PLACENTAL DRUG TRANSFER 6519

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Discussion of drug transfer from mother to fetus across the placenta requires consideration of the functioning of the placenta in normal and abnormal pregnancy.

The placenta is a unique organ—an allograft resistant to immunological destruction and functioning to a large extent autonomously, independent of homeostatic regulatory mechanisms in the mother. During gestation its activity changes from an actively proliferating, almost malignant tissue in the early stages of pregnancy, through mature function to a senescent-like structure at term. In the nine months of human gestation, the placenta may be said to parallel the life span of an individual. Throughout this time it provides the only communication between the fetus and the outside world and on its continued activity depend fetal growth and survival.

One of the most important aspects of placental function is the ability of the organ to transfer material to the fetus against a concentration gradient, and thereby ensure adequate levels of substances essential for fetal growth and the biosynthesis of metabolic co-factors in fetal tissues. The recognition that the placenta has an active and selective role in transfer mechanisms is relatively recent. For years, the use of the term "placental barrier" typified a concept of the placenta as an organ whose prime function was to protect the fetus against injury and infection, and provide a physical barrier to the passage of noxious substances from mother to fetus. On this basis, placental transfer would conform essentially to that across semi-permeable membranes and be determined by physical characteristics such as the thickness of the membrane, membrane pore size, molecular weight of substances on either side of the membrane, perfusion pressure i.e., maternal blood pressure, and placental flow.

But few, if any, of the substances essential for fetal development cross the placenta by a process of simple diffusion. The majority, such as vitamins, amino acids, and certain ions are transferred from mother to fetus against a concentration gradient. An adequate level of these essential nutrients is maintained on the fetal side of the barrier through the continued selective activity of the placental cells.

Placental Transfer Mechanisms

The possible mechanisms by which substances cross the placenta and reach the fetus may be considered, as with other natural membranes, under four main headings—simple diffusion, facilitated diffusion, active transport, and special processes. These mechanisms have been discussed in several reviews (1–3) and will not therefore be considered in detail here.

Simple diffusion.—In this instance substances cross the placenta from regions of higher to lower concentration so as to equalize concentrations on either side of the barrier, the driving force for such transfer being molecular thermal agitation. The rate at which placental transfer occurs by these means is thought to be governed by standard physiochemical considerations, depending on the concentration of the substance on the maternal side of the barrier, the thickness of the membrane and surface area available for transfer, and a diffusion constant (K) particular to the substance being transferred. The value of the diffusion constant depends, among other things, on molecular size and spatial configuration, ionic dissociation, and lipid solubility. The latter property is of particular importance for drug transfer across the placenta, since this organ is considered to resemble other natural membranes in this respect, particularly the blood brain barrier (4) and hence has a lipoid structure. One would therefore expect the passage of lipid soluble substances across the placenta to be accelerated compared with those that are less fat soluble.

Facilitated diffusion.—Placental transfer by this mechanism also occurs in accordance with the concentration gradient but differs from simple diffusion in that the rate of transfer is much greater than predicted on physicochemical grounds alone, as in the case of glucose and other sugars. Specialized cellular systems related to specific molecular and spatial characteristics have been postulated for this purpose. Exogenous substances, with a structural similarity to the particular endogenous compound transferred by this mechanism, compete with it for the transport carrier system while other substances may competitively inhibit transfer.

Active transport across a membrane.—This implies molecular transfer against an electrochemical gradient and must entail the expenditure of metabolic energy. The particular processes involved in this mode of placental transfer are still largely speculative, but temporary combination with specialized components of the cell membrane and enzyme action have been suggested. This mechanism is responsible for the transfer of vitamins, amino acids, and essential ions such as calcium from mother to fetus. The metabolic conversion of one substance into the other prior to transport, as occurs with riboflavin, may be considered a variety of active transfer.

Special processes.—These include pinocytosis and breaks in the placental barrier. The former is the phenomenon in which droplets of plasma are engulfed by microscopic invaginations of the cell membrane and thereby transferred direct to the fetus; this mechanism may be responsible for antibody transfer from mother to fetus. Breaks between the cells in the placental membrane are thought responsible for red blood cell transfer between the two circulations.

