minutes; this equilibrium was maintained for at least one hour.⁸⁰ Buthalitone sodium was investigated by Kane and Stephens. In 34 obstetrical patients in whom 400 mg. to 500 mg. of the drug had been given 5 to 31 minutes prior to delivery, cord plasma concentrations tended to be significantly lower than those of the maternal plasma, but showed great variations from patient to patient.⁸¹ Methitural was compared to thiopental and thiamylal by Flowers and found to cross the placenta at the same rapid rate.⁸²

The lack of correlation between the infant blood levels of barbiturate and the response of the baby at birth is analogous to the inconsistency in the dose response to barbiturates seen in adults.⁸³

TRANQUILIZERS: All tranquilizing drugs studied, in either animal or man, have been shown to pass the placental barrier.

Chlorpromazine was given to pregnant dogs in daily doses of 200 mg./kg. prior to delivery. The pups were sacrificed at various times after birth, and the chlorpromazine content of their tissues was determined. Immediately following delivery, various amounts of the drug were present in bile, liver, kidney, lung, and brain tissues.⁸⁴ Lacomme and Le Lorier investigated the effect of an intravenous infusion of chlorpromazine 50 mg. in 500 ml. of glucose solution in 445 parturients. The drug was not demonstrable in cord blood, but was found in traces in two amniotic fluids, while three others gave negative results. Of 10 neonatal urines studied, four were negative for chlorpromazine, three revealed traces, and the remaining three concentrations of 0.5 mg./liter, 1.4 mg./liter, and 5.2 mg./liter, respectively. There was no apparent connection between the amounts of chlorpromazine infused and the concentration detected in maternal urine or neonatal urine. There was likewise no relationship between the condition of the infant at birth and the amount of chlorpromazine found in its urine.⁸⁵ Behn and his associates gave a mixture of equal amounts of chlorpromazine and promethazine (50 mg. intramuscular or 33 mg. intravenous) as premedication in two Cæsarian sections. Within 48 to 60 hours, about 0.5 to 1.0 per cent of the administered dose was discovered in the urine of the newborn by photometry and paper chromatography.⁸⁶

Prochlorperazine was tested in dogs in a manner similar to that described for chlorpromazine. Various amounts of the drug was found in liver, kidney, lung and brain tissues of the pups sacrificed immediately after birth.⁸⁷

Methylpentynol was studied in humans by Bourne. There was no noticeable depression of the newborn's respiration, tone, or cry. A small series of cord blood examinations were made (method not stated); methylpentynol was not demonstrable in the infant's circulation at birth.⁸⁸ Marley and Vane, investigating the distribution of methylpentynol in cats, examined fetuses, placentae, and amniotic fluids following intravenous administration of the drug to a pregnant animal. Employing a modified method which resulted

in a tenfold increase in sensitivity over previous techniques, they detected methylpentynol in fetal tissues and in amniotic fluid. Fetal liver and heart were found to contain about the same concentration of the drug as the whole fetus.⁸⁹

Adelman and his associates presented data obtained from 25 obstetrical patients who had received 50 mg. of promethazine intravenously 5 to 10 minutes prior to the expected time of delivery. In no instance could the drug be discovered in the cord blood in spite of levels of 0.2 mg./100 ml. in maternal venous blood.⁹⁰ This is in contrast to the findings of Potts and Ullery who evaluated the maternal and fetal effects of intravenously given combinations of equal portions of promethazine and meperidine (50 mg. each per milliliter). In 23 cases, promethazine levels were determined in samples of maternal and of umbilical cord blood, both drawn at the time of delivery. Cord blood samples gave positive results for the drug from minutes to 4 hours after the injection of the combination to the mother.⁹¹ Crawford gave mothers a single, set dose of promethazine intravenously at a noted time before parturition. Samples of maternal venous blood and of whole cord blood were taken simultaneously at the moment of birth. There was no time lag in the passage through the placenta. The concentration of fetal blood reached that of maternal blood in 10 to 20 minutes.⁹²

Considering the results obtained, one may assume that tranquilizers are transmitted from mother to fetus to a variable extent, but that sensitive methods of detection must be employed to quantitate the amounts in the neonate.

OTHER SEDATIVE DRUGS: Other sedative drugs, although not popular as routine analgesics in obstetrics, have been evaluated as to their transplacental passage.

Ethyl bromide, according to Mueller (quoted by Preyer¹³), was exhaled by the newborn infant when the mother had inhaled larger amounts.

Chloral hydrate was given to pregnant dogs for several weeks; the pups were removed by Cæsarian section and gave evidence of the

same characteristic pathological changes in liver, heart, and kidneys found in the mothers' organs.⁹³ Bernstein and his group sedated 52 unselected patients in active labor with chloral hydrate by oral or rectal administration. Colorimetric determinations revealed levels in the babies' blood which bore no direct relationship to the time of the first cry.⁹⁴

Paraldehyde was detected on the breath of all neonates for several hours after birth following its use in 150 parturients.⁹⁵ The drug was quantitatively determined by Gardner and his associates in 13 maternal and cord blood specimens subsequent to rectal or oral administration of 30 ml. At the time of delivery, the mean for the mothers was 16.6 mg. per cent and the mean for the infants 15.5 mg. per cent.⁹⁶

Ethyl alcohol, utilized in slow intravenous infusions during labor, was reported in two separate studies as producing cord blood levels of alcohol which were slightly below those of the maternal blood.^{97, 98} Chapman and Williams found averages of 0.065 per cent in maternal venous blood and of 0.043 per cent in umbilical cord blood.⁹⁸

Thus, all four of these drugs have been proven to cross the placental barrier without delay.

