Uptake, Distribution and Placental Transport of Drugs and Anesthetics

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The depth of anesthesia achieved in a pregnant woman and the severity of depression found in her newborn infant are primarily related to the concentration of anesthetic agent found in their respective brains. In turn, cerebral drug levels are dependent upon the concentration of agent in arterial blood, cerebral blood flow, tissue solubility and the rate of diffusion across the blood-brain and placental barriers. The arterial tension of inhalation anesthetics may be said to equal alveolar tension because diffusion through the respiratory membrane in the normal lung is rarely a limiting factor. Finally, alveolar concentration approaches inspired concentration at a rate determined by three factors: (1) lung washout (primarily ventilation), (2) uptake by pulmonary blood, and (3) inspired concentration. All the above factors influence the eventual saturation of the brain and, therefore, the speed of induction of anesthesia.

This report will examine these various physical processes and their relationship to the obstetric patient. Regrettably, though a wealth of theoretical and experimental data have been accumulated on the uptake and distribution of anesthetic agents, no studies have been performed in the pregnant woman.1,2,3 This is particularly unfortunate since gestation is known to be associated with many changes in pulmonary function, acid-base balance, and circulation, which may significantly alter the mother's response to anesthesia.4,5 Much of this discussion, therefore, will of necessity be speculative, based on the limited information available. No attempt will be made to review all phases of uptake and distribution, since comprehensive accounts may be found elsewhere.1-5,6

Lung Washout

The rate of replacement or washout of lung air by inhalation anesthetics is related to the respiratory minute volume and the volume of air remaining in the lungs upon normal expiration (i.e., the functional residual capacity or FRC).2 This residual air dilutes each inspired breath of gas. Normal ventilation allows a rapid introduction of the inspired gas concentration into the alveoli. Within two minutes, if the effect of ventilation were unopposed, the alveolar concentration would be 95 per cent of the inspired concentration.7

Changes in Pulmonary Function with Pregnancy

Normal pregnancy is associated with a chronic hyperventilation. The 42 per cent increment in respiratory minute volume found in full-term women chiefly represents a 39 per cent increase in tidal volume.8 Since the respiratory rate increases only slightly (10 per cent or one breath per minute increase), effective alveolar ventilation is augmented by more than 68 per cent.8 The per cent increase in minute volume of ventilation is greater than the percentage increase in oxygen consumption.9 This, therefore, inevitably leads to a reduction in alveolar and arterial blood carbon dioxide tension. The chronic hyperventilation of pregnancy is augmented by painful stimulation and excitement during labor, sometimes to the point of marked carpopedal spasm and other signs and symptoms of tetany.9 Deep breathing is further enhanced by the intense motivation that many of the women have toward obtaining pain relief.

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Dynamic ventilatory studies have shown that the maximum breathing capacity, the air velocity index, and timed vital capacity all remain within normal limits during pregnancy.\textsuperscript{8} Also, intrapulmonary mixing studies reveal no defect of gas distribution at any time during pregnancy.\textsuperscript{8} On the other hand, there is a progressive decrease of the expiratory reserve and residual volumes, resulting at term in an 18 per cent reduction in the functional residual capacity.\textsuperscript{8} The volumetric loss of the expiratory reserve volume (the quantity of air which can be forcibly exhaled after a normal expiration) is compensated by a corresponding increase in the inspiratory capacity (the maximum volume of air which can be inhaled after a normal expiration).\textsuperscript{8} Consequently, the vital capacity and total lung volume remain essentially unchanged.

It is not entirely sure why certain of the lung volumes change during pregnancy. It is tempting to explain these entirely on the basis of the elevated diaphragm observed in roentgenograms of the chest. However, it should be borne in mind that the functional residual capacity is determined not only by expansile properties of the chest wall (including the diaphragm), but also by the tendency of the lungs to collapse.\textsuperscript{10} Nevertheless, there is evidence that the changes in the lung volumes which have been described are accentuated by the dorsal recumbent position, because the mass of the intra-abdominal contents exert a greater effect on the diaphragm.\textsuperscript{9}