Very few, if any, vital materials cross by simple diffusion. Oxygen and carbon dioxide may in fact be the only substances essential for the fetus that cross the placenta by simple diffusion in accordance with physiochemical laws. And even in this instance it is difficult, in view of the high oxygen consumption of the placenta itself (5) to prove that oxygen and carbon dioxide are transferred by these means. Fetal requirements are essentially supplied by the preferential selective activity of the placenta in transporting substances of physiological importance.

On the other hand, drugs and other exogenous compounds are thought to cross, in the main, by simple diffusion; facilitated diffusion and active transport probably apply only in rare instances where drugs have a structural similarity to endogenous material normally transported by these means from maternal to fetal circulations. This situation has been postulated in respect of 5-fluorouracil in view of its similarity to endogenous pyrimidines (6). Similarly, since amino acids are preferentially transferred across the placenta, one may speculate on the possibility that drugs containing amino acids with a structure similar to essential amino acids might have accelerated transplacental transport. It is therefore of interest that levels of labelled α methyl dopa were higher in the fetus than in the mother (7). Antimetabolites such as purine analogs may also be actively transported, but in view of the structural specificity that would be required for placental transfer by these means, it is unlikely that many compounds foreign to the body are transported in this fashion.

As for pinocytosis or pores in the placental barrier, while the former mechanism may be responsible for the transfer of viruses and immunological proteins to the fetus, it does not apparently relate to drug transfer, nor is there any evidence that pores in the placental membrane are normally of importance in the passage of drugs.

Since the majority of drugs are thought to cross by a process of simple diffusion in accordance with their lipid solubility (4, 8), one would expect poor fetal penetration of highly ionized drugs with low lipid solubility, such as tubocurarine, and more rapid transfer of drugs with high lipid solubility and low degrees of dissociation such as antipyrine or thiopental. Overall this is a useful and valid concept, but its application may be limited in individual cases. Placental impermeability to compounds such as d-tubocurarine is in fact relative rather than absolute. When curare, for example, is given in large amounts, as may be required to control epileptiform convulsions,

enough of the drug may cross the placenta to produce a paralyzed and curarized infant at birth (9). Thus any substance, if present in sufficient concentration on the maternal side of the barrier, will eventually reach the fetus. What matters, however, is the rate of transfer, i.e., the amount that effectively reaches the fetus in a given period of time, the form in which it is presented to the fetus, the ability of the fetus to modify the drug or alter its responses thereto, and the potential influence of the drug on placental function. Morphological factors are also relevant, for anatomically, the placental barrier for drugs is a heterogenous layer of cells interposed between fetal and maternal circulations, the structural characteristics of which vary during the course of gestation. There is a reduction both in thickness and number of layers towards term with a simultaneous increase in surface area but varying changes in permeability (10), possibly because of the different changes in organic and inorganic constituents of the placenta during pregnancy. In toxemia however, where structural changes have been demonstrated in the placenta, permeability is altered and amino acid transfer impaired (10), though whether the passage of drugs to the fetus is accelerated or decreased in these circumstances is not known.

Various aspects of placental drug transfer and perinatal pharmacology have been discussed previously (3, 4, 8, 11–15) and will only be summarized here. This review has been limited to studies of the transplacental passage of certain groups of drugs and compounds of pharmacological or clinical interest, the selection reflecting not personal bias but the fact that quantitative studies of the kinetics of placental drug transfer in humans are lamentably few.

Anesthetic, Hypnotic, and Analgesic Transfer

Anesthetic and hypnotic transfer.—Since in respect of drug transfer, the placenta is considered to resemble the blood brain barrier, one would expect anesthetics, hypnotics, and tranquilizers to cross the placenta readily and rapidly. That transfer may be limited, however, is suggested by the fact that maternal sedation and anesthesia are not inevitably accompanied by fetal depression.

The local anesthetics used for regional anesthesia (para-cervical, epidural) in labor cross without difficulty. Mepivacaine (16, 17), lidocaine (18, 19), and related compounds (20) have been detected in cord blood within 2 minutes of maternal intravenous injection, and remain in measurable amount on the fetal side of the circulation for at least 30 minutes; in some instances up to 100 minutes.