BELLADONNA DERIVATIVES: The two commonly used belladonna drugs have been assayed by qualitative means only.

Atropine was shown by Preyer to cross the placenta in fewer than 15 minutes. After observing infants to be born with dilated non-reacting pupils subsequent to the administration of 0.2 mg. of drug to the mother, he injected 1 ml. of a 1 per cent watery solution of atropine sulfate under the skin of guinea-pigs. The maternal animal exhibited mydriasis some 7 minutes later; all fetuses delivered by section manifested the same.¹³ Johnson and Hellman made cardiophonographic studies on the effect of atropine on maternal and fetal heart rates. One milligram of the drug, injected into a maternal vein over the course of 2 minutes, led to an initial bradycardia in both mother and fetus. This was followed 30 to 40 seconds later by a tachycardia occurring synchronously in mother and fetus. The immediate and simultaneous effect

on both hearts points to a direct drug action in the fetus.⁹⁹

Scopolamine was demonstrated by Holzbach (quoted by Snyder⁵⁵) to pass from mother to infant. When birth occurred as soon as 15 minutes after injection, scopolamine was present in the infant's urine. Dreisbach and Snyder studied scopolamine in cats. Following injection of the drug into the maternal animal, they tested the offspring's urine by introducing it into the conjunctival sac of a normal cat; mydriasis followed in every instance.¹⁰⁰

Both atropine and scopolamine appear to cross the placental barrier rapidly. Flowers found a difference in the reaction time of infants whose mothers had been sedated with analgesics alone as compared to those who had received analgesics and scopolamine. In the former group he had a 3 per cent incidence of delayed reaction time, whereas in the latter this rose to 10.3 per cent.¹⁰¹ It follows that mothers of compromised or premature infants should be given atropine rather than scopolamine.

MUSCLE RELAXANTS: The fate of the muscle relaxants is controversial to date. There may be a dissimilarity in their passage across the placenta not only between the nondepolarizing and the depolarizing agents, but also between the various individual members of the two groups.

Nondepolarizing Drugs. As early as 1885, Preyer investigated curare in rabbits, guinea-pigs, and their offspring. He discovered that fetuses require large doses of the drug to be affected. When he injected curarin into pregnant rabbits, they became paralyzed; the fetuses remained active as long as the mother was ventilated artificially. When he injected curarin into one of several guinea-pig fetuses *in utero*, the mother became apneic and paralyzed, whereas the young ones kept on moving in a normal manner. Only after administration of large amounts did the fetuses become paralyzed, too. He concluded that curare passed readily from fetus to mother, but that the transfer from mother to fetus could not be proven because of the different degree in sensitivity.¹³

The first laboratory investigations following the introduction of curare into obstetrical

anesthesia corroborated Preyer's findings. Harroun and Fisher administered intocostin to 10 bitches in doses calculated to produce apnea. The dogs' lungs were artificially ventilated, and Cesarean section was performed under local anesthesia. All 69 pups were "squirring in utero as if they would break out of the abdomen by their own effort."¹⁰² Buller and Young kept pregnant rabbits apneic for 3 hours by intermittent injections of *d*-tubocurarine; the total dose was equivalent weight for weight to the therapeutic dose in man. The fetuses were examined at $\frac{1}{2}$ to 1 hour intervals; they remained lively. In 7 rabbits, the drug was injected into the umbilical artery of one fetus in the litter. A dose of 0.5 mg. inhibited the response of the mother's gastrocnemius muscle to stimulation and a dose of 1.0 mg. decreased her respiratory movements as recorded from a diaphragmatic slip.¹⁰³ Pittinger and Morris demonstrated transmission of the drug from the maternal to the fetal side of the placenta by injecting 45–60 mg. of *d*-tubocurarine into the uterine artery of pregnant bitches. Curarization was evident in all pups whose maternal-fetal circulation was intact.¹⁰⁴ The authors also determined plasma concentrations of *d*-tubocurarine at the time of delivery in 6 mothers and 5 of their infants. The mothers had received 21–60 mg. of the drug intravenously from 2 to 78 minutes prior to the sampling. Five other mothers and their newborns were used as controls. With consideration of the "blank" values obtained in the blood of noncurarized humans, the concentration in maternal plasma ranged from 0.0019 mg./ml. to 0.0082 mg./ml. and the concentration in cord plasma averaged 0.0001 mg./ml.¹⁰⁵ Beck injected each of three white mice with 1 ml. each of catheterized maternal urine and three other mice with 1 ml. of the infant's first urine following 10 cesarian sections during which the mothers had been given curarine (average dose 0.25 mg./kg. body weight). Biological test for curare in the mice was positive when maternal urine had been used and negative when neonatal urine had been injected.¹⁰⁶ However, when Beck and Nold observed fetal movements *in utero* with the help of an external tocograph, they found cessation of normal activity fol-

lowing administration of 6–9 mg. of curarine in unsedated women in labor; fetal movements promptly returned on injection of tensilon or as soon as the effect of curare had worn off.¹⁰⁷ A bio-assay method for the detection of curare in which the drug antagonizes the acetylcholine contracture of the frog's rectus abdominis muscle, was utilized by Crawford and Gardiner. Six mothers received 15 or 20 mg. of *d*-tubocurarine at varying intervals prior to delivery; traces of the drug were demonstrable in all fetal sera.¹⁰⁸