\textit{Effects of Increased Ventilation.} With a constant inspired concentration, the alveolar tension is determined by a balance struck between anesthetic input through ventilation and anesthetic loss through uptake by pulmonary blood.\textsuperscript{1,11} Any alteration in this balance which increases input in relation to uptake will increase alveolar concentration.\textsuperscript{1} It follows, therefore, that the hyperventilation of pregnancy should reduce the difference between inspired and alveolar tension by bringing more anesthetic into the lungs per unit time. This probably occurs since the effective alveolar ventilation is increased in pregnancy out of proportion to the overall increase in respiratory minute volume.\textsuperscript{8} However, the relative effect of an increment in ventilation varies considerably with the solubilities of the different gases.\textsuperscript{1,12} Alterations in ventilation have a small effect on the less soluble gases, such as nitrous oxide and ethylene, because uptake by blood plays a relatively minor role in determining their alveolar concentrations. Conversely, there will be a marked effect with the more soluble agents, such as ether and chloroform. With these anesthetics, a doubling of ventilation during induction may lead to a doubling of alveolar concentration.\textsuperscript{11,12} This is well illustrated by the common clinical observation of an extremely rapid induction with ether in the laboring obstetric patient requiring as little as 2 to 3 minutes, whereas in the nonpregnant woman the duration may be several times as long. Nitrous oxide, on the other hand, shows only a minor increase in the speed of induction during pregnancy.

\textit{Effects of Reduced Functional Residual Capacity.} The effects of increased ventilation on alveolar concentration are enhanced by the reduced functional residual capacity (FRC) associated with pregnancy. The resultant alveolar tension of each inspired breath of gas depends on the degree of dilution by the functional residual air volume.\textsuperscript{2} This volume, therefore, usually acts as a buffer to changes in anesthetic and normal respiratory gas tensions.\textsuperscript{1} The larger the volume, the more slowly the change occurs in concentration. Conversely, the pregnant woman with her small FRC, will more readily and rapidly fill her lungs with gas at a certain tension than the nonpregnant. In other words, a decreased FRC accelerates the rise of alveolar anesthetic concentration by reducing lung washout time. The effect appears greatest with the less soluble gases, and least with the highly soluble gases.\textsuperscript{1,12} In both instances, the apparent difference is seen primarily during the first few minutes of induction. Patently, this is the most important period in obstetric anesthesia since it determines the amount of gas reaching the infant's circulation.

Using electronic analogs, Severinghaus\textsuperscript{13} has found that the effect of alterations in lung volume (FRC) is surprisingly small when alveolar ventilation is held constant. Once again it appears that alveolar ventilation and the degree of uneven ventilation are more important than alveolar volume in determining the rate of change of alveolar concentration.\textsuperscript{14} Normal
pregnancy, as mentioned above, is associated
with a uniform distribution of inspired gases.8
The diminished functional residual capacity
of pregnancy not only permits more rapid in-
duction and recovery from inhalation anes-
thesthesia, but also, arterial blood levels of oxy-
gen, carbon dioxide and pH undergo greater
changes during the breathing cycle.14 This
is of considerable importance to the anesthe-
siologist, since the mother is thereby particu-
larly prone to rapid changes in respiratory blood
gas levels during disturbances of ventilation.
As a result, she may quickly develop hypoxia,
hypercapnia, and acidosis, or alternatively,
hypocapnia and alkalosis. The tendency to-
ward rapid fluctuations in the acid-base status
and blood gas levels of these patients is aug-
mented by the presence of a high oxygen con-
sumption and a compensated CO2 deficit.5

Anesthetic Uptake by Pulmonary Blood
The rise in alveolar concentration produced
by ventilation is opposed by loss (uptake) of
the anesthetic agent to the pulmonary blood.1
The greater the loss, the lower is the ensuing
alveolar concentration. The three factors which
determine the extent of anesthetic uptake are
(1) solubility in blood, (2) cardiac output and (3) alveolar-venous blood tension gradient.

BLOOD SOLUBILITY
In any patient, this is the most important
factor in determining the speed of induction
and recovery from anesthesia. In this regard,
it is the primary determinant of uptake and
distribution in the body.18 The solubility of
an anesthetic in blood is best described as an
index of the capacity of blood to hold that
anesthetic agent.1 More precisely, it is defined
as a partition coefficient, or the ratio of the
concentration of anesthetic gas in blood to the
concentration of that gas in air at equilib-
rrium.2,15 Numerically, it is expressed as the
Ostwald solubility coefficient.15 A soluble gas
is more easily carried away by blood and con-
sequently the alveolar tension of that gas will
build up more slowly. That is, the greater the
blood solubility, the lower the alveolar concen-
tration relative to the inspired concentration.1

The solubility of an anesthetic agent is pri-
marily dependent upon the nature of the sol-
vent, and any variation in the composition of
the solvent alters anesthetic solubility.15 Com-
monly used anesthetics are most soluble in
lipids, less in proteins, and least in aqueous
solutions containing electrolytes.15 It follows,
that alterations in blood constituents during
pregnancy may affect the solubilities of anes-
thetic agents.