After intravenous administration of lidocaine 30 seconds to 40 minutes before an uncomplicated vaginal delivery, the drug could be found in the umbilical vein within 2–3 minutes of maternal injection, and in the umbilical artery within 6 minutes (19). A particular feature of interest in this study was the relatively large gradient between maternal and fetal blood lidocaine which was maintained for as long as 40 minutes. Since protein

binding of the drug in fetal serum was no different from that in maternal blood, and placental tissue apparently did not metabolize the drug, these findings suggest that the placental "barrier" may, in certain instances, be valid functionally as well as anatomically. Lipid solubility is thus not the only factor to be considered in assessing the effect on fetal activity of anesthetic drugs given to the mother.

Similar conclusions were drawn from studies of the distribution of labelled thiopental in maternal and fetal rat tissues (21). Radioactivity in different maternal and fetal tissues of near-term pregnant rats after maternal injection of ^{14}C labelled thiopental was measured in whole body radio-autograms. Transfer of thiopental to the fetus was much slower than to the maternal brain. In this instance also, the placenta provides a barrier, albeit relative, but one that effectively protects the fetus from concentrations of thiopental that are anesthetic to the mother. The placenta apparently delays the transfer of the drug more than would be expected from knowledge of the kinetics of the anesthetic's transfer to the brain, and thus effectively limits the amount of drug reaching the fetus.

Molecular characteristics other than lipid solubility also influence transplacental passage. Procaine for example, crosses without difficulty, but was detected in umbilical vein blood only after injection of more than 4 mg/kg to women in labor shortly before delivery (22), whereas mepivacaine or lignocaine were found in fetal blood after maternal injection of much smaller amounts. These differences in transfer have been related to relative molecular stability (22), the amide linkage of lignocaine, mepivacaine, and prilocaine being relatively resistant to enzymic attack, whereas procaine and petrocaine are readily hydrolyzed. Additionally, the consistently higher maternal levels and inconstant placental/fetal gradient with prilocaine have been explained as due to redistribution within the placenta rather than in terms of a "barrier" (23).

Paracervical and epidural anesthesia are frequently followed by fetal bradycardia, the incidence, degree, and duration of which are related to the concentration of anesthetic used (24, 25). The occurrence of fetal bradycardia as an accompaniment of regional maternal anesthesia, has been attributed to many factors—an obstruction to uterine blood flow, direct injection into the fetus (probably only rarely responsible), maternal hypotension, or a direct influence on fetal function resulting from placental transfer of the drug. This last explanation is most likely, and is supported by recent sophisticated studies in labor (26). Mepivacaine transfer after paracervical block was assessed by gas-chromatographic analysis of fetal scalp blood. The occurrence of fetal bradycardia was associated with significantly higher levels of mepivacaine in scalp samples than in cases with no bradycardia, and scalp anesthetic concentration in cases of bradycardia was greater than the concentration in maternal arterial blood; umbilical vein or arterial mepivacaine levels at birth were consistently lower than those in arterial blood. The presence of higher anesthetic levels in fetal than in ma-

ternal blood was attributed to passage of significant amounts of mepivacaine through the uterine arterial wall into the intervillous blood pool by passive diffusion alone rather than to active placental transfer of the drug or its fetal retention secondary to the acidosis associated with bradycardia (26).

The safety of local anesthetics has been claimed to be increased by addition of epinephrine so as to reduce drug absorption from the injection site. The fetus may not, however, benefit from such addition, for though maternal anesthetic levels after epidural anesthesia were reduced in women given lignocaine together with epinephrine, compared with levels in those where no epinephrine was added, cord blood anesthetic levels were similar in the two groups (27, 28). The effects of epinephrine on the placental vasculature and on metabolic processes in this organ (29–31) are, furthermore, reasons for *not* adding epinephrine to solutions used for regional anesthesia in labor.

