

# Perinatal Pharmacology: Placental Transfer, Fetal Localization, and Neonatal Disposition of Drugs

Bernard L. Mirkin, Ph.D., M.D.\*

THE RESPONSE of mammalian organisms to pharmacologically active molecules appears to be markedly influenced by the maturational status of the cells, tissues, and organ systems affected. Perinatal pharmacology is concerned with the disposition and effects of xenobiotic and endogenous chemicals throughout the entire continuum of development. Thus, events occurring at or near the time of conception, during gestation (prenatal), at parturition (parapartum), and in early extrauterine life (neonatal) all fall within the purview of this discipline.

## Factors Modulating Placental Transfer and Fetal Localization of Drugs

The movement of compounds across the placenta is regulated by many factors, and the bidirectional transfer of molecules between the fetal and maternal circulations is dependent upon the smooth integration of these different processes. For quite obvious reasons, a detailed analysis of placental transfer in man has not been possible because of the ethical and experimental difficulties such studies present. As a consequence, most of the meaningful data relating to the placental transfer of drugs has been obtained from a variety of animal models, and the relevance of such studies for man must be carefully evaluated.

In general, the passage of pharmacologic agents across the placenta is influenced by the physicochemical properties of the drug and the physiologic characteristics of the maternal-placental-fetal unit. The factors that appear most significant in this regard are discussed below.

\*Professor of Pediatrics and Pharmacology; Director, Division of Clinical Pharmacology, University of Minnesota Health Sciences Center, Minneapolis, Minnesota 55455.

Address reprint requests to Dr. Mirkin.

## PHYSICO-CHEMICAL PROPERTIES OF DRUGS

### Lipid Solubility and Extent of Ionization

Drug molecules that are lipophilic and exist primarily in their unionized state at physiologic pH's tend to diffuse more rapidly across the placenta and into the fetal circulation. Compounds such as antipyrine and thiopental, poorly ionized at physiologic pH, traverse the placenta very rapidly. By comparison, bases with high  $pK_a$ 's and acids with low  $pK_a$ 's diffuse across biological membranes quite slowly. Skeletal muscle relaxants, such as succinylcholine and *d*-tubocurarine, which contain quaternary nitrogens, and the sulfated mucopolysaccharides, like heparin, are highly ionized. As a consequence, their transfer across the placenta is extremely retarded, and low concentrations are achieved within the fetal circulation.<sup>1,2</sup>

Some drugs such as the salicylates that are almost completely ionized at pH 7.4 appear to cross the placenta quite rapidly. The reason for this is that even though very small amounts of the molecule exist in an unionized state at physiologic pH, the amount present readily traverses the placenta because of its high lipid solubility.<sup>3</sup>

### Protein Binding

The effect of protein binding on the placental passage of a drug appears to vary markedly in accordance with whether the compound is lipophilic and nonpolar or whether it is lipophobic and highly polar. Compounds in the former category do not appear to be markedly influenced by protein binding, since the transfer of these drugs seems to be proportional to placental blood flow. Those agents that diffuse across the placenta at slower rates, due to their higher degree of ionization and lower lipid solubility, may be significantly affected by protein binding,

since diffusion seems to be rate-limiting for such compounds.

A marked difference in the protein binding of drugs to fetal and maternal sera has been demonstrated. The amount of drug bound to maternal serum proteins is substantially greater than that occurring in fetal serum. This has been shown in both animal and human studies with a variety of compounds, *e.g.*, sulfonamides, barbiturates, hydantoin anticonvulsants, and local anesthetic agents.<sup>4,5</sup> It has been suggested that greater amounts of free drug are available for diffusion across the placenta when protein binding is decreased.

#### *Molecular Weight*

A majority of drugs have molecular weights ranging from 250 to 500 and can cross the placenta quite readily depending on their state of ionization and lipid solubility. Compounds with molecular weights ranging from 500 to 1,000 are generally considered to possess slower rates of transfer than those with lower molecular weights. Recently, it has been demonstrated that digoxin (molecular weight: 792) readily crosses the rodent<sup>6</sup> and human placentas, but not the ovine placenta.<sup>7</sup> Chemical compounds with molecular weights greater than 1,000 have been reported to be severely impeded in their passage across the placenta. It is important to note that certain proteins whose molecular weights exceed 1,000 are able to pass the placenta, and the influence of molecular weight on placental transfer rate constants should be studied further.

#### CHARACTERISTICS OF THE MATERNAL- PLACENTAL-FETAL UNIT

##### *Placental Blood Flow*

The transfer of drugs and other compounds across the placenta is altered by hemodynamic changes in either the maternal or fetal contribution to total placental blood flow. The extent to which highly lipid-soluble drugs cross from the mother to the

fetus appears to be directly proportional to maternal placental blood flow.

Alterations in placental blood flow may be caused by uterine contractions induced by spontaneous labor, removal of amniotic fluid, or oxytocic drugs. Maternal uteroplacental perfusion can be reduced from 85 per cent of total uterine flow to 75 per cent by constriction of myometrial arterioles, as well as by obstruction of the uterine venous outflow during contraction. A placental hypoperfusion state of brief duration may ensue, with marked effects upon drug transfer.

Changes in fetal hemodynamics may also affect drug transfer to and from the fetal environment. The transfer of local anesthetics from the mother to the fetus can significantly depress the fetal circulation so that clearance of these compounds from the fetus is impaired.<sup>8</sup>

The relative *pH*'s of the maternal and fetal circulations modify the placental transfer of drugs, particularly those compounds possessing *pK<sub>a</sub>*'s close to the *pH* of blood. The *pH* of umbilical vessel blood is normally 0.10 to 0.15 *pH* units lower than that of maternal systemic blood; consequently, the concentration of unionized basic drug is higher in the maternal circulation than in the fetal circulation. The net effect of this *pH*-dependent partitioning is an overall transfer of drug from mother to fetus, so that the fetal concentration at equilibrium may exceed that of the mother.

##### *Placental Maturation*

The diffusion rates of a drug parallel the changes in placental function that occur during the life span of this organ. The thickness of the trophoblastic epithelium decreases in the last trimester so that the width of the tissue layer(s) interposed between the fetal capillaries and maternal blood stream decreases from 25 $\mu$  early in gestation to 2 $\mu$  at birth.

Most of the available information relating to drug transfer at different stages in gestation has come from studies in the pregnant rodent. These data suggest that drug transfer is slowest in mid-gestation and most rapid in the first and last trimesters. Before any

†Fehr P, and Mirkin BL: Pharmacokinetics of barbiturate transfer in the ovine maternal-placental-fetal unit (submitted for publication, *Obstet Gynecol*, 1975).