Normal gestation is characterized by changes
in hematocrit, acid-base balance, plasma pro-
teins and lipids. It is now well established
that hematocrit, hemoglobin, and red cell
values are usually diminished during uncompli-
cated pregnancy.16 Venous hematocrit, for in-
stance, falls from 39.4 to 32 per cent.17 This
is especially important because of the lipid
rich red cell envelope which has a particular
affinity for highly fat soluble agents, such as
chloroform, methoxyflurane, halothane and tri-
chloroethylene.16,18 Gestation is also associated
with a decrease in maternal buffer anions,
total base, CO2 content and dissolved CO2.19,20
The diminution in the body’s buffering ca-
pacity, including the alkaline reserve, originally
led to the belief that a metabolic acidosis de-
veloped during normal pregnancy. It has
since been found that these changes represent
a compensated CO2 deficit rather than a true
acidosis, since the pH remains normal and no
fixed acids accumulate in the blood.19,20 The
plasma protein concentration decreases ap-
proximately 7 per cent by the ninth month
of gestation.21,22 Serum lipids, on the other
hand, rise progressively throughout pregnancy
except for a slight decrease shortly after the
first missed period.23,24 The hyperlipemia is
due primarily to a rise in plasma fats rather
than any change in red cell fatty content.
Total lipids are increased 46 per cent, with an
elevation of over 100 per cent in neutral fat
and about 25 per cent in phospholipids and
cholesterol.23

No data are currently available on the solu-
bility of anesthetic agents in the blood of preg-
nant women. As a rule, it is extremely difficult
to predict accurately a partition coefficient for
an anesthetic agent in a complex biological
solvent.15,25 However, it appears unlikely
that the magnitude and direction of the
changes in blood constituents during preg-
nancy, described above, would have a signifi-
cant overall effect on anesthetic solubility.
CARDIAC OUTPUT

In normal lungs, the partial pressures of gases in pulmonary venous blood achieve equilibrium with that of the various gases in the alveoli. Therefore, the rate at which anesthetics are removed from the lungs by blood is not only dependent upon anesthetic solubility, but also on the volume of blood perfusing the lungs. Pulmonary blood flow determines the quantity of blood to which the alveolar gas is exposed per unit time. The blood carries the agent away from the alveoli and as a result, tends to lower its partial pressure in the alveoli. This initially delays the achievement of an alveolar concentration equal to the inspired level. The volume of pulmonary blood flow usually equals the output of the right side of the heart, since this entire volume passes through the lungs. Therefore, the greater the cardiac output, the more slowly will alveolar tension approach the inspired tension, and the slower will be the induction of anesthesia.

During pregnancy there are significant and progressive increases in cardiac output, pulse rate, pulse pressure and circulating velocity until the seventh or eighth month of gestation. These circulatory alterations then reverse their direction and approach normal nonpregnant levels at term. Cardiac output reaches a maximum increase of about 40 per cent by the twenty-fifth to twenty-seventh week. Hence, it would appear that this augmented pulmonary blood flow should lower the alveolar concentration and tend to prolong induction because of the greater quantity of anesthetic removed from the lungs. However, Eger has shown that with agents of low solubility, such as nitrous oxide and ethylene, changes in cardiac output have little effect on alveolar tension. This is probably related to the relatively small proportion of these gases that is taken up regardless of blood flow and, in part, to the influence of the "concentration effect" (see below). On the other hand, with the more soluble agents, such as ether and halothane, an increase in cardiac output results in a considerable reduction in alveolar tension because uptake by blood is of much greater importance. Despite this retarding effect, induction with ether is characteristically rapid in the pregnant woman. This would indicate that the increased ventilation of pregnancy is of greater importance than the increased cardiac output in determining the rate of induction. Eger's data would seem to substantiate this concept.