The effect of inhalation anesthetics on maternal circulatory and respiratory systems complicates evaluation of the kinetics of their transplacental passage but overall, gaseous anesthetics, and especially those with high lipid solubility, predictably reach the fetus with great rapidity, cyclopropane for example being detected in cord blood within 90 seconds of maternal administration (8, 32). In animal experiments trichlorethylene has been reported in higher concentration in fetal than in maternal blood (32). Clinical consequences of such accelerated transfer require study, with particular reference to the production of toxic metabolites of trichlorethylene and their transfer to the fetus. Methoxyflurane, highly lipid soluble and poorly dissociated, is as expected, transferred early and relatively unrestricted to the fetus, umbilical vein levels being 65 percent of those in maternal plasma within 2 minutes of anesthetic administration to the mother (33). Increasing amounts were transferred with increasing duration of anesthesia, in proportion to the amount given and with correspondingly greater fetal central nervous system depression (34, 35).

Generalizations concerning the extent and consequences of placental anesthetic transfer are, however, unwarranted. Each compound should be tested individually before assuming that predictions of placental transfer based on lipid solubility and other molecular characteristics are justified.

Barbiturates, irrespective of their duration of action, cross rapidly (32), but there seems to be no correlation between fetal barbiturate levels and depression of neonatal function. The passage of barbiturates is again not dependent on their lipid solubility, and studies in dogs have shown that equilibrium between maternal and fetal levels of sodium barbital (a long acting barbiturate of low lipid solubility), is established relatively early, as with the short acting highly lipid soluble sodium pentobarbital (36). The extent to which barbiturates are bound by plasma protein may also influence their transfer across the placenta (37).

Advantage has recently been taken of the rapid transfer of barbiturates

and of their influence on fetal hepatic activity, for the drugs affect bilirubin metabolism, apparently by stimulating the liver to produce glucuronyl transferase, the enzyme essential for excretion of bilirubin. Thus pre-natal administration of phenobaritone would be expected to reduce the level of serum bilirubin and hence have potential application in cases of hyperbilirubinemia as in Rhesus hemolytic disease.

Antidepressants.—These are among the most widely used drugs in modern medicine, yet surprisingly little is known of their transfer across the placenta and effects on fetal function, particularly in primates.

Since imipramine is highly lipid soluble, one would expect rapid transference across the placenta; this has been confirmed in animal studies, both for the parent compound (38) and its desmethyl derivative (39). Negligible amounts of amitriptyline, on the other hand, were found in the fetus even after relatively large doses had been given to pregnant mice near term (40). The importance of determining transfer rates of such drugs resides not only in direct effects exerted on the fetus but also as a result of potentiation of norepinephrine and other amines by these drugs.

Phenothiazines are readily transferred both in animals and man (8, 32) with suggestive evidence of concentration in fetal brain and liver.

Alcohol.—The transfer of alcohol across the placenta is of current clinical interest in view of its reputed prevention of premature labor. Clinically, pregnant women have frequently noted reduced motor activity of the fetus after maternal alcohol ingestion and though there has been no agreement on the gradient between mother and fetus, a recent study in sheep indicates rapid transfer with fetal levels approximating closely to maternal values (41).

Analgesics.—These appear to cross without difficulty (32) but there is little quantitative data from studies in humans. In a comparative study of pentazocine and pethidine in normal labor, cord levels of pethidine were considerably higher than those of pentazocine even after simultaneous administration of identical amounts of the two analgesics (42), but as the authors emphasize, this does not necessarily imply lesser fetal effects with pentazocine.

Transfer of narcotic drugs across the placenta has long been recognized on clinical grounds. Myosis, respiratory depression, and even withdrawal symptoms have been observed in infants born to addicts (32, 43), and after acute administration of morphia in labor detectable amounts of the narcotic were recovered from infants' stools (43). Quantitative studies in rats also showed that considerable amounts crossed the placental barrier, equilibrium between maternal and fetal plasma levels being established at around 2 hours but with a slower rate of conjugation and greater brain concentration in the fetus than in the mother (44). Permeability of the placental barrier

to morphine in rats was also influenced by previous maternal exposure to the drug (45). Maternal plasma levels of free and conjugated ^{3}H dihydromorphine 1½ hours after injection were significantly lower in tolerant than in control animals, whereas fetal plasma levels were higher at this time, suggesting accelerated placental drug transfer. In tolerant animals there was also a tendency for earlier morphine deposition in fetal brain. Comparable human data are not available.