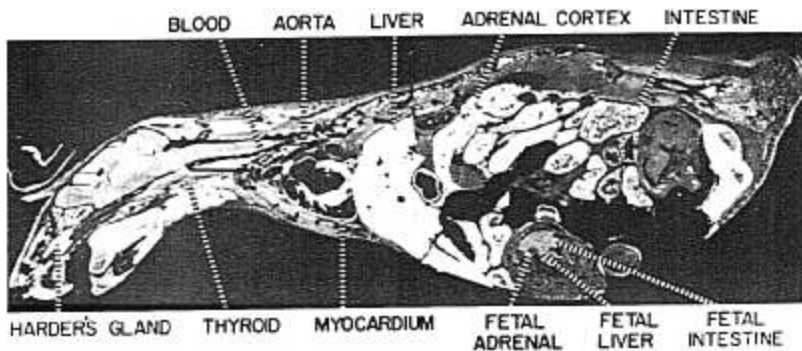


FIG. 1. Distribution of  $^{14}\text{C}$ -diphenylhydantoin in the pregnant mouse. Whole-body autoradiogram 9 hours after an intravenous injection into the mother. White areas correspond to radioactivity. Note the high concentrations in the myocardium, liver, adrenal glands, and intestines of both mother and fetus (Waddell and Mirkin, 1972; reproduced by courtesy of publisher).

generalized conclusions are warranted, much further investigation must be undertaken.

#### Placental Metabolism of Drugs

Numerous aromatic oxidase reactions (e.g., hydroxylation, N-dealkylation and demethylation) can be demonstrated in placental tissue extracts incubated with appropriate substrate(s) *in vitro*. While this metabolic capacity exists beyond any doubt, there is considerable question regarding the physiologic importance of such drug-metabolizing reactions under *in vivo* conditions.

The drug-metabolizing activity of the placenta is significantly lower than that of either the maternal or the fetal liver when compared on a unit weight basis. Thus, the role of the placenta as a site for xenobiotic drug metabolism in the maternal-placental-fetal unit may not be extremely important under *in-vivo* conditions. It should be noted, however, that the role of the placenta with respect to metabolic biotransformation of endogenous substrates such as the steroid hormones is of major biological significance.

#### Fetal Localization of Drugs

Pharmacologically active molecules that have crossed the placenta are carried by the

umbilical vein into the fetal circulation. These substances may undergo biotransformation in the fetal liver, may bypass the fetal liver via the ductus venosus to enter specific fetal structures and/or body compartments, may be eliminated by the fetal kidney into the amniotic fluid and swallowed by the fetus to create an amniotic-enterohepatic recirculation, or may be returned to the maternal circulation through the umbilical artery and placenta.

The fetal distribution of drugs is influenced by the permeability of the membranes surrounding specific organs or body compartments. As a general rule, the diffusion of drugs across these limiting structures is greater during fetal existence than at later stages in maturation. Most drugs have a rather ubiquitous distribution pattern in the fetus. However, unexpectedly high concentrations of some active compounds can accumulate in tissues not normally thought of as primary target organs (Fig. 1).

Diphenylhydantoin, following administration to pregnant mice, develops the highest concentrations in the maternal liver and maternal and fetal hearts, with the brain (ostensibly the primary target organ) having virtually the lowest concentration of any tissue studied. As has been mentioned, the blood-brain barrier is more permeable to

many drugs early in development, and it is surprising to find relatively low concentrations of diphenylhydantoin in the brain of the fetal rat.<sup>9</sup> Since the fetal brain possesses a low myelin content and a high water content, its affinity for lipophilic drugs is decreased, and this may counteract the increased membrane permeability present at this point in ontogenesis.

The overall distribution of drugs in fetal tissues is determined to a large extent by selective tissue uptake. Nonspecific lipid solubility appears to be an important determinant in this regard, since many drugs are concentrated in organs with high lipid fractions (e.g., liver, ovary, and adrenal glands). Thus, the unusually elevated levels of diphenylhydantoin that have been found in the ovary, particularly in the corpora lutea, may reflect the high affinity the compound has for lipids.<sup>9</sup> Other types of specific binding sites may function in selective tissue uptake, and it has been proposed that specialized cellular binding proteins constitute another mechanism for selective drug distribution. An example of this type can be found in the hepatic parenchymal cell, which contains a specific protein responsible for the binding of organic anions. This protein is lacking at particular stages in development and in certain disease states, so that binding is impaired.

The fetal circulation and its pattern of dispersion to different organs play an extremely important role in determining the pattern of drug distribution in the fetus. The quantity of drug delivered to a given organ is directly proportional to the magnitude of its blood flow. All drugs entering the fetal circulation via the umbilical vein are directed to the fetal liver, where blood may be diverted into the portal vein to perfuse the hepatic parenchyma or into the ductus venosus (and perhaps other intrahepatic channels) to bypass the liver and enter the inferior vena cava.<sup>10</sup> The extent to which umbilical venous flow is shunted between these two potential circuits constitutes a major factor in determining the concentration of drug reaching the fetal right heart. These mechanisms are probably of greater importance during the initial passage of a drug through the fetal circulation (e.g., after a

rapid maternal intravenous injection), and would be less significant when steady-state conditions had been established.

Any increase in the quantity of blood flowing through the ductus venosus will decrease the proportion of drug carried to the fetal liver, and probably diminish the amount of drug metabolized immediately following its placental transfer and passage into the fetal circulation. The human fetal liver is able to oxidize numerous drug substrates with surprising effectiveness in comparison with most subhuman species. While the true significance of hepatic drug metabolism by the fetus remains to be elucidated, it is certainly possible that the diversion of drug into the ductus venosus will not only decrease the amount of drug metabolized per unit time but significantly elevate the concentrations of pharmacologically active material presented to the fetal heart and central nervous system. Tissue concentrations (i.e., in the heart and brain) may be significantly higher because of the elevated gradient resulting from higher blood concentrations.

The complexities of drug transfer in the maternal-placental-fetal unit are schematically illustrated in figure 2, and it is well to note that this simplistic model based on existing information will probably require major modifications as new data are acquired.

### Neonatal Disposition of Drugs

Survival of the fetus during its transition from intrauterine to extrauterine existence is dependent upon the maturation of different mechanisms required to establish self-sufficiency. Maternal systems for the elimination of drugs are no longer available, and the neonate must utilize its own, frequently immature, physiologic and biochemical processes for this task. The well-described limitations of the neonate in this regard have led to the generalized and perhaps erroneous belief that most, if not all, therapeutic agents are more toxic to the newborn than to the adult.