ALVEOLAR-VENOUS TENSION GRADIENTS

The partial pressure of gas in the mixed venous blood returning to the lungs limits the amount of agent that will be removed by blood. If the tension in venous blood is low, then a greater amount of anesthetic will move into the blood and lower the alveolar concentration, thereby prolonging induction. Anesthetic uptake by pulmonary blood ceases when alveolar tension equals venous tension, regardless of the solubility or cardiac output. The partial pressure in venous blood depends upon the amount of anesthetic taken up by the tissues. Tissue uptake, similar to uptake by the pulmonary blood, is determined by: (1) the solubility (partition coefficient) of the agent in tissue relative to blood, (2) the cardiac output in general, but in particular the blood flow per unit volume of tissue, and (3) the arterial blood-tissue tension gradient.

Tissue uptake by highly perfused organs (vessel rich group or VRG) such as the brain, liver, heart and kidney is initially high, but is virtually complete within the first 5 to 15 minutes. Since in the nonpregnant state approximately 75 per cent of the cardiac output goes to this group, as these tissues become saturated, venous and alveolar anesthetic concentrations rise markedly. The VRG is the primary determinant of tissue uptake during the first 10 minutes, whereas other tissues such as muscle and fat continue to absorb agent for prolonged periods.

A detailed consideration of the changes that take place during pregnancy in blood volume and regional blood flow is presented elsewhere in the symposium. In brief, early in pregnancy, the increase in cardiac output is distributed principally to the kidneys; whereas in the final months, perfusion of the uterus and upper extremities predominates. Uterine blood flow, at term, is about 500 to 750 ml. per minute and the placental site (intervillous space) is estimated to be perfused by 75 per cent of this total blood flow. This is roughly of the
same magnitude as the flow through a single normal adult kidney. On a milliliter per 100 grams per minute basis, the pregnant uterus receives much less blood than the kidneys and brain, but more than skeletal muscle and gut. The increased blood flow through the uterus is apparently achieved at no expense to the perfusion of other maternal organs since, for example, the blood flow through the liver and brain is not altered during pregnancy. Total blood volume, it is generally agreed, rises progressively with gestation until about the eighth month and then declines slowly. The increase in plasma volume is greater than the increase in red cell mass, therefore, the hematocrit and hemoglobin values are somewhat diminished.

In effect, these changes in blood volume, renal and uterine blood flow represent an increase in the VRC. Although this increase in perfusion per unit volume of tissue allows greater uptake by the tissues, it also results in a more rapid rate of tissue saturation. The latter promotes a more rapid decrease in the uptake by tissues and consequently, leads to a rise in alveolar concentration. Therefore, it would seem that the increase in the VRC found with pregnancy should tend to decrease the initial rise of the alveolar concentration curve, especially for soluble gases.

**Effect of Inspired Concentration**

The third and final factor that determines the rate at which alveolar and inspired concentrations approach one another is the “concentration effect” described recently by Eger.

He has found that a higher inspired concentration of anesthetic results in a relatively faster rise in alveolar concentration. If the inspired concentration is 100 per cent, the rise in alveolar tension is equally rapid for all anesthetics, regardless of differences in solubility. Therefore, the influence of pulmonary capillary uptake through solubility no longer opposes the ventilatory input of anesthetic. As an example, the alveolar concentration curves of ether and nitrous oxide are identical when a 100 per cent concentration is inspired. In a converse fashion, the lower the concentration the greater the effect of solubility.

**Distribution**

The concentration of an anesthetic agent throughout various body tissues, once introduced into the circulation either by inhalation or intravenous injection, is directly related to:

(a) the arterial blood level of the drug, (b) perfusion or blood flow per unit of tissue, (c) tissue solubility (partition coefficient), and lastly, (d) rate of diffusion across the tissue membrane. In general, blood flow and arterial concentration are the main determinants of the speed with which tissues become saturated. If the arterial concentration of a substance is constant, the most highly perfused tissues should reach equilibrium with the blood most rapidly. For instance, the more rapid the cerebral blood flow, other things being equal, the more anesthetic gas or vapor will reach the brain per minute and, therefore, hasten the induction of anesthesia. However, this concept assumes a free and unlimited diffusion from blood to tissue. It is now widely accepted that many body membranes, including the brain and placenta, exhibit a selective permeability to foreign substances so that some drugs will pass readily and others will penetrate only with great difficulty.