Gallamine was investigated together with curare in the above mentioned studies by Beck and by Crawford. In both of Beck's reports, the results for gallamine were equal to those of curare.^{106, 107} Crawford and Gardiner, in contrast, observed that gallamine appeared in the fetal serum in readily detectable and possibly significant amounts. Thirteen mothers had received doses of gallamine which were equipotent to those used for *d*-tubocurarine. The fetal levels of gallamine could not be related to dose per unit weight nor to the concentration in maternal serum.¹⁰⁸ Pittinger and Morris evaluated the effects of gallamine in mongrel dogs near term. They exteriorized both uterine horns, isolated one horn by clamps, and injected the drug into the uterine artery supplying the unisolated horn. All pups were exposed and the difference in activity, respiration, muscle tone, and squealing was compared between the litter in the isolated and the young ones in the unisolated horn. Evidence of transplacental passage of the drug became manifest in only two of the 4 bitches studied.¹⁰⁹ A study by Schwarz in which he analyzed the iodine content of the infant's blood at the time of delivery, corroborated Crawford's findings. Six to 9 minutes following injection of 80 mg. of gallamine into the mother, significant increases in the neonatal iodine content were noted.¹¹⁰

Depolarizing Drugs. Decamethonium was studied in various animals. Young injected the drug into rabbit and guinea-pig does and observed no decrease in the mass reflex response to a pinch applied to one hind leg of the fetuses. She also injected the drug into the umbilical artery in doses equivalent

weight for weight to 50–100 times the therapeutic dose in man, and found no evidence of passage into the maternal blood stream.^{111, 112} Pittinger and Morris, in their dog experiments, observed no effect on the fetuses following decamethonium.¹⁰⁹ Only Ellerker, in clinical observations during 13 cesarian sections, in which 2–3 mg. of the drug were given 15 minutes prior to delivery, concluded that the babies were more flaccid and reluctant to breathe than following the same type of anesthesia without the use of the drug.¹¹³

Succinylcholine was reported by three different authors to be capable of depressing the infant when used clinically in humans. Little and his coworkers observed one completely flaccid newborn following a dose of 20 mg. of succinylcholine, whereas babies whose mothers had received only 10 mg. were breathing normally.¹¹⁴ Gillies and his associates described two patients who underwent Cesarean section under inhalation anesthesia with succinylcholine in doses of 100 mg. and 200 mg., respectively. The infant whose mother had received 200 mg. was born flaccid; the other baby was lively.¹¹⁵ Jüngling saw two limp and apneic neonates delivered shortly after the mother had been given 40 mg. of succinylcholine for the purpose of facilitating endotracheal intubation. At the time of delivery, both mothers were still under the influence of the relaxant.¹¹⁶ Other investigators noted no ill effects,^{117, 118} although Dance and Ward stated that they routinely discontinue the administration of a succinylcholine infusion about 3 minutes prior to the time of delivery.¹¹⁸ In experiments on rabbits, Thesleff found normal muscular activity of the fetuses after the mother had been injected with 50 to 100 mg. of succinylcholine intravenously.¹¹⁹ In dogs, on the other hand, the drug was shown by Pittinger and Morris to pass the placental barrier with ease.¹⁰⁹ The most recent investigation by Moya and his group indicates that, used in humans in single doses up to 300 mg., no demonstrable amount of succinylcholine crossed the placenta. Only after injection of over 300 mg. was the drug detected in the infant in important quantities. In rabbits, approximately 1,000 times the minimum paralyzing dose was

necessary before all fetuses were delivered flaccid and unresponsive to stimulation.¹²⁰ In a follow-up study, Moya examined the ability of the placenta to destroy succinylcholine. Using the frog rectus abdominis bio-assay method, he observed that destruction of the drug by the placenta does not significantly contribute to the blood-placental "barrier."¹²¹

Summarizing the above reports, curare preparations are transmitted more easily from fetus to mother than from mother to fetus; gallamine passes the placental barrier with little difficulty; many of the depolarizing muscle relaxants are capable of crossing the placenta, but do so with considerable individual variations as to amount and rate. One may hypothesize that in most species muscle relaxants are bound rapidly at the neuromuscular junction of the adult and, thus, do not reach the placental barrier. Moya postulated that the relation of the low fat solubility of succinylcholine to the lipid nature of the placental membrane may account for the apparent barrier at the placental site.¹²² In view of the individual variations in transplacental passage and in view of the greater sensitivity of neonates to the nondepolarizing as compared to the depolarizing agents,¹²³ one should recommend the use of the latter group in obstetrical anesthesia.

LOCAL ANESTHETIC DRUGS: The placental transmission of local anesthetic drugs has not been investigated. But clinical experience has shown that, barring maternal systemic complications, regional block techniques (local infiltration, pudendal, peridural, spinal) afford optimal conditions for the newborn.^{45, 55, 63, 117, 124, 125} Lack of neonatal depression or excellent "Apgar scores" have been reported following regional anesthetics utilizing procaine,^{126, 128} chlorprocaine,¹²⁷ tetracaine,¹²⁸ piperocaine,¹²⁹ dibucaine¹³⁰ and lidocaine.^{126, 129, 131} Vigorous crying babies were also seen following the intravenous administration of 1 per cent procaine solution during labor and delivery. In 12 cases studied by Allen¹³² and in 20 cases described by Johnson and Gilbert,¹³³ the rate of infusion ranged up to 20 ml. per minute at the time of parturition. In spite of central nervous system involvement in the mother (semiconsciousness, unconsciousness, tendency to convulsion), only one of the infants ex-

hibited an otherwise unexplainable depression at birth (case 5¹³³).