### COMPARATIVE TOXICITIES OF DRUGS IN IMMATURE AND ADULT MAMMALS

The pharmacologic potencies of drugs administered in the newborn period are most

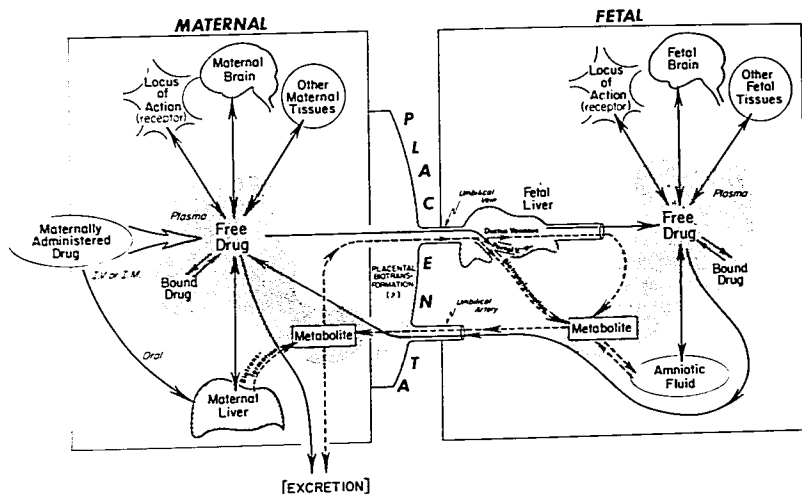


FIG. 2. Schematic representation of drug disposition in the maternal-placental-fetal unit (Mirkin, 1973; reproduced by permission of publisher).

easily compared by obtaining their respective  $LD_{50}$ 's. It should be recognized that this type of experimental approach is relatively nonspecific, compares only acute toxicity, may not identify the mechanism of action, and tends to distinguish gross differences rather than subtle ones.

Central nervous system depressants such as chloral hydrate, phenobarbital, meprobamate, and chlorpromazine appear to be more toxic to the neonate than to the adult. Analgesics derived from the morphine alkaloids also follow this pattern, whereas meperidine has about the same  $LD_{50}$  in both newborn and mature animals. In contrast, central nervous system stimulants such as strychnine, d-amphetamine and pentylenetetrazol (Metrazol) have significantly lower  $LD_{50}$ 's in the neonatal than in the adult rat (see table 1).

These toxicity data indicate that the neonatal animal should not be categorized as uniformly more sensitive to, or indeed more susceptible to, the toxic effects of a particular

drug or group of drugs. It has become increasingly important, therefore, to identify those processes that modulate drug disposition in developing organisms, so that more accurate predictions of pharmacologic reactivity can be achieved.

#### FACTORS INFLUENCING ABSORPTION, DISTRIBUTION, METABOLISM AND EXCRETION

All pharmacologically active compounds entering the body are involved in a rather complex series of reactions, collectively designated the process of drug disposition. Extensive modification of these interrelated processes occurs during mammalian development. A major task for perinatal pharmacology is the identification of meaningful correlations which may exist between changes in functional capability and biologic maturation, particularly as they relate to pharmacologic reactivity. Each of the primary determinants of drug disposition is discussed from this viewpoint.

*Absorption*

The movement of a drug from its site of administration into the systemic circulation is generally considered to constitute the process of absorption. It determines the quantity and rate at which a drug enters the blood stream. Most drugs traverse biologic membranes exclusively by simple diffusion, and the transfer rates of such compounds are concentration-related. Specific physicochemical characteristics of the drug molecule and biological properties of the organism play significant roles in these kinetic events.

The major factors that appear to regulate absorption are the following.

*Physicochemical characteristics of the drug molecule (pK<sub>a</sub>, lipid solubility, molecular weight):* Compounds possessing high lipid solubility or pK<sub>a</sub>'s that allow large proportions of their molecules to exist in the unionized state at the site of absorption will be readily absorbed. Thus, acidic or basic drugs with low pK<sub>a</sub>'s (e.g., acetylsalicylic acid, pK<sub>a</sub> 3.5; caffeine, pK<sub>a</sub> 0.8) will be readily absorbed in the acidic environment of

the stomach but less well absorbed in the more alkaline milieu of the small intestine.

*Characteristics of the membrane(s) a drug must cross before entering the circulation:* Since most membranes are lipoprotein in composition, compounds with high lipid solubility tend to pass through more readily. This appears to be important, not only for absorption from the gastrointestinal tract, but for absorption from the skin and lungs as well.

*Blood flow at the site of administration:* The rate of removal of a drug from an intramuscular or subcutaneous locus is to a large extent blood-flow-limited. Most molecules cross the capillary membranes by either diffusion or filtration; diffusion is the dominant mode of transfer for lipid-soluble drugs, whereas non-lipid-soluble compounds are filtered across the capillary wall. Most drugs, regardless of lipid solubility, traverse capillary walls at rates that far exceed those observed with other membranes. Consequently, the uptake of drug from a parenteral site of administration is more likely to be blood-flow-limited than to be diffusion-

TABLE 1. Comparison of Acute Drug Toxicity in the Newborn and the Adult Rat

	Route of Administration	Toxicity Ratio $\left[ \frac{\text{Adult LD}_{50}}{\text{Neonatal LD}_{50}} \right]$
<i>More toxic to the newborn</i>		
Chloral hydrate	Oral	1.8
Acetylsalicylic acid	Oral	2.7
Desipramine	Oral	2.5
Phenobarbital	Oral	2.6
Chlorpromazine	Intraperitoneal	4.2
Meprobamate	Oral	4.3
Morphine	Intraperitoneal	6.4
Picrotoxin	Intraperitoneal	6.0
Dicumarol	Oral	10.4
<i>Equally or less toxic to the newborn</i>		
d-Amphetamine	Oral	0.5
Strychnine	Subcutaneous	0.4
Pentylenetetrazol	Subcutaneous	0.6
Mercurial diuretics	Subcutaneous	0.6
Isopropylnorepinephrine	Oral	0.6
Codeine	Subcutaneous	0.7
Menadiolone	Intraperitoneal	0.9
Meperidine	Intraperitoneal	1.0
Digitalis	Intravenous	0.6-1.0

Adapted from Yeary.<sup>11</sup>

regulated. Cardiovascular shock, local vasoconstriction (e.g., following sympathomimetic agents), and impaired regional perfusion (e.g., as occurs in diabetes or intrapulmonary shunting) are clinical situations in which drug uptake or absorption from a particular site is diminished due to restricted blood flow.

Significant biochemical and physiologic changes occur in the human neonatal gastrointestinal tract shortly after parturition. There is a marked increase in gastric acidity, a prolongation of gastrointestinal transit time, and an increase in membrane permeability to specific substrates. Each modification in function exerts a marked effect upon the rate and extent of drug absorption, which ultimately influences the duration and intensity of drug action.