In recent years, the kinetics of drug transfer across the blood-brain barrier and other membranes have been most extensively studied by Brodie and his associates. Since there appears to be a similarity of the blood-placental barrier to the blood-brain barrier, a brief review of the latter will be helpful in understanding the problems of placental permeability to drugs.

**Blood-Brain Barrier**

Studies with a wide array of drugs have shown conclusively that foreign organic substances penetrate the blood-brain barrier as though the boundary had the characteristics of a lipid barrier. In this regard, both the lipid solubility and the degree of ionization of a drug play important roles in determining the speed of transfer. The rates of passage of a large number of organic agents have been correlated with their degree of ionization and lipid solubility. The substances were found to be transferred mainly in their undissociated or nonionized form, and only
sightly in their highly charged or ionized state. Furthermore, nonionized drugs with high fat solubilities are transferred rapidly, whereas lipid insoluble drugs penetrate poorly despite a low degree of ionization. Although both lipid solubility and degree of ionization are important in governing the transfer of drugs, the rate of entry is primarily controlled by the lipid solubility of the nonionized drug molecule. The dissociation constant (pKa) is important mainly because it determines the plasma concentration of the nonionized moiety of the drug.

The lipoid theory of membrane transfer is consistent with a generally accepted concept that considers the plasma membrane boundary of cells throughout the body as a fat-like layer interspersed with small pores. Therefore, small molecules, such as nitrous oxide and ethylene, despite their lipid insolubility could pass through the sub-microscopic holes. For most drugs, however, with a molecular weight greater than 100, penetration through pores is probably unimportant compared to fat solubility.

There is no evidence of any significant alteration in the blood-brain barrier during pregnancy. Cerebral blood flow, as noted previously, remains normal despite the great increase in uterine blood flow.

**Blood-Placental Barrier**

The basic function of the placenta is to bring the maternal and fetal circulations into close proximity in order to permit effective exchange of naturally occurring materials.Originally, the role of the placenta was considered to be similar to a simple, passive, semi-permeable filter which permitted the transfer of small molecular weight substances such as carbohydrates and barred larger compounds such as proteins. This concept of a simple sieve-like role for the placenta has been replaced by a more complex but still poorly understood one in which the placenta selectively controls the rates of transfer of a wide variety of materials. It is now believed that any substance found in the maternal or fetal blood should be able to cross the placenta to some extent unless it is destroyed or altered during passage. A very low degree of permeability, however, may slow the entry to a rate which renders a drug physiologically inactive and pharmacologically undetectable. Page has suggested that the important question is not whether a given substance does or does not pass the so-called placental barrier, but the rate and mechanism of transfer.

For purposes of this discussion, the placental membrane or barrier may be defined as those tissues which are interposed between the fetal and maternal plasma. At term, these consist of the fetal capillary wall or endothelium, the stroma which separates the capillary wall from the basement membrane of the villus, and lastly, a continuous layer of syncytium. It is the syncytial layer which is responsible for the active enzyme transfer of certain materials. Beneath the parenchymal layer of syncytium lies an occasional Langhans' cell which has persisted throughout pregnancy.

**Basic Mechanisms of Placental Transfer**

The following mechanisms are currently accepted as significant in the transport of substances across the placenta: simple diffusion, facilitated diffusion (carrier systems), active transport (enzymatic), and special processes (pinocytosis and leakage).

Diffusion, whether it be simple or facilitated, is the movement of molecules from an area of high concentration to one of low concentration, to establish equal concentrations on both sides of a membrane. The driving force for this movement is thermal agitation of the molecules: no expenditure of metabolic energy is required. For all practical purposes, foreign compounds cross the placental barrier almost purely by simple diffusion. In rare instances, a drug (e.g., antimitobolites) may closely resemble a naturally occurring material and as a result, be transported by an active enzymatic process. Pinocytosis is the process by which microscopic invaginations of the villi engulf tiny droplets of plasma and discharge them into the fetal circulation at a relatively slow rate. The speed and quantities of substance transferred by such a mechanism are

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*The pKa is the pH at which the concentrations of the nonionized and ionized forms are equal. For both acids and bases it is the negative logarithm of the acidic dissociation constant.
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undoubtedly too low to be of significance in the transmission of drugs, but may be important immunologically. Minute "leaks," due to breaks in the placental villi, have been implicated as a route of transfer of intact red cells to the fetus from the maternal circulation, but are of no clinical importance in the passage of drugs.\(^{35,43}\)