Transfer of Drugs Used for Chemotherapy of Infectious Disease

Most of the antibacterial agents commonly used appear to cross the placenta without difficulty, though quantitative data on the kinetics of their penetration in man are available in only a few instances. The extent of placental transfer has frequently been inferred from the presence or absence of toxic fetal effects, though the latter also relates to the ability of the fetus and particularly of the immature fetal liver to metabolize the drug in question.

Sulphonamides.—Those used therapeutically are all readily transferred across the placenta in amounts sufficient to exert significant antibacterial effects (4) but in view of the risk of fetal kernicterus, some workers feel that sulphonamide administration within a few days of delivery is potentially dangerous (46).

Isoniazid transfer.—This may be associated with fetal levels even greater than those on the maternal side (47) suggesting active placental transfer of this drug. The known hazards of isoniazid, particularly concerning the central nervous system and fetal vulnerability in this respect, necessitate caution in its use for pregnant women with tuberculosis.

Nitrofurantoin.—Quantitative data on nitrofurantoin transfer are lacking but neonatal hemolysis has been reported after its administration to pregnant women (47), presumably a consequence of the influence of the drug on glucose-6-phosphate dehydrogenase deficient neonatal red blood cells.

Antibiotics.—On the whole, these rapidly achieve bacteriostatic concentrations in fetal blood, with penetration up to 75 percent of maternal levels or even greater within 90 minutes.

The passage of erythromycin and streptomycin is apparently less rapid than that of penicillin (47) but the relative rate of transfer does not necessarily correlate with fetal effects, and neonatal deafness has been reported after maternal streptomycin (47).

The extremely rapid placental transfer of the tetracyclines and chloromycetin may have unfortunate fetal consequences, for the former interferes

with skeletal growth and causes discoloration of the teeth (48, 49), and the latter may induce a characteristic neonatal 'gray syndrome'—failure to feed, hypothermia, cyanosis, and even death (50). The immaturity of the fetal liver, and the consequently reduced metabolism of such drugs after reaching the fetus, may further increase fetal hazards of maternal chloramphenicol administration. Transplacental passage of a new tetracycline, clomocycline (a methylol derivative of chlortetracycline, with an antibacterial spectrum almost identical with that of chlortetracycline) seems however, to be limited (51), though fetal and neonatal effects of its administration have not yet been studied.

Perhaps because of these unfortunate experiences, transfer of the synthetic penicillins has been studied in more detail. Bacteriostatic levels of ampicillin were found in both maternal plasma and liquor when the antibiotic was given shortly before amniotomy (52). The concentration in liquor was similar to or even greater than in maternal plasma and considerably greater than that in cord blood, the high concentration in liquor probably reflecting levels in fetal urine, as evidenced by ampicillin concentrations in neonatal urine, rather than preferential transfer across the placenta.

Bactericidal levels of cephalothin were found in liquor within 15 minutes of maternal intravenous administration (53) and continued to rise for at least a further hour (54); cord blood concentration was bactericidal as long as 6 hours after a single dose of 1 gram. Caphalothin levels in infants at birth were much lower than those in maternal blood, probably in consequence of rapid fetal metabolism or excretion of the drug rather than limited placental transfer (55). Useful levels of cephaloridine were found in the amniotic fluid within 1½ hours of an intramuscular maternal injection and in cord blood within 6 hours; amniotic levels increased with higher maternal doses (56). At 12 hours maternal levels were falling, but amniotic levels remained high and even increased, again possibly because of excretion into amniotic fluid from the fetal kidney (57). Cephalothin and cephaloridine transfer have also been studied early in human gestation (58, 59) when fetal organs were found to retain the antibiotic, with increasing concentration at a time of falling maternal levels.