Compounds partially or totally inactivated by the low pH of the gastric contents (e.g., penicillin G, insulin) cannot be administered via the oral route if a satisfactory therapeutic response is desired. Any change in gastrointestinal transit time also exerts an important effect on the extent of drug absorption. Shortening of the gastric emptying time tends substantially to increase overall absorption, as it leads to a more rapid entry of drug into the lower gastrointestinal tract, with its greater absorptive surface area. Compounds with low  $pK_a$ 's (e.g., salicylate), which appear to be in a disadvantageous position insofar as their partitioning is concerned, manifest enhanced absorption when the gastric emptying time is decreased. An increase in lower gastrointestinal tract motility, such as may occur in diarrheal conditions, tends to decrease overall absorption, since contact time with this large absorptive area is diminished. Thus, the bioavailability of many pharmacologically active molecules may be substantially modified by developmental changes that affect gastrointestinal motility and physiology.

The newborn is able to absorb a wide variety of chemical substances better than or as well as the adult. Some differences in absorption between premature and full-term infants following administration of suspensions containing equivalent doses (mg/kg) of sulfonamide have also been reported. The

premature infants developed lower peak blood levels and appeared to absorb the sulfonamide less efficiently than full-term infants. Riboflavin is also absorbed to a much greater extent in older infants than it is in less mature newborns.<sup>12</sup> This difference has been attributed to a deficiency in the active transport system required for movement of riboflavin across the intestinal membranes of the neonate.

A wide variety of antibiotic agents has been studied in sick infants, and the absorption patterns of these agents have been determined. Penicillin (procaine or phenoxyl) is well absorbed from the gastrointestinal tract of the neonate (premature and full-term); slightly higher blood concentrations have been found in the premature infant. Serum levels of nafcillin and ampicillin are much higher in the human neonate than in adults receiving comparable (mg/kg) doses. The percentage of ampicillin absorbed in the newborn also seems to be considerably greater, with about 66 per cent of the dose absorbed compared with 30 per cent in the adult.

The penicillins, tetracyclines, cephalosporins and their semisynthetic derivatives, as well as chloramphenicol, appear to be well absorbed in young infants. Therapeutically effective serum concentrations that persist for prolonged periods can be readily achieved by this route of administration. This pharmacokinetic pattern is attributable to the faster absorption as well as to the lesser capacity for renal elimination and hepatic degradation in the neonate.

Other types of therapeutic agents, such as digoxin, are quite well absorbed in the newborn, and recent studies suggest an uptake pattern in infants that resembles that of the adult.<sup>13</sup> Peak serum levels of the cardiac glycoside occur one hour after an oral dose, with excellent absorption observed even in the presence of severe congestive heart failure (Fig. 3). In addition to the aforementioned drugs, comprehensive data describing absorptive patterns in the newborn have been described for the following compounds: anticonvulsants (phenobarbital, diphenylhydantoin, diazepam); acetylsalicylic acid; aminophylline; cardiovascular agents (pro-

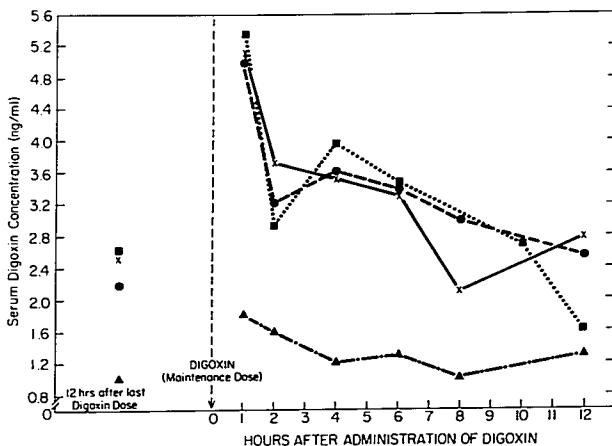


FIG. 3. Serum digoxin concentrations following administration of digoxin by oral and parenteral routes. Control levels (left of vertical dotted line) were obtained 12 hours after administering the last dose of digoxin and prior to the next digoxin half-daily maintenance dose (HDM). Serum digoxin concentration is shown in ng/ml:  $\blacktriangle$ — $\bullet$ — $\bullet$ — $\blacktriangle$  Group I (oral; HDM:  $0.005 \pm 0.0015$  mg/kg);  $\times$ — $\times$ — $\times$  Group II (oral; HDM:  $0.011 \pm 0.0002$  mg/kg);  $\bullet$ — $\bullet$ — $\bullet$  Group III (im; HDM:  $0.010 \pm 0.0006$  mg/kg);  $\square$ — $\square$ — $\square$  Group IV (iv; HDM:  $0.009 \pm 0.0026$  mg/kg) (Larese and Mirkin, 1974; reproduced by permission of publisher).

pranolol). While these examples differ significantly with respect to the mechanisms involved, they clearly illustrate that the absorption of different types of substrates from the gastrointestinal lumen may be modified by biological maturation.

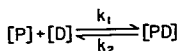
Drug absorption from other sites must be considered, particularly since they are frequently used in the treatment of sick infants. The mottling of skin commonly observed in the newborn reflects vasomotor instability, and has promoted concern that the newborn infant may resemble the diabetic patient in manifesting delayed uptake or absorption of drugs from intramuscular sites of administration. Experiments utilizing neonatal and adult animals have shown the rates of disappearance of morphine from an intramuscular site of administration to be the same in the two age groups.<sup>14</sup> Comparable assessments in man have not been made, but certainly the therapeutic effectiveness of intramuscular injections in young infants and neonates has been extensively documented.

#### Distribution

This process regulates the concentration of drug achieved in a specific body compartment or tissue, and thereby influences the quantity of drug reaching a desired site of action. Many factors influence the distribution pattern of a pharmacologic agent, among which tissue mass, blood flow, lipid content, and permeability of the membranes surrounding the tissue appear to be most important. Chemical compounds generally enter muscle, bone, and visceral structures more slowly than highly perfused organs (*e.g.*, liver, kidney, and brain). Despite the limitations described, the relative mass of muscular and visceral structures is so great that any significant uptake by these tissues can greatly modify the overall distribution of drugs in the body.

The composition of the tissues into which drugs distribute is very important in determining the volume of distribution of a drug. The human neonate has a much higher



PROTEIN BINDING OF DRUGS

[P] = free protein concentration

[D] = free drug concentration

[PD] = drug-protein complex concentration

At equilibrium:

$$k_1 [P] [D] = k_2 [PD]$$

$$\frac{[PD]}{[P] [D]} = \frac{k_1}{k_2} = K = \text{association or affinity constant}$$

FIG. 4. Equilibrium reaction describing formation of drug-protein complex.

proportion of its body mass in the form of water than the adult. A difference between full-term infants (70 per cent of body weight as water) and small premature infants (85 per cent of body weight as water) can also be observed. Furthermore, the premature infant has a much smaller total fat content, so organs that generally accumulate high concentrations of lipophilic drugs in adults and older children may have less affinity for such compounds in these less mature subjects.