**Factors in Transfer of Drugs**

Foreign substances diffuse across the placenta at a speed governed mainly by certain physicochemical factors in accordance with Fick's law of diffusion.\(^{35,39,43,46}\) The rate of diffusion is a function of the difference in concentration of the substance on the two sides of the membrane (i.e., concentration gradient between maternal and fetal blood), the surface area available for transfer, and the thickness of the membrane. The relationship is most apparent from the equation:

\[
\frac{Q}{t} = K \frac{A(C_m - C_f)}{X}
\]

where \(Q/t\) is the rate of diffusion (quantity per unit time), \(A\) is the available area, \(C_m\) is the maternal blood concentration, \(C_f\) is the fetal blood concentration, \(X\) is the thickness of the membrane, and \(K\) the diffusion constant of the drug which is related to its molecular size, spatial configuration, degree of ionization, lipid solubility, and partition coefficient. This concept of diffusion is somewhat simplified since it does not take into account the volume of maternal and fetal blood flow and of course, does not hold true for facilitated or active transport.

**Effects of Maternal and Fetal Blood Flow.**

Uptake of anesthetic agents by fetal blood passing through the placenta is directly related to the same three factors that determine uptake at the lungs by pulmonary blood, namely, (a) the solubility of the agent in fetal blood relative to maternal blood, (b) the umbilical blood flow, and (c) the intervillous space-fetal blood concentration gradient.

The solubility of an anesthetic in fetal blood may differ from maternal blood since the hematocrit is usually significantly higher. Anesthetics with high fat solubilities, such as trichlorethylene and halothane, will concentrate in the lipid layer of the red cell wall. Direct measurements of umbilical blood flow have not been carried out in man. However, based on animal experiments it is estimated that the fetal blood flow through the placenta is slightly less than the maternal blood flow through the intervillous space.\(^{35,40}\)

The concentration in the intervillous space, analogous to the concentration in the alveolar space, is determined primarily by the arterial blood ("inspired") concentration, perfusion ("ventilation"), volume ("FRC") of the intervillous space, and uptake by the fetal circulation ("pulmonary blood flow"). On the other hand, compared to normal lungs, diffusion through the placenta is limited by a thicker membrane, smaller surface area, and of greatest importance, the lipoidal character of the blood-placental barrier.\(^{30,35,46}\) Placental diffusion is enhanced, however, by the countercurrent flow of maternal and fetal blood. According to this doctrine, blood in maternal and fetal placental vessels flows in opposite directions.\(^{30}\) This arrangement, used frequently in engineering, is highly efficient in establishing chemical equilibrium between the two blood streams.\(^{29}\)

**The Placenta as a Lipoid Barrier.** It has recently been suggested that the concept of a lipoid barrier may apply to the transfer of drugs across the placenta.\(^{35,50,45}\) Therefore, as with the blood-brain barrier, the rate of entry is governed principally by the fat solubility of the nonionized drug molecule. Other factors, such as concentration gradient and molecular size, are usually of secondary importance. This theory is based primarily upon isolated observations of poor penetration by drugs with high degrees of dissociation or low lipid solubilities (e.g., succinylcholine,\(^{46}\) \(d\)-tubocurarine\(^{51}\) and THAM\(^{48}\)). Conversely drugs that are found mainly as fat soluble, undissociated molecules at physiologic pH ranges, penetrate the barrier almost instantaneously and rapidly achieve equilibrium. Antipyrine\(^{53}\) and thiopental\(^{54}\) are only two examples of many such compounds. Fragmentary evidence of this kind can only hint at the fundamental mechanism of the blood-placental barrier to drugs. Regrettably, there is little precise quantitative information available on the kinetics of drug penetration. A systematic investigation of a broad spectrum of compounds with various lipid solubilities and dis-
sociation constants is greatly needed. Only then can a conclusive overall formulation be made of the behavior of the placenta with respect to drugs.

**Molecular Size.** The molecular weight of a compound must obviously play a role in the rate of its passage across the placenta. The higher the molecular weight, as a rule, the lower the diffusibility. Substances of low molecular weight diffuse freely across the placenta, but with increasing size the factor of lipid solubility becomes progressively more important. Drugs with a molecular weight less than 600 cross relatively easy. By contrast, the placenta is virtually impermeable to compounds with molecular weights over 1,000. Drugs in the molecular weight range of 600 to 1,000 have not been studied.