Snyder stated that "no direct effect of the local anesthetic agent upon the child has been observed."⁵⁵ Since all regional anesthetic drugs are hydrolyzed rapidly in both maternal blood and liver, it may be assumed that only the non-narcotic break-down substances pass through the placenta.¹³⁴

DISCUSSION AND SUMMARY

A review of the pertinent literature dealing with the placental transfer of drugs used in anesthesia would indicate that: (1) Gases which are able to cross the pulmonary barrier and every known anesthetic, hypnotic, sedative drug which is capable of passing the blood-brain barrier, will also traverse the placental barrier; (2) "Prophylactic" oxygen inhalation enhances the oxygen transfer to the infant primarily by raising the intervillous space P_{O_2} , and (3) Neuromuscular blocking agents which do not cross the blood-brain barrier easily, are not transferred readily across the placental barrier.

In addition to the physical factors discussed, the rate and amount of placental transport are dependent upon various physiological factors, most importantly: (1) the effective extent of the placental site, (2) the integrity of the placental barrier as to permeability, active transport mechanisms, and enzyme content, and (3) the state of maternal, placental, and fetal circulations. Maternal hemodynamics are altered in response to uterine contractions and by most drugs used for sedation and anesthesia. Changes in heart rate are caused by the belladonna derivatives, by intravenous injection of meperidine, by ether or cyclopropane anesthesia, and by the circulatory adjustments to demand hypoxia occurring during bearing down efforts. Decreases in systemic pressure are common after spinal and peridural blocks, during halothane anesthesia, or following the use of tranquilizers. Placental circulation has been discussed except for the alterations secondary to anesthesia. All inhalation anesthetics with the exception of nitrous oxide have been shown to depress uterine activity,^{135, 136} thus increasing the effects of a relaxed myometrium

on blood flow. Conduction anesthesia per se has no effect on uterine musculature. This factor may be of significance in cesarian sections and may explain the difference in the degree of depression reported in infants born under regional anesthesia as compared to general anesthesia.^{45, 117} Fetal circulation has been known to become faster or slower due to hypoxia or to pressure on the infant's head.¹³⁷ In addition, it has been postulated that the fetus may be able to increase or decrease his capillary bed to meet his demands.

Circulatory changes are variable on an individual basis and are unpredictable as to their extent. Therefore, one may conclude that the administration of drugs during childbirth should be governed by the degree of danger inherent in the transport of unexpectedly large amounts to the fetus.

REFERENCES

1. McGaughey, H. S., Jones, R. C., Talbert, L., and Anslow, W. P.: Placental transfer in normal and toxic gestation, *Amer. J. Obstet. Gynec.* **75**: 482, 1958.
2. Ramsey, E. M.: Vascular adaptations of uterus to pregnancy, *Ann. N. Y. Acad. Sci.* **75**: 726, 1958.
3. Anderson, W. A. D.: *Pathology*, ed. 3. St. Louis, C. V. Mosby Co., 1957.
4. Page, E. W.: Functions of human placenta, *Mod. Med.* **28**: 26, 1960.
5. Villee, C. A.: *Biochemical Aspects*, pp. 100-108, *The Placenta and Fetal Membranes*. Baltimore, Williams & Wilkins, 1960.
6. Boyd, J. D.: in *Proceedings of the Conference*, p. 149, *ibid.*
7. Shanklin, D. R.: The human placenta, clinicopathologic study, *Obstet. Gynec.* **11**: 129, 1958.
8. Barcroft, J.: *Researches on Prenatal Life*. Springfield, Illinois, Charles C Thomas, Publisher, 1946.
9. Page, E. W.: Transfer of materials across human placenta, *Amer. J. Obstet. Gynec.* **74**: 705, 1957.
10. Dempsey, E. W.: *Histophysical Considerations*, pp. 29-35, *The Placenta and Fetal Membranes*. Baltimore, Williams & Wilkins, 1960.
11. Ramsey, E. M.: The Placental Circulation, pp. 36-62, *ibid.*
12. Plentl, A. A.: Dynamics of amniotic fluid, *Ann. N. Y. Acad. Sci.* **75**: 746, 1959.
13. Preyer, W.: *Specielle Physiologie des Embryo*. Leipzig, T. Grieben, 1885.