Different placental transfer rates after intravenous administration of identical doses of two synthetic penicillins—sodium methicillin and dicloxacillin—have been related to differential serum protein binding of the antibiotics (60). Peak levels of dicloxacillin were rapidly attained in maternal blood, with detectable levels still present after 4 hours; no equilibrium was established with fetal blood over this period and only small amounts were found in amniotic fluid. On the other hand, methicillin attained significantly lower maternal peak levels with rapid clearance thereafter, and barely detectable levels at 4 hours; equilibration between fetal and maternal blood was achieved within an hour (the fetal concentration being at least three times that recorded for dicloxacillin) with progressively increasing levels in amniotic fluid. The apparent impermeability of the placental barrier to di-

cloxacillin would seem to be determined not by molecular weight (510) but by the fact that 95 percent of the antibiotic is bound to serum albumin; by contrast only 40 percent of methicillin is protein bound. With increased protein binding of dicloxacillin there would be diminished clearance rate from maternal blood, reduced placental transfer, and consequently higher maternal and lower fetal blood levels, the low amniotic fluid levels of the antibiotic reflecting the low concentration in blood supplying the fetal kidney.

Rifampicin concentration in fetal rats and rabbits approximated to those found in the dam (61) but there are as yet no human data. Very similar levels of griseofulvin were found in cord and maternal blood 2½ hours after an oral dose (62).

Since viruses cross the placenta without difficulty (63), it is possible that antiviral agents may also do so though there are as yet no data on this matter.

Anti-protozoal agents.—Quinine, primaquine, pentaquine, and metronidazole readily cross the placenta. There is little published data concerning fetal effects of such transfer (32) though one would predict hemolytic consequences in cases of glucose-6-phosphate dehydrogenase deficiency.

Ion Transfer

Dissociation of drugs in body fluids may release ions that are subsequently transported across the placenta and influence fetal activity independently of the residual part of the molecule. For a general discussion of placental ion transfer the reader is referred to the classic reviews of Snoek et al (64) and Sternberg (2). Active placental transport has been presumed for ions such as calcium and iron, which are present in fetal blood in greater amounts than on the maternal side of the barrier, though the precise mechanism of their transfer is obscure. The avidity of the fetus for these elements is such that despite competing maternal demands they are preferentially shunted to the fetus across the placenta against a concentration gradient. In the maternal circulation these ions are carried in a complex form, 60 percent of the calcium, for example, being carried bound to protein while iron is carried in the complex, transferrin. It seems unlikely however, that the carriers themselves cross the placenta. No generalizations can be made about possible mechanisms; closely related elements may be transferred at very different rates and each ion has to be considered individually.

Iron.—Iron is essential for fetal hemopoiesis and is transferred rapidly, virtually unidirectionally across the placenta in increasing amounts with increasing gestational age (65, 66). Placental iron transport has been studied in several animal species and also in man. In rodents, placental iron transfer is apparently determined by selective placental activity and may not necessarily relate to fetal requirements, for after removal of the fetus, labelled iron continued to accumulate in the placenta (67). Transfer mechanisms

have been studied in rabbits, using labelled transferrin (68). The maternal iron transferrin complex is thought to become attached to the placenta, iron being then transferred to the placental cell and desaturated transferrin returned to the maternal circulation. A specialized chelator and iron carrier is thought to be located in the placenta itself. The mechanism of iron transport to the placenta is thus analogous to its transport across the reticulocyte membrane. In both instances iron is transferred against the concentration gradient and detached from transferrin, leaving behind desaturated transferrin. But unlike the reticulocyte, the placenta is not the final resting place of maternal iron and serves only as a temporary station for onward movement to the fetus. Studies of chelated iron transport in pregnant guinea pigs have further shown that placental iron transport relates also to the form in which it is administered to the mother (69), the guinea pig placenta being found impermeable to several low molecular weight chelates of iron, certain amino acid iron chelates, and also to ferrioxamine, though allowing the passage of iron bound to DTPA and EHPG. Placental iron transfer in the guinea pig thus also resembles that of iron complexes across the intestinal wall.