**Concentration Gradient.** Regardless of its physical nature, the rate of passage through the placental membrane of any substance is at least partially dependent upon the concentration gradient. For example, highly ionized drugs of low lipid solubility, such as succinylcholine and curare may be found in fetal blood if high concentration gradients are produced by the use of extremely large doses in the mother. The gradient achieved across the placenta is primarily a function of the quantity of drug administered to the mother; however, other factors such as distribution throughout the maternal and fetal extracellular space, binding to protein elements in plasma and tissues, excretion and metabolism by the mother, infant and placenta are also important.

**Surface Area and Thickness of Membrane.** As gestation progresses, the placental membrane increases in surface area and decreases in thickness. At term, it is estimated that the membrane’s surface area is about one fifth that of the pulmonary alveoli and is three times as thick. There is an increase in placental permeability to radioactive sodium until the thirty-sixth week; followed by a decline to the time of delivery. It would seem that increasing the surface area and decreasing the thickness of the placenta should favor the transfer of anesthetic drugs, however, appropriate studies confirming this have not been conducted.

**Other Factors.** Pathologic changes in the placenta associated with systemic maternal diseases, such as preeclampsia, erythroblastosis and diabetes mellitus may alter the permeability of the placenta. Furthermore, inborn errors of maternal metabolism (e.g., atypical cholinesterase) may permit dangerous levels of drugs to accumulate. Alterations in maternal and fetal blood flow through the placenta induced by contractions, position of the mother, anesthesia or cord compression may also effect transmission to an unknown degree. This is especially important with the highly fat soluble, poorly ionized compounds with no demonstrable barrier to their transfer. Their rates of penetration are limited primarily by the volume of blood perfusing the placenta. Destruction by the placenta may also play an important role with some drugs. Finally, it is conceivable that conditions such as profound maternal asphyxia, hypotension, dehydration, or hemorrhage may weaken or eliminate the selectiveness of the placental lipid barrier.

**Transfer of Specific Drug Groups**

The passage of drugs across the placenta has been the subject of a number of recent comprehensive reviews. The following discussion will be limited to a brief summary of the placental transfer of groups of drugs and anesthetics commonly used in the management of pain during labor and delivery. For detailed accounts the reader is referred to the above reviews and the original articles.

**Gaseous and Volatile Anesthetics.** Inhalation agents, as a whole, rapidly traverse the placenta. Their high speed of transfer is related to the rapid rates of diffusion, relatively high fat solubility, and usually low molecular weight. Administered in anesthetic concentrations, the degree of neonatal narcosis is proportionate to the depth and duration of maternal anesthesia. Analgesic concentrations, with the mother awake, oriented and cooperative, produce no significant depression of the newborn regardless of the duration of administration.

**Barbiturates.** With refinements in the technique of blood analysis, earlier reports of a placental barrier to barbiturates have been disproven. The ultrashort-acting barbiturates, such as thiopental, thiamylal and
methohexital,65 cross the placenta almost immediately and within two to three minutes establish equilibrium between maternal and fetal blood. This is probably related to the fact that these drugs are weak acids which occur largely as lipid soluble nonionized molecules in the physiologic range of pH. Longer acting barbiturates are not without their effects on the fetus; however, satisfactory maternal sedation can usually be obtained with doses which will not cause serious neonatal respiratory depression.63 No correlation has been shown between the infant's condition at birth and his blood barbiturate level.64

**Tranquilizers.** Although the placental transfer of the phenothiazine family of drugs is now generally accepted, it was by no means an easy task to confirm this fact. Attempts to assay chlorpromazine in fetal blood have been uniformly unsuccessful.66 However, the drug has been identified in newborn tissue 67 and urine 68 following administration of the drug to the mother. A rapid disappearance from the maternal blood stream with binding by her tissues may explain the difficulty of finding chlorpromazine in the fetal circulation. Initial investigations in man of the placental transfer of promethazine failed to demonstrate the drug in fetal blood.69 Several independent studies have since shown that this drug rapidly crosses the placental barrier and can be found in umbilical vein blood as early as 1½ minutes after a maternal intravenous injection.70 71