14. Page, E. W.: in Proceedings of the Conference, pp. 194-195, The Placenta and Fetal Membranes. Baltimore, Williams & Wilkins, 1960.
15. Barron, D. H.: The Placenta as the Fetal Lung, pp. 63-70, *ibid.*
16. Romney, S. L.: in Proceedings of the Conference, p. 137, *ibid.*
17. Ramsey, E. M.: in Proceedings of the Conference, p. 153, *ibid.*
18. Prystowsky, H.: in Proceedings of the Conference, p. 154, *ibid.*
19. McRoberts, W. A.: Postural shock in pregnancy, *Amer. J. Obstet. Gynec.* **62**: 627, 1951.
20. Howard, B. K., Goodson, J. H., and Mengert, W. F.: Supine hypotensive syndrome in late pregnancy, *Obstet. Gynec.* **1**: 371, 1953.
21. Assali, N. S., Dasgupta, K., Kolin, A., and Holms, L.: Measurement of uterine blood flow and uterine metabolism; changes during spontaneous and induced labor in unanesthetized pregnant sheep and dogs, *Amer. J. Physiol.* **195**: 614, 1958.
22. Wright, H. P., Morris, N., Osborn, S. B., and Hart, A.: Effective uterine blood flow during labor, *Amer. J. Obstet. Gynec.* **75**: 3, 1958.
23. Bartels, H.: Chemical Factors Affecting Oxygen Carriage and Transfer from Maternal to Foetal Blood, pp. 29-41, Symposium on Oxygen Supply to the Human Fetus. Oxford, Blackwell Scientific Publications, 1959.
24. Sjöstedt, S., Rooth, G., and Caligara, F.: Oxygen tension in cord blood after normal delivery, *Acta Obstet. Gynec. Scand.* **39**: 34, 1960.
25. Van Slyke, D. D.: General Principles of Oxygen Transport and Transfer, pp. 5-28, Symposium on Oxygen Supply to the Human Fetus. Oxford, Blackwell Scientific Publications, 1959.
26. Prystowsky, H., Hellegers, A., Cotter, J., and Bruns, P.: Fetal Blood Studies; on relationship between the position of oxygen dissociation curve of human fetal blood and adult-fetal hemoglobin, *Amer. J. Obstet. Gynec.* **77**: 585, 1959.
27. Eastman, N. J., Geiling, E. M. K., and de Lawder, A. M.: Fetal Blood Studies; oxygen and carbon dioxide dissociation curves of foetal blood, *Bull. Johns Hopkins Hosp.* **53**: 246, 1933.
28. Prystowsky, H.: Fetal Blood Studies; oxygen pressure gradient between maternal and fetal bloods of human in normal and abnormal pregnancy, *Bull. Johns Hopkins Hosp.* **101**: 48, 1957.
29. Eastman, N. J.: Discussion, *Amer. J. Obstet. Gynec.* **70**: 798, 1955.
30. McClure, J. H.: Newborn blood oxygen. Method of increasing partial pressure of oxygen in blood of newborn infant, *Obstet. Gynec.* **11**: 696, 1958.
31. McClure, J. H., and James, J. M.: Oxygen administration to mother and its relation to blood oxygen in newborn infant, *Amer. J. Obstet. Gynec.* **80**: 554, 1960.
32. Prystowsky, H.: Fetal Blood Studies; Effect of prophylactic oxygen on oxygen pressure gradient between maternal and fetal bloods of human in normal and abnormal pregnancy, *Amer. J. Obstet. Gynec.* **78**: 483, 1959.
33. Vasicka, A., Quilligan, E. J., Aznar, R., Lipsitz, P. J., and Bloor, B. M.: Oxygen tension in maternal and fetal blood, amniotic fluid, and cerebrospinal fluid of mother and baby, *Amer. J. Obstet. Gynec.* **79**: 1041, 1960.
34. Quilligan, E. J., Vasicka, A., Aznar, R., Lipsitz, P. J., Moore, T., and Bloor, B. M.: Partial pressure of oxygen in intervillous space and umbilical vessels, *Amer. J. Obstet. Gynec.* **79**: 1048, 1960.
35. Rudolph, A. M., Golinko, R. J., and Auld, P. A. M.: Studies on umbilical arterial and venous pressures and oxygen saturation in fetus in utero, *Amer. J. Dis. Child.* **100**: 529, 1960.
36. Rudolph, A. M.: Albert Einstein College of Medicine, Personal communication.
37. James, L. S.: Effect of pain relief for labor and delivery on fetus and newborn, *ANESTHESIOLOGY* **21**: 405, 1960.
38. Whipple, G. H.: Pregnancy and chloroform anesthesia. Study of maternal, placental, and fetal tissues, *J. Exp. Med.* **15**: 246, 1912.
39. Smith, C. A.: Effect of obstetrical anesthesia upon oxygenation of maternal and fetal blood with particular reference to cyclopropane, *Surg. Gynec. Obstet.* **69**: 584, 1939.
40. Smith, C. A.: Effect of nitrous oxide oxygen ether anesthesia upon oxygenation of maternal and fetal blood at delivery, *Surg. Gynec. Obstet.* **70**: 787, 1940.
41. Cohen, E. N., Paulson, W. J., Wall, J., and Elert, B.: Thiopental, curare and nitrous oxide anesthesia for Cesarean section with studies on placental transmission, *Surg. Gynec. Obstet.* **97**: 456, 1953.
42. Romney, S. L., Gabel, P. V., and Kaneoka, T.: Albert Einstein College of Medicine Personal communication.
43. Rovenstine, E. A., Adriani, J., and Studdiford, W. E.: Gas changes in maternal and fetal blood during cyclopropane obstetric anesthesia, *Calif. West. Med. J.* **53**: 59, 1940.
44. Hingson, R. A., and Hellman, L. M.: Anes-