While membrane permeability is frequently considered to be greater in immature mammals, comparative pharmacologic studies have revealed very significant differences among species. Consequently, considerable attention should be given to the animal model utilized in a given study. The rat, rabbit and chicken have high degrees of permeability to drugs, in terms of movement from the blood stream to the brain, whereas the guinea pig is much more resistant to such transfer at birth. Autoradiographic studies have demonstrated that a drug such as phenobarbital enters the white matter of the kitten's brain much more readily than that of the adult cat. The alleged basis for this is that as myelination becomes more complete during ontogenesis, it concurrently leads to a decreased ease of drug transfer across the blood-brain interface.<sup>15</sup>

Young rats (16 days postnatal) have lower

LD<sub>50</sub>'s and are more sensitive to morphine than older rats (32 days postnatal). Brain concentrations of morphine determined at equivalent intervals after injection are two to four times greater in the 16-day-old rats than in the 32-day-old animals. Interestingly, the LD<sub>50</sub>'s of meperidine and heroin did not change with increasing age. This distinction has been attributed to the low lipid solubilities of the latter compounds and their relatively poor affinities for the central nervous system, at least when compared with morphine.<sup>14</sup> A somewhat comparable study has been carried out in the human neonate, which was approximately ten times more sensitive to the respiratory depressant effects of morphine than to those of meperidine, when the two compounds were administered in equianalgesic doses.<sup>16</sup>

It should be emphasized that the increased toxicities of certain analgesics in the young mammal may not be exclusively related to their accumulation in the brain. The concentrations of both morphine and meperidine in the neonatal rat brain are about two or three times those in the adult; however, the neonatal LD<sub>50</sub> for meperidine is similar to that of the adult. Therefore, the greater toxicity of morphine in the less mature mammal may also reflect an increased sensitivity of specific receptors in the brain to the compound.<sup>17,18</sup>

Another major factor that influences drug distribution is the extent to which the compound is protein-bound. The extent to which drugs are bound to plasma proteins of the fetus and neonate is less than that observed in the adult. Consequently, a greater proportion of the drug is present in its unbound or free form, and available for diffusion. The general equilibrium equation for drug-protein interactions is illustrated in figure 4. Drugs that have high affinity constants (*i.e.*, K<sub>1</sub> considerably greater than K<sub>2</sub>) will tend to have low volumes of distribution due to retention within the plasma compartment, whereas the converse is true when the affinity constant is low.

#### Metabolism

Drugs may act as substrates for a wide variety of mammalian enzyme systems, and the metabolism or biotransformation of

pharmacologically active agents constitutes a major mechanism for the termination of drug action. Since most drugs exist mainly in their nonpolar states at physiologic pH, they are able to penetrate membranes that delineate body compartments and also tend to undergo reabsorption by the renal tubule. The biochemical reactions that xenobiotic compounds undergo convert them to more polar compounds, thereby decreasing their lipid solubility and enhancing their water solubility, so that clearance from the organism is enhanced.

The process of biotransformation occurs primarily in the liver, and more specifically involves the drug-metabolizing system of the hepatic endoplasmic reticulum. Microsomal fractions isolated from liver homogenates contain most of the drug-metabolizing activity of this organ. The microsomal enzyme system can catalyze an extraordinary number of metabolic reactions, which are mainly oxidative in nature but also include reductive and conjugating reactions. A drug commonly undergoes two or three such reactions before it is cleared from the organism.

The versatility of the liver appears somewhat less remarkable if the drug metabolizing reactions are visualized as simply representing different types of hydroxylation reactions. From this perspective, the microsomal drug-metabolizing system can be considered to represent a mixed-function oxidase system in which the key components are NADPH, NADPH-cytochrome C reductase (the flavin enzyme that oxidizes NADPH), cytochrome P-450, and NADPH-cytochrome P-450 reductase.

The ontogenesis of drug-metabolizing activity has been studied in many mammalian species utilizing both *in-vivo* and *in-vitro* techniques. As a rule, the capacity for drug metabolism in the early neonatal period is substantially less than that present in later stages of postnatal development. The point in development at which enzymatic activity is maximal depends, of course, on the enzymatic system under investigation. Certain reactions such as sulfuration and glucuronidation achieve levels of activity during neonatal life that are much greater than those occurring in the adult.

One of the earliest reports in which the

ontogenesis of drug metabolism was studied used homogenates prepared from the livers of guinea pigs and rats of various ages. This investigation revealed that newborn guinea pigs had virtually no capacity for carrying out N-dealkylation, side-chain oxidation, or glucuronidation,<sup>19</sup> nor did rats or rabbits.<sup>20</sup> These observations are of great historical interest since parallel studies performed with specimens of human fetal and neonatal liver also confirmed the presence of low enzymatic activity and the absence of cytochrome P-450 in such tissues. For more than a decade, it appeared as if the human fetus and neonate also possessed an extremely impaired capability for the biotransformation of drugs. Consequently, data published between 1970 and 1972 showing that extracts of human fetal liver contained quantities of cytochrome P-450 and NADPH-cytochrome C reductase sufficient to catalyze drug-metabolism reactions were extremely surprising, in view of the many investigations in which cytochrome P-450 and cytochrome P-450-dependent reactions were not detectable.

Subsequent studies explained why the very significant discrepancy between later investigations and earlier efforts had arisen.<sup>21</sup> In essence, it was demonstrated that the sedimentation characteristics of fetal liver homogenates differed markedly from those of adult livers. The fetal liver was more resistant to homogenization than that of the adult, and the highest enzymatic activity was obtained in the low-speed centrifugation fractions, whereas, with the adult liver, maximum activity was observed in the high-speed fraction. When the appropriate fractions were studied, the enzyme levels in fetal and adult livers were found to be quite comparable when expressed either as activity or as amount per gram of liver tissue. In the fetus,  $8.6 \pm 1.7$  nmoles of cytochrome P-450 were present, compared with 10.0 nmoles in the adult. The activity of NADPH-cytochrome C reductase was  $1,620 \pm 320$  in the fetus and 2,000 in the adult (expressed as nmoles cytochrome C reduced per minute). These similarities are even more striking when one recognizes that the human fetal liver constitutes about 4 per cent of the total body weight, compared with 2 per cent in the adult. An important lesson to be learned from

this experience is that direct extrapolation of animal data to man is not without hazard.

Another major aspect of drug metabolism in mammalian organisms is that related to the phenomenon of enzyme induction. In the present context it refers to any increase in drug-metabolizing activity that can be attributed to the prior administration of a specific drug molecule. It is not certain whether this is due to an enhancement of pre-existing enzymatic activity or *de novo* synthesis of new enzyme provoked by administration of the xenobiotic agent.

The induction of hepatic microsomal systems has been extensively investigated. As early as 1960, a significant increase in glucuronyl transferase activity was observed in the livers of newborn rats and guinea pigs given injections of benzpyrene. When the same experiment was performed with fetal livers obtained from pregnant rats receiving benzpyrene, no induction of enzymatic activity was noted. Studies carried out in pregnant rabbits given phenobarbital also demonstrated no enzyme induction in homogenates of fetal livers obtained more than four or five days prior to parturition. This species was similar to the rat, in that induction was achieved only when the inducing agent was administered during the last few days of gestation, but not earlier.