In humans, as in animals, maternal plasma is the major if not sole source of fetal iron, and placental iron transfer is extremely rapid, only a small fraction being retained by the placenta (70). There is no evidence of a large placental iron pool on which the fetus can draw in accordance with need. As in animals, it also seems unlikely that transferrin itself crosses the placenta. To reach the fetus, iron must first be released from maternal transferrin to which it is normally very tightly bound. Simple dissociation of the complex and movement of free iron across the barrier is unlikely and receptors in the placental cells have been postulated, as in erythrocytes. However, the mechanism for releasing iron into fetal plasma from the placenta is not known, nor are the factors which might accelerate or inhibit this mechanism understood. Placental transfer was studied with isotopically labelled iron in pregnant women undergoing hysterotomy before 30 weeks or near term with an anencephalic fetus or other major abnormality (70). Iron was transferred from mother to fetus even though maternal levels were about half those in the fetus, the percentage saturation of transferrin in fetal blood much greater, and fetal total iron binding capacity lower. Transferrin saturation was apparently greater on the fetal side than in maternal plasma at all stages of gestation, but in this small series plasma iron was higher in maternal than fetal blood in three cases investigated before 17 weeks, while in the remaining five (20, 22, 32, 33 and 35 weeks gestation respectively) plasma iron was higher on the fetal side. The amount of iron transferred to the fetus therefore seems to increase with the stage of gestation, perhaps in association with increasing iron binding capacity on the fetal side, though total iron binding capacity, i.e., transferrin was greater in the mother. Placental transfer of different iron complexes in humans or fetal consequences of a major increase in maternal iron level have not yet been

investigated and to infer similar differential placental transfer of iron complexes in humans to that demonstrated in the guinea pig in the absence of specific human studies, is unjustified.

Iodine.—Iodine transfer, e.g. after maternal ingestion of expectorants or cough suppressants, may have considerable clinical importance. In the fetus as in the neonate, iodides induce thyroid enlargement. The size of the goiter may be such as to cause obstructed labor and hypothyroidism; retarded bone development and even cretinism may be present at birth (71, 72).

The placenta, in common with the endometrium, ovary, salivary, and mammary glands, is one of the extra-thyroidal sites of iodine concentration, but iodine uptake in these regions, unlike that in the thyroid, is not influenced by TSH. Iodine would seem to be rapidly transferred across the placenta, even against a concentration gradient, but whether it crosses bound to protein or as the free ion, is not known. The extent to which iodine is bound to protein in human fetal blood also requires investigation.

In rabbits and guinea pigs fetal plasma iodine concentration one hour after a subcutaneous injection of ^{131}I to the dam, was 1½–5 times maternal levels (73). Quantitative aspects of placental iodine transfer in humans have not been studied and pose technical difficulties in view of competing claims of the maternal thyroid. In the animal studies cited above, propylthiouracil was first given to the mother to prevent thyroid binding of iodine despite the unknown influence of such drug administration on both placental and fetal function, emphasizing once again the difficulty in interpreting these studies.

Calcium.—Calcium is present in higher concentration in fetal than in maternal plasma. Active placental transport is generally assumed but it has also been suggested that the difference in maternal and fetal calcium levels may result from homeostatic mechanisms operating at different levels in maternal and fetal organisms (74).

Strontium, with a close electrochemical affinity to calcium, is not transferred across the placenta to the same extent, the strontium/calcium ratio in the fetus being much lower than that in the mother both in rodents (75) and humans (76). There is thus considerable placental discrimination between the two elements especially early in gestation, but no information on the mechanisms involved.

Magnesium.—Magnesium in the form of parenteral magnesium sulphate is recognized therapy for eclampsia and pre-eclampsia in many obstetric centers. Serum levels of magnesium were increased in the fetus and approached maternal blood levels after magnesium sulphate administration to the mother. There was no relation between magnesium concentration in cord blood and the fetal Apgar score, regardless of the total dose of magnesium sulphate given (77).