- thetia for Obstetrics. Philadelphia, J. B. Lippincott, 1956.
45. Apgar, V., Holaday, D. A., James, L. S., Prince, C. E., Weisbrot, I. M., and Weiss, I.: Comparison of regional and general anesthesia in obstetrics with special reference to transmission of cyclopropane across placenta, *J. A. M. A.* **165**: 2115, 1957.
46. Smith, C. A., and Barker, R. H.: Ether in blood of newborn infant. Quantitative study, *Amer. J. Obstet. Gynec.* **43**: 763, 1942.
47. Dotzauer, G.: Diaplacentare Aetherwerte bei Narkosen unter der Geburt, *Deutsch. Z. ges. gerichtl. Med.* **40**: 170, 1950.
48. Dybing, O., and Stormorken, H.: Passage of ether from mother to fetus, *Acta Pharmacol. Toxicol.* **8**: 271, 1952.
49. Helliwell, P. J., and Hutton, A. M.: Trichloethylene anesthesia; distribution in foetal and maternal circulation of pregnant sheep and goats, *Anaesthesia* **5**: 4, 1950.
50. Sheridan, C. A., and Robson, J. G.: Fluothane in obstetrical anesthesia, *Canad. Anaesth. Soc. J.* **6**: 365, 1959.
51. Shute, E., and Davis, M. E.: Effect on infant of morphine administered in labor, *Surg. Gynec. Obstet.* **57**: 727, 1933.
52. Goodfriend, M. J., Shey, I. A., and Klein, M. D.: Effects of maternal narcotic addiction on newborn, *Amer. J. Obstet. Gynec.* **71**: 29, 1956.
53. Kunstadter, R. H., Klein, R. I., Lundeen, E. C., Witz, W., and Morrison, M.: Narcotic withdrawal symptoms in newborn infants, *J. A. M. A.* **168**: 1008, 1958.
54. Vincow, A., and Hackel, A.: Neonatal narcotic addiction, *Gen. Pract.* **22**: 90, 1960.
55. Synder, F. F.: *Obstetric Analgesia and Anesthesia. Their Effects upon Labor and the Child.* Philadelphia, W. B. Saunders Co., 1949.
56. McNab, J. A.: Obstetrical analgesia and anesthesia, *Canad. Med. Ass. J.* **72**: 681, 1955.
57. Lund, C. J., and Harris, J. W.: Use of heroin (diacetyl-morphine) in labor, *Amer. J. Obstet. Gynec.* **45**: 980, 1943.
58. Paterson, S. J., and Prescott, F.: Nalorphine in prevention of neonatal asphyxia due to maternal sedation with pethidine, *Lancet* **1**: 490, 1954.
59. Hughes, H. J., and Philpott, N. W.: Evaluation of nisentil as analgesic agent in labour, *Canad. Med. Ass. J.* **71**: 6, 1954.
60. Gillam, J. S., Hunter, G. W., Darner, C. B., and Thompson, G. R.: Meperidine hydrochloride and alphaprodine hydrochloride as obstetric analgesic agents. Double-blind study, *Amer. J. Obstet. Gynec.* **75**: 1105, 1958.
61. Davis, M. E., Andros, G. J., and King, A. G.: Use of methadone-scopolamine in obstetric analgesia, *J. A. M. A.* **148**: 1193, 1952.
62. Myers, J. D.: Preliminary clinical evaluation of dihydrocodeine bitartrate in normal parturition, *Amer. J. Obstet. Gynec.* **75**: 1096, 1958.
63. Little, D. M., and Tovell, R. M.: Role of analgesia and anesthesia in production of asphyxia neonatorum, *J. Indiana Med. Ass.* **42**: 201, 1949.
64. Apgar, V., Burns, J. J., Brodie, B. B., and Papper, E. M.: Transmission of meperidine across human placenta, *Amer. J. Obstet. Gynec.* **64**: 1368, 1952.
65. Eisenbrandt, L. L., Adler, T. K., Elliott, H. W., and Abdou, I. A.: Role of gastrointestinal tract in excretion of C¹⁴-labeled methadone by rats, *J. Pharmacol. Exp. Ther.* **98**: 200, 1950.
66. Eckenhoff, J. E., Hoffman, G. L., and Funderburg, L. W.: N-allylnormorphine: antagonist to neonatal narcosis produced by sedation of the parturient, *Amer. J. Obstet. Gynec.* **65**: 1269, 1953.
67. Greene, B. A.: Role of N-allylnormorphine in prevention and treatment of narcotic depression of newborn, *Amer. J. Obstet. Gynec.* **70**: 618, 1955.
68. Barr, W., and Barr, G. T. D.: N-allylnormorphine in treatment of neonatal asphyxia, *J. Obstet. Gynaec. (Brit. Emp.)* **63**: 216, 1956.
69. Dille, J. M.: Studies on barbiturates; placental transmission of nonanesthetic doses of barbital, *Amer. J. Obstet. Gynec.* **32**: 328, 1936.
70. Flowers, C. E.: Placental transmission of sodium barbital, *Obstet. Gynec.* **9**: 332, 1957.
71. Ploman, L., and Persson, B. H.: On the transfer of barbiturates to human foetus and their accumulation in some of its vital organs, *J. Obstet. Gynaec. (Brit. Emp.)* **64**: 706, 1957.
72. Nyberg, F. F., Kendrick, J. G., Evans, J. A., and Stofer, B. E.: Infant depression following Delvinal analgesia, *Obstet. Gynec.* **11**: 184, 1958.
73. Lovitt, W. V., Freimuth, H. C., and Englehart, W. P.: Maternal and fetal blood barbiturate concentration following obstetrical anesthesia and analgesia, *Maryland Med. J.* **4**: 325, 1955.
74. Fealy, J.: Placental transmission of pentobarbital sodium, *Obstet. Gynec.* **11**: 342, 1958.
75. Dreisbach, R., and Synder, F. F.: Effect on fetus of pentobarbital sodium and pentothal sodium, *J. Pharmacol. Exp. Ther.* **79**: 250, 1943.