The effects of drugs with known inducing actions have been studied in pregnant women. It is clear that the elimination of bilirubin is facilitated and serum bilirubin levels are decreased in neonatal infants delivered from mothers receiving phenobarbital intrapartum. This has generally been assumed to reflect an increase in glucuronyl transferase activity in the human neonate. Current studies from England have suggested that while bilirubin levels are decreased, glucuronyl transferase activity may not be altered significantly (Davies *et al.*, personal communication, 1974). Consequently, one must question whether the inducing action of phenobarbital also affects hepatic transport and clearance mechanisms rather than only conjugation of this particular substrate.

### Excretion

While many routes of drug elimination exist in the body, such as the skin, the respiratory tract, and the biliary system, the dominant pathway is that of renal excretion. It should be noted that both non-metabolized and metabolized drugs may be removed from the body via the kidney. Therefore, any impairment of renal function sufficient to cause renal insufficiency, whether it results from pathophysiologic or maturational phenomena, can significantly alter the rate of removal of a given drug from the body. Prolongation of a drug's action by extending its serum or tissue half-life may increase its overall toxicity. As a result, in the presence of renal insufficiency it may be necessary to use lower drug doses to obtain a satisfactory therapeutic response.

Glomerular filtration in the human neonate is approximately 30 to 40 per cent and tubular secretion 20 to 30 per cent that of the adult when calculated on the basis of 1.73 m<sup>2</sup> surface area. A substantial increase in function occurs during the initial five postpartum days in the human infant. On day 5, glomerular filtration rate and renal plasma flow have increased 50 per cent from the initial postpartum period; on the seventh postpartum day, glomerular filtration is approximately 50 per cent of the adult value, and by 12 months it is equal to that of the adult.

The clearance rates of compounds primarily dependent upon the kidney for elimination tend to be significantly lower in the neonate. Penicillin, for example, is cleared from premature infants at a rate which is 17 per cent that of the adult when compared on the basis of surface areas and 34 per cent when adjusted to body weight. Decreased rates of renal elimination have also been observed with other semisynthetic penicillin derivatives (*e.g.*, ampicillin, methacillin, cephaloridine and oxacillin) and aminoglycoside antibiotics (*e.g.*, kanamycin, neomycin and streptomycin) in the neonate. Total body clearance of digoxin is directly dependent upon adequate renal function, and accumulation can occur in circumstances where glomerular filtration is decreased. Despite

this, however, it is worth recalling that the dose of digoxin required for an adequate therapeutic response in the newborn is twice that administered to the adult on a mg/kg basis.

### Pharmacokinetics in the Maternal- Placental-Fetal Unit†

#### BARBITURIC ACID DERIVATIVES

Most of the pharmacologically active derivatives of barbituric acid that have been studied can traverse the mammalian placenta with relative ease. Equilibrium between the maternal and fetal circulations is established within minutes in most circumstances.<sup>22,23†</sup>

The kinetics of barbiturate transfer across the placenta are markedly influenced by the specific physicochemical characteristics of the agent under investigation. Compounds in this class as a rule have rather low molecular weights, are weak acids, and exist to a large extent in the unionized state at physiologic pH, which further enhances lipid solubility. Fehr and Mirkin† demonstrated significant differences in placental transfer rates among a homologous series of barbituric acid derivatives. Pentobarbital ( $pK_a$ , 8.02) diffused more readily than amobarbital ( $pK_a$ , 7.78) even though they possess similar partition coefficients. In contrast, amobarbital, which has greater lipid solubility than butethal, diffused across the placenta more rapidly, despite the fact that the two compounds have similar  $pK_a$ 's.

#### Thiobarbiturates

The thiobarbiturates are very lipid-soluble and readily diffuse across the placenta. While there is some delay in their passage from the maternal circulation to the fetal environment, these compounds can be detected in the fetal circulation a few minutes after injection into the mother. Following a single pulse dose, the maternal blood level falls very rapidly, as

†A detailed review of this topic is presented in Mirkin BL (editor): Perinatal Pharmacology. New York, Academic Press, in press 1975 (chapter 1).

does the maternal-fetal concentration gradient, so that the total amount of drug transferred across the placenta is limited by these factors.<sup>24</sup> Barbituric acid derivatives such as phenobarbital, which sustain elevated maternal blood levels over longer periods, generally achieve higher total concentrations in fetal tissues.

Studies in pregnant mice have shown that tissue concentrations in the fetus peak 10 minutes after a maternal injection, with the fetal liver, brain and lung accumulating most of the drug. The drug levels in these tissues remain relatively constant over a 60-minute period, with the exception of the brain, in which further accumulation appears to occur.<sup>25</sup>

In man, the fetal liver also appears to take up a major proportion of most barbiturates that enter directly into the fetal circulation. The distribution of thiopental in two anencephalic fetuses has been studied after intravenous administration of the drug to the mother. Subcutaneous tissue was found to contain the highest concentrations of thiopental (88.0 and 43.3  $\mu\text{g/g}$ ), with substantial amounts in the liver (38.0 and 65.0  $\mu\text{g/g}$ ), and the lowest levels in the spinal cord. These data have been used to support the view that the fetal liver prevents the fetal brain from exposure to high concentrations of drugs entering the fetal circulation via placental transfer or by direct transuterine administration to the fetus. Explicit experimental confirmation of this hypothesis is lacking (see section on Fetal Localization of Drugs).

#### Other Barbiturates

Secobarbital readily moves across the human placenta, and an apparent equilibrium state between maternal and fetal circulations is established within 4 to 5 minutes.<sup>23</sup> The ratio between mixed umbilical cord and maternal serum concentrations of secobarbital is less than 0.35 after 2 minutes, increasing to 0.71 after 3 minutes. The fetus rarely develops a blood level greater than 20 per cent of the initial maternal secobarbital concentration, and levels in cord blood appear to

correlate poorly with the extent of neonatal depression.

Recently, the umbilical cord and maternal plasma levels of amobarbital were shown to be identical in subjects delivered at various times after maternal drug administration.<sup>26</sup> The mean maternal and fetal plasma amobarbital levels were  $1.91 \pm 0.35$  and  $1.61 \pm 0.30$   $\mu\text{g/ml}$ , respectively. As anticipated, the average plasma half-life of this drug in newborn infants was  $38.9 \pm 4.8$  hours, or two and a half times greater than that of their mothers, which was  $15.8 \pm 1.7$  hours. Amobarbital is eliminated primarily by conversion to hydroxy-amobarbital; this metabolite can be found in the blood of mothers and infants who have received the parent compound.