**Narcotics and Their Antagonists.** There is voluminous indirect evidence, based on clinical observations of newborn babies, that all narcotics pass the placental barrier.35, 60, 61 In contrast to this, there is little information based on direct chemical analysis of biological material obtained from the infant. Morphine,72 methadone 73 and meperidine 74 have been demonstrated in infant tissues following delivery, however, the kinetics of placental transfer have not been studied adequately. The two most commonly used narcotic antagonists, nalorphine and levorphanol, have not been studied at all. They should, however, be able to cross the placenta readily because these drugs represent only slight modifications in the molecular structure of morphine and levorphanol.63

**Skeletal Muscle Relaxants.** The single most important characteristic common to all muscle relaxants is the presence of a quaternary ammonium group in the molecule. As a result, at normal pH range, these compounds are highly ionized and possess a low degree of lipid solubility.75 Because of these properties the placenta forms a relative barrier to the passage of most relaxants.35 Usual clinical doses have no demonstrable effects on the newborn and, with the exception of gallamine,51 significant quantities of the drugs cannot be detected biochemically in the infant's blood stream. If the concentration gradient across the placenta is extremely high, the relaxants may be found in cord blood and possibly produce clinical effects in the newborn. However, this can be achieved only by injecting large doses of the drug into the uterine artery or by using massive intravenous doses, far beyond the usual clinical range. In rabbits, for example, 1,000 times the minimum maternal paralyzing dose is necessary to permit sufficient quantities of succinylcholine to pass the placenta and clinically affect the newborn rabbits.50

**Summary and Conclusions**

Quantitative studies dealing with the uptake and distribution of anesthetic agents in pregnant women are not yet available. Based on the known alterations in cardiopulmonary function that take place during pregnancy, it may be predicted with reasonable confidence, that the uptake of inhalation agents is significantly accelerated. It follows, therefore, that the speed of induction is also more rapid, especially for the highly soluble anesthetics. The hyperventilation of pregnancy reduces the difference between inspired and alveolar tensions by bringing more anesthetic into the lungs. This effect is enhanced by the reduced FRC associated with pregnancy. Of the two factors, increased ventilation and reduced FRC, the effect of ventilation appears to be more important in determining the rate of change in alveolar concentration. The increased cardiac output found during gestation tends to oppose the rise in alveolar concentration by increasing the loss of anesthetic agent to the pulmonary blood.

The concept of a lipoid barrier appears to apply to the transfer of drugs across the pla-
The authors wish to acknowledge the assistance of Dr. Edmond I. Eger, II, who reviewed the manuscript and made many valuable suggestions.

References


ASCORBIC ACID  By means of a radioisotope which quantitates erythrocyte sequestration, the effects of ascorbic acid, low molecular weight dextran, and 5 per cent dextrose primer on erythrocyte sequestration in the microcirculation following extracorporeal circulation in dogs were evaluated. When ascorbic acid was administered, only 4.6 per cent of the erythrocyte mass was sequestered. Ascorbic acid is now being used as the anti-sludging agent in clinical perfusions. (Tanaka, T., and others: Experimental Techniques For the Prevention of Sludging of Erythrocytes in Extracorporeal Circulation. J. Thor. Cardiov. Surg. 49: 275 (Feb.) 1965.)

METABOLIC ALKALOSIS  Metabolic alkalosis postoperatively in surgical patients is due to excessive loss of gastric juice, to aldosteronism, to hypopotassemia or to iatrogenic faults in treatment. It may lead to death. Errors in treatment of this alkalosis are: plasma or plasma expander without free water to combat the hypotonic dehydration and lack of potassium and sodium chloride in the infusion. Avoidance of potassium because of the observed oliguria or because of the paradoxical aciduria are further faults. Potassium is dangerous in renal insufficiency but therapeutic in hypokalemic hypochloremic alkalosis. Another fault is the application of corticosteroids because of circulatory insufficiency which accompanies grave alkalosis and which accelerates death. Metabolic alkalosis with normal potassium may be treated with 0.83 per cent ammonium chloride up to 100 ml. especially if sodium is elevated, or if alkalosis is grave, with 0.1 normal hydrochloric acid intravenously if renal function is impaired. (Sømerkamp, H.: Metabolic Alkalosis as a Problem in Surgical Patients (German), Bruns. Beitr. Klin. Chir. 109: 483 (Dec.) 1964.)