76. Hellman, L. M., Shettles, L. B., Manahan, C. P., and Eastman, N. J.: Sodium pentothal anesthesia in obstetrics, *Amer. J. Obstet. Gynec.* **48**: 851, 1944.
77. McAllister, H. A., and Flowers, C. E.: Evaluation of Pentothal sodium for delivery, *South. Med. J.* **49**: 1028, 1956.
78. McKechnie, F. B., and Converse, J. G.: Placental transmission of thiopental, *Amer. J. Obstet. Gynec.* **70**: 639, 1955.
79. Crawford, J. S.: Some aspects of obstetric anaesthesia; use of thiopentone sodium, *Brit. J. Anaesth.* **28**: 146, 1955.
80. Kahn, J. B., Nicholson, D. B., and Assali, N. S.: Placental transmission of thiobarbiturate in parturient women, *Obstet. Gynec.* **1**: 663, 1953.
81. Kane, P. O., and Stephens, C. J.: Buthalitone sodium. Its effect on foetus and its rate of passage across human placenta, *Brit. J. Anaesth.* **31**: 533, 1959.
82. Flowers, C. E.: The placental transmission of barbiturates and thiobarbiturates and their pharmacological action on mother and infant, *Amer. J. Obstet. Gynec.* **78**: 730, 1959.
83. Richards, R. K., and Taylor, J. P.: Some factors influencing distribution metabolism and action of barbiturates, *Rev. Anesth.* **17**: 414, 1956.
84. Smith, Kline & French Laboratories: Science Department Information dated April 1956.
85. Lacomme, M., and Le Lorier, G.: Nouveaux essais d'utilisation du Largactil en analgésie obstétricale, *Bull. Federation French Speaking Gynec. Obstet. Soc.* **7**: 119, 1955. Translated by Medical Literature Service, College of Physicians, Philadelphia.
86. Behn, W., Frahm, M., and Fretwurst, E.: Ueber den diaplacentaren Uebergang von Phenothiazin-Derivaten, *Klin. Wochschr.* **34**: 872, 1956.
87. Smith, Kline & French Laboratories: Science Department Information dated May 1957.
88. Bourne, G.: Methylpentynol in labour, *Lancet* **2**: 522, 1954.
89. Marley, E., and Vane, J. R.: Distribution of methylpentynol and of methylpentynol carbonate in tissue and body fluids of cats, *Brit. J. Pharmacol.* **13**: 364, 1958.
90. Adelman, M. H., Fisch, H., Jacobson, E., and Katz, J.: Studies of promethazine with measurements of concentrations in venous blood, fetal cord blood, and cerebrospinal fluid, *ANESTHESIOLOGY* **19**: 93, 1958.
91. Potts, C. R., and Ullery, J. C.: Maternal and fetal effects of obstetrical analgesia. Intravenous use of promethazine and meperidine, Scientific Exhibit presented at the Meeting of the American Medical Association, Miami Beach, Florida, 1960.
92. Crawford, J. S.: Placental interference and neonatal metabolism of phenothiazine derivatives. Data presented at the Second World Congress of Anaesthesiologists, Toronto, 1960.
93. Campbell, R. E.: Effects of chloral hydrate on maternal and fetal organism from standpoint of experimental study, *Amer. J. Obstet. Gynec.* **28**: 83, 1934.
94. Bernstein, J. B., Meyer, A. E., and Hayman, H. B.: Maternal and foetal blood estimation following administration of chloral hydrate during labour, *J. Obstet. Gynaec. (Brit. Emp.)* **61**: 683, 1954.
95. Moore, S. F., and McCurdy, R. A.: Use of paraldehyde analgesia in labor, including studies of effect upon uterine contraction, *Amer. J. Obstet. Gynec.* **32**: 97, 1936.
96. Gardner, H. L., Levine, H., and Bodansky, M.: Concentration of paraldehyde in blood following its administration during labor, *Amer. J. Obstet. Gynec.* **40**: 435, 1940.
97. Belinkoff, S., and Hall, O. W.: Intravenous alcohol during labor, *Amer. J. Obstet. Gynec.* **59**: 429, 1950.
98. Chapman, E. R., and Williams, P. T.: Intravenous alcohol as obstetrical analgesia, *Amer. J. Obstet. Gynec.* **61**: 676, 1951.
99. Johnson, H., and Hellman, L. M.: University of the State of New York Downstate Medical College, Personal communication.
100. Dreisbach, R., and Snyder, F. F.: Effect of scopolamine on the fetus, *Proc. Soc. Exp. Biol. Med.* **48**: 197, 1941.
101. Flowers, C. E., Littlejohn, T. W., and Wells, H. B.: Pharmacologic and hypnoid analgesia. Effect upon labor and the infant response, *Obstet. Gynec.* **16**: 210, 1960.
102. Harroun, P., and Fisher, C. W.: Physiological effects of curare. Its failure to pass the placental membrane or inhibit uterine contractions, *Surg. Gynec. & Obstet.* **89**: 73, 1949.
103. Buller, A. J., and Young, I. M.: Action of *d*-tubocurarine chloride on foetal neuromuscular transmission and placental transfer of this drug in rabbit, *J. Physiol.* **109**: 412, 1949.
104. Pittinger, C. B., and Morris, L. E.: Placental transmission of *d*-tubocurarine chloride from maternal to fetal circulation in dogs, *ANESTHESIOLOGY* **14**: 238, 1953.
105. Pittinger, C. B., Morris, L. E., and Keettel, W. C.: Vaginal deliveries during profound curarization, *Amer. J. Obstet. Gynec.* **65**: 635, 1953.
106. Beck, H.: Zur Frage der Placentapassage der Muskelrelaxantien Curarin und Flaxedil, *Ztschr. f. Geburtshilfe Gynaek.* **146**: 253, 1956.
107. Beck, H., and Nold, B.: Ist die Placenta für Muskelrelaxantien durchlässig? *Anaesthesist* **6**: 93, 1957.
108. Crawford, J. S., in collaboration with Gardiner, J. E.: Some aspects of obstetric anes-