Fehr and Mirkin† have demonstrated that an equilibrium state between the maternal and fetal circulations may be established 20 minutes after intravenous administration of amobarbital (5 mg/kg) to the pregnant ewe. Low concentrations of amobarbital were detected in both maternal and fetal plasmas for six and a half hours, with reversal of the placental gradient discernible late in this period. Fetal plasma concentrations were only 50 to 60 per cent of corresponding maternal levels under experimental conditions in which steady-state blood levels were maintained by constant infusions of drug.

#### Long-acting Barbiturates

Umbilical cord blood levels of phenobarbital in infants delivered from epileptic mothers treated with phenobarbital or primidone during pregnancy are identical to maternal values.<sup>27</sup>

A neonatal barbiturate withdrawal syndrome with symptoms closely resembling those observed during narcotic abstinence has recently been described.<sup>28,29</sup> In one study of 15 infants who manifested neonatal barbiturate withdrawal, a majority of the subjects had normal birth weights and satisfactory one-minute Apgar scores. The most common symptoms noted were overactivity, restlessness, disturbed sleep, excessive crying, tremors, hyperreflexia, and hypertonia. The acute episode was followed by a subacute phase of hyperphagia, periods of prolonged crying, episodic irritability, hyperacusis and sweating, which persisted for several months. In general, the onset of

these symptoms occurred later than onset in a control group of infants delivered from narcotic-addicted mothers.

#### NARCOTIC ANALGESICS

The placental transfer of narcotics from the mother to the fetus has been well described in the pediatric literature, and is based primarily on detailed clinical observation.<sup>30</sup> Changes in the rate and rhythm of the fetal heart, pin-point pupils, addiction of the fetus *in utero*, the presence of withdrawal symptoms in infants born to addicted mothers, as well as respiratory depression at birth, have all been clearly documented.<sup>31</sup>

Despite the plethora of qualitative data describing the placental passage of narcotic agents, quantitative information regarding man is extraordinarily scarce. Fetal distribution has been studied primarily in subhuman species, although the presence of narcotic drugs in biologic fluids obtained from the human fetus has been reported by several investigators (*vide infra*).

#### Morphine

Sanner and Woods<sup>32</sup> demonstrated that <sup>3</sup>H-dihydromorphine rapidly crossed the rat placenta when the drug was administered to the mother. Equilibrium between maternal and fetal plasma <sup>3</sup>H-dihydromorphine concentrations was established two hours after injection, with maternal levels approximately two and a half times greater than those assayed in corresponding fetal plasma samples. Despite the markedly lower drug levels observed in fetal plasma, the <sup>3</sup>H-dihydromorphine content ( $\mu\text{g/g}$ ) of fetal brain was approximately three times that of the maternal brain. Conjugated <sup>3</sup>H-dihydromorphine could not be detected in maternal brain specimens even after 16 hours, but low concentrations of the conjugate were present in fetal brain two hours after injection. These data implied that the fetal distribution of <sup>3</sup>H-dihydromorphine and its metabolite(s) differed significantly from that of the adult.

Inturrisi *et al.*<sup>33</sup> have shown that methadone crosses the placenta in man, and the compound has been identified in amniotic fluid as early as the sixteenth week of gestation. Maternal plasma concentrations of

methadone ranged from 0.005 to 0.48 mg/ml, compared with umbilical cord plasma levels, which ranged from 0.03 to 0.25 mg/ml, and those of amniotic fluid, 0.07 to 0.39 mg/ml (all specimens obtained at equivalent time periods). The ratio of umbilical cord to maternal plasma concentrations was 0.60 and the amniotic fluid to maternal plasma ratio was 0.73, confirming the view that maternal plasma levels of methadone are generally higher than those in fetal plasma and amniotic fluid. Infants delivered from these addicted mothers excreted methadone in their urine for at least three days following birth.

### Meperidine

Pharmacokinetic studies carried out in the pregnant ewe have revealed that fetal blood levels of meperidine peak less than 10 minutes after an intravenous infusion. Serum concentrations in the fetus are generally higher than those assayed in corresponding maternal plasma specimens. There appears to be no lag phase in removal of the drug from the fetal circulation since the elimination curves from both the maternal and fetal circulations are parallel exponential functions.<sup>34</sup>

Meperidine has been extracted and qualitatively determined in urine<sup>16</sup> and blood obtained from neonates following maternal administration of the drug.<sup>25</sup> The kinetics of placental transfer in man have been described by Crawford and Rudefsky,<sup>36</sup> who found meperidine in fetal blood 2 minutes after intravenous administration to the mother. In contrast to the data of Jenkins *et al.*<sup>34</sup> and Apgar *et al.*,<sup>25</sup> none of the fetal meperidine plasma concentrations reported in this study exceeded the corresponding maternal level. The ratio of maternal to fetal plasma concentrations in the initial minutes after injection was 3:1, and this value approached unity as a function of time.

Marked differences in the amount of drug excreted by the neonate have been observed, depending upon whether the mother received the compound intravenously or intramuscularly. Following 50-mg maternal doses of meperidine, the mean urinary excretion of meperidine in neonates was 151  $\mu$ g when the drug was given intramuscularly, compared with 431  $\mu$ g when administered intravenously. If these data are quantitatively

accurate (*i.e.*, truly represent total clearance by the neonate) they suggest that less than 1 per cent of the meperidine given intramuscularly reached the fetus. This observation may explain the frequently cited "clinical rule" that adverse effects in the neonate, such as diminished respiratory minute volume and decreased oxygen saturation,<sup>37</sup> are observed when meperidine is given two to three hours prior to delivery, but not when it is administered within one hour of parturition by the intramuscular route.<sup>38,39</sup>

### Pentazocine

The analgesic properties of pentazocine are equivalent to those of meperidine. It has been proposed as a satisfactory alternative for producing obstetric analgesia.<sup>40</sup> This agent crosses the placenta less readily than meperidine, and the ratio of fetal to maternal blood concentrations is 0.6.<sup>41,42</sup> The fetal blood levels of pentazocine have not been reported to be higher than corresponding maternal drug concentrations in any of the published studies. It is clinically important to note that the adverse effects of pentazocine, particularly respiratory depression, do not differ significantly from those of meperidine when the former compound is utilized in equipotent doses.<sup>43,44</sup>

The author received partial support from USPHS grant HD 08580 (NICHD) during the preparation of this manuscript.