- thesia; use of muscle relaxants, *Brit. J. Anaesth.* **28**: 154, 1955.
109. Pittinger, C. B., and Morris, L. E.: Observation of placental transmission of gallamine triethiodide (Flaxedil), succinylcholine chloride (Anectine) and decamethonium bromide (Syncurine) in dogs, *Anesth. Analg.* **34**: 107, 1955.
110. Schwarz, R.: Chemische Untersuchungen zur diaplacentaren Passage von Gallamin, *Anaesthesist* **7**: 299, 1958.
111. Young, I. M.: Action of decamethonium iodide (C 10) on foetal neuromuscular transmission and its transfer across placenta, *J. Physiol.* **109**: 31 P, 1949.
112. Young, I. M.: Abdominal relaxation with decamethonium iodide (C 10) during Caesarian section, *Lancet* **2**: 1052, 1949.
113. Ellerker, A. R.: Decomethonium as a curarizing agent in general anaesthesia, *Brit. Med. J.* **2**: 398, 1950.
114. Little, D. M., Hampton, L. J., and Grosskreutz, D. C.: Succinylcholine (Diacetylcholine): controllable muscle relaxant, *Anesth. Analg.* **32**: 171, 1953.
115. Gillies, D. M., Cullen, W. G., and Griffith, H. R.: Succinylcholine as relaxant in abdominal surgery, *Anesth. Analg.* **33**: 251, 1954.
116. Jüngling, O.: Zwei Fälle von Neugeborenenasphyxia nach Verwendung von Succinylcholin bei der Narkose zum Kaiserschnitt, *Anaesthesist* **6**: 92, 1957.
117. Bannister, W. K.: Controlled respiration during cesarian section, *J. A. M. A.* **162**: 1028, 1956.
118. Dance, C., and Ward, R.: Succinylcholine for Cesarian section, *Anesth. Analg.* **37**: 249, 1958.
119. Thesleff, S.: Pharmacological properties of succinylcholine iodide. With particular reference to its clinical use as muscular relaxant, *Acta Physiol. Scand.* **26**: 103, 1952.
120. Kvisselgaard, N., and Moya, F.: Investigation of placental thresholds to succinylcholine, *ANESTHESIOLOGY* **22**: 7, 1961.
121. Moya, F., and Margolies, L.: Hydrolysis of succinylcholine by placental homogenates, *ANESTHESIOLOGY* **22**: 11, 1961.
122. Moya, F., and Kvisselgaard, N.: Placental transmission of succinylcholine, *ANESTHESIOLOGY* **22**: 1, 1961.
123. Stead, A. L.: Response of newborn infant to muscle relaxants, *Brit. J. Anaesth.* **27**: 124, 1955.
124. Apgar, V.: Comparison of results to infant following maternal regional or general anesthesia for delivery, *New York J. Med.* **57**: 2955, 1957.
125. Greenhill, J. P.: *Obstetrics*, ed. 12. Philadelphia, W. B. Saunders Co., 1960.
126. Hanley, B. J., and McNulty, J. V.: Regional anesthesia in obstetrics, *Amer. J. Obstet. Gynec.* **77**: 853, 1959.
127. Saber, R. H., and Covalesky, B.: Technic for obstetric anesthesia in small military hospital, *Milit. Med.* **122**: 413, 1958.
128. Bush, R. C.: Caudal analgesia for vaginal delivery, *ANESTHESIOLOGY* **20**: 31, 1959.
129. Hingson, R. A., and Edwards, W. B.: Continuous caudal anesthesia during labor and delivery, *Anesth. Analg.* **21**: 301, 1942.
130. Schmitz, H. E., and Baba, G.: Low spinal nupercaine anesthesia in obstetrics, *Amer. J. Obstet. Gynec.* **54**: 838, 1947.
131. Chaplin, R. A., and Renwick, W. A.: Lumbar epidural anaesthesia for vaginal delivery, *Canad. Anaesth. Soc. J.* **5**: 414, 1958.
132. Allen, F. M.: Intravenous obstetrical anesthesia, *Amer. J. Surg.* **70**: 283, 1945.
133. Johnson, K., and Gilbert, C. R. A.: Intravenous procaine for obstetrical anesthesia, *Anesth. Analg.* **25**: 133, 1946.
134. Abramson, H. (editor): *Resuscitation of the Newborn Infant. Principles and Practice*, St. Louis, C. V. Mosby, 1960.
135. Vasicka, A., and Kretchmer, H.: Intra-amniotic pressure observations following prochlorperazine and anesthesia during labor, Scientific Exhibit presented at the Meeting of the American Society of Anesthesiologists, Miami Beach, Florida.
136. Kretchmer, H.: Western Reserve School of Medicine, Personal communication.
137. Prystowsky, H.: Fetal blood studies; some observations on transient fetal bradycardia accompanying uterine contractions in human, *Bull. Johns Hopkins Hosp.* **102**: 1, 1958.