### References

1. Cohen EN: Thiopental-curare-nitrous oxide anesthesia for cesarean section, 1950-1960. *Anesth Analg* (Cleve) 41:122, 1962
2. Kivalo I, Saarikoski S: Placental transmission and foetal uptake of C<sup>14</sup>-dimethyltubocurarine. *Br J Anaesth* 44:557, 1972
3. Oh Y: Determination of drug transfer across biological membranes: Comparative study on the passage of drugs into the central nervous system and their placental transfer and fetal localization in the pregnant rat. Ph.D. Thesis, Graduate School, University of Minnesota, 1973.
4. Mathers LE, Climie CR, Thomas J: Maternal plasma levels and placental transfer of bupivacaine following epidural analgesia. *Br J Anaesth* 41:1035, 1969
5. Shoeman DW, Kauffman RE, Azarnoff D, et al: Placental transfer of diphenylhydantoin in the goat. *Biochem Pharmacol* 21:1237, 1972
6. Singh S, Mirkin B: Placental transfer and pharmacokinetics of digoxin in the pregnant rat. *Proc Fifth Int Congr Pharmacol*, 1972, p 215

7. Singh S, Fehr P, Mirkin BL: Placental transfer and pharmacokinetics of digoxin in the pregnant ewe. *Pediatr Res* 7:318, 1973
8. Heymann MA: Interrelations of fetal circulation and the placental transfer of drugs. *Developmental Pharmacology Symposium*. Edited by BL Mirkin. *Fed Proc* 37:44, 1972
9. Waddell WJ, Mirkin BL: Distribution and metabolism of diphenylhydantoin-C<sup>14</sup> in fetal and maternal tissues of the pregnant mouse. *Biochem Pharmacol* 21:547, 1972
10. Meyer WW, Lind J: Über die Struktur und den Verschlussmechanismus des ductus venosus. *Z Zellforsch* 67:390, 1965
11. Yeary RA: Drug toxicity in newborn animals. *Appl Ther* 9:918, 1967
12. Yaffe S, Juchau M: Perinatal pharmacology. *Annu Rev Pharmacol* 14:219, 1974
13. Laresse R, Mirkin BL: Kinetics of digoxin absorption and relation of serum levels to cardiac arrhythmias in children. *Clin Pharmacol Ther* 15:387, 1974
14. Kupferberg H, Way E: Pharmacologic basis for the increased sensitivity of the newborn rat to morphine. *J Pharmacol Exp Ther* 141:105, 1963
15. Domek NS, Barlow CF, Roth LH: An ontogenetic study of phenobarbital-C<sup>14</sup> in cat brain. *J Pharmacol Exp Ther* 130:285, 1960
16. Way W, Costley E, Way E: Respiratory sensitivity of the newborn infant to meperidine and morphine. *Clin Pharmacol Ther* 6:454, 1965
17. Bopp B, Kupferberg H: Distribution and toxicity of a series of 4-phenyl piperidine narcotic analgesics in maturing rats. *Fed Proc* 28:609, 1969
18. Mirkin BL: Developmental pharmacology. *Annu Rev Pharmacol* 10:255, 1970
19. Jondorf W, Maikel R, Brodie B: Inability of newborn mice and guinea pigs to metabolize drugs. *Biochem Pharmacol* 1:352, 1958
20. Fouts JR: Hepatic microsomal drug metabolism in the perinatal period. *Diagnosis and Treatment of Fetal Disorders*. Edited by K Adamson. New York, Springer-Verlag, 1968, p 291.
21. Ackerman E, Rane A, Ericsson J: The liver microsomal system in the human fetus: Distribution in different centrifugal fractions. *Clin Pharmacol Ther* 13:652, 1972
22. Flowers CE: The placental transmission of barbiturates and thiobarbiturates and their pharmacological action on the mother and infant. *Am J Obstet Gynecol* 78:730, 1959
23. Root B, Eichner E, Sunshine I: Blood secobarbital levels and their clinical correlation in mothers and newborn infants. *Am J Obstet Gynecol* 81:948, 1961
24. Kosaka Y, Takahashi T, Mark L: Intravenous thiobarbiturate anesthesia for cesarean section. *ANESTHESIOLOGY* 31: 489, 1969
25. Cassano BC, Ghetti B, Gliozzi E, et al: Autoradiographic distribution study of "short acting" and "long acting" barbiturates. *Br J Anaesth* 39:11, 1967
26. Krauer B, Draffin GH, Williams FM, et al: Elimination kinetics of amobarbital in mothers and their newborn infants. *Clin Pharmacol Ther* 14:442, 1974
27. Melchior JC: Placental transfer of phenobarbitone in epileptic women and elimination in newborns. *Lancet*, October 1967, p 860
28. Blyer WA, Marshal RE: Barbiturate withdrawal syndrome in a passively addicted infant. *JAMA* 221:185, 1972
29. Desmond MM, Schwanecke RP, Wilson GS, et al: Maternal barbiturate utilization and neonatal withdrawal symptomatology. *J Pediatr* 80:190, 1972
30. Shute E, Davis ME: The effect on the infant of morphine administered in labour. *Surg Gynecol Obstet* 57:727, 1933.
31. Zelson C: Infant of the addicted mother. *N Engl J Med* 288:1293, 1973
32. Sanner JH, Woods LA: Comparative distribution of tritium labelled dihydromorphine between maternal and fetal rats. *J Pharmacol Exp Ther* 148:176, 1965
33. Inturrisi CE, Blinick G, Lipsitz PJ: Methadone levels in human maternal, fetal and newborn biofluids. *Pharmacologist* 15 #2, fall 1973
34. Jenkins VR, Talbert WM, Dilts PV: Placental transfer of meperidine hydrochloride. *Obstet Gynecol* 39:254, 1972
35. Appar V, Burns JJ, Brodie BB, et al: The transmission of meperidine across the placenta. *Am J Obstet Gynecol* 64:1368, 1952
36. Crawford JS, Rudefsky S: The placental transmission of pethidine. *Br J Anaesth* 37:929, 1965
37. Roberts H, Kane KM, Percival H, et al: Effects of some analgesic drugs used in childbirth. *Lancet* 1:128, 1957.
38. Colburn DW, Saltzman M: The Apgar scoring system in evaluation of the newborn infant. *NY State J Med* 60:246, 1960
39. Snider SM, Moya F: Effect of meperidine on the newborn infant. *Am J Obstet Gynecol* 89:1009, 1964
40. Duncan SL, Ginsburg J, Morris NF: Comparison of pentazocine and pethidine in normal labor. *Am J Obstet Gynecol* 105:197, 1969
41. Beckett AH, Taylor RF: Blood concentrations of pethidine and pentazocine in mother and infant at time of birth. *J Pharm Pharmacol* 19:suppl 50 S, 1967
42. Mowat J, Garrey MM: Comparison of pentazocine and pethidine in labor. *Br Med J* 2:757, 1970
43. Moore J, McNabb TC, Glynn JP: The placental transfer of pentazocine and pethidine. *Br J Anaesth* 45: suppl 798, 1973
44. Mowat J, Garrey MM: Comparison of pentazocine and pethidine in labor. *Br Med J* 2:757, 1970
45. Moore J, Hunter RJ: Comparison of the effects of pentazocine and pethidine administered during labor. *J Obstet Gynecol Br Commonwealth* 77:830, 1970