Actinide.—Actinide transfer has been studied in the rat, using radio-nucleides (78). Plutonium, uranium, and neptunium have many common properties and knowledge of their relative tissue distribution in different circumstances is important in determining their potential radiation hazard. The amount transferred to the fetus or retained in the placenta was, however, different in each instance and varied also with the physiochemical form in which the actinide was administered (78). The placenta and fetal membranes appeared to limit transfer of the radio-nucleides from the maternal to fetal circulation, relatively small amounts (around 1 percent of the dose administered to the dam) being transferred to the fetus. Similar concentrations of uranium were present in the fetus and placenta but neptunium was found in higher concentration in the placenta than in the fetus. When plutonium was given as a colloid the majority was removed by the reticuloendothelial system whereas more was deposited in the placenta after administration of an ionic form.

Hormone Transfer

With the increasing availability and therapeutic use of natural or synthetic hormones, the extent and consequence of their passage across the placenta is now more than an academic exercise. Though placental hormone transfer may relate to some extent to their fat solubility in that unconjugated fat soluble steroids diffuse with relative ease whereas the water soluble protein hormones cross more slowly, the determining factor would seem to be a highly selective influence, the placenta acting as a regulator of hormone transfer between mother and fetus.

Catecholamine transfer.—Catecholamine transfer across the placenta has been presumed in view of the tachycardia or irregularity of the fetal heart associated with maternal anxiety or after intravenous infusion of catecholamines in pregnant women (79), though the latter could equally well be explained by fetal asphyxia consequent on the constrictor influence of epinephrine and norepinephrine on the placental vessels. Direct passage of labelled catecholamine was, however, demonstrated after administration of ^{14}C epinephrine or norepinephrine to pregnant women with anecephalic or hydrocephalic fetuses (80). Indirect confirmation of catecholamine transfer was also provided in pregnant monkeys with chronically implanted catheters (32), intravenous administration of as little as 2 μg. epinephrine or norepinephrine to the mother being associated with a rise in fetal blood pressure and heart rate.

Insulin transfer.—This has been inferred since fetal blood glucose fell after insulin injection in pregnant rats (81). Conflicting results have, however, been derived from studies in primates with labelled ^{131}I insulin. In man, significant amounts of the intact hormone were apparently not transferred, either early in gestation (82) or at term (83) though radioactivity

was detected in fetal plasma after maternal injection of labelled insulin. But with repeated sampling from catheters implanted in pregnant monkeys with intact amniotic sacs, limited selective transfer of insulin was found (84). The interpretation of these findings would be facilitated by data concerning the activity of placental insulinase and other relevant enzymes but these are not available.

Glucagon transfer.—The transfer of glucagon has recently been investigated in sub-human primates and bidirectional transplacental passage inferred in consequence of changes in plasma insulin and glucose levels after injection of the hormone and determination of ^{131}I labelled glucagon (85).

Oxytocin.—It is not surprising, in view of the difficulty of assaying this hormone, that quantitative aspects of oxytocin transfer across the placenta have not been studied. From the similarity to insulin, both structurally and in respect of certain physico-chemical characteristics, one might conclude that insignificant amounts of oxytocin would cross the placenta, and that the amount reaching the fetus would be further reduced through inactivation of the hormone by placental oxytocinase.

Tetra-iodothyronine (T4), tri-iodothyronine (T3), and thyroid stimulating hormone (TSH).—The extent to which thyroid hormones cross the placenta has generally been determined indirectly in animals from observation of changes in fetal thyroid function (81, 86). Bidirectional placental transfer of ^{131}I labelled T_3 has also been studied in rhesus monkeys (87); most of the radioactivity transferred from mother to fetus was found in the form of iodide with traces only of T_3 or T_4, suggesting rapid de-iodination of the hormone. T_3 was, however, more readily transferred in the reverse direction, from fetus to mother but with small amounts only of labelled iodide being detected on the maternal side; the biological significance of these differences in gradient is not clear.

In humans, both indirect methods (88) and direct determination using ^{131}I labelled hormones (89, 90) have been used, from which it has been concluded that limited amounts of T_3 and T_4 cross the barrier, the rate being greatest with T_3. Hence T_3 has been advocated as replacement therapy in pregnant women though the possibility that the fetus uses T_3 in preference to T_4 or that the former is detoxified more rapidly by the placenta also requires investigation (91). In either event, maternal thyroid hormones are not apparently readily available for fetal use.

Fetal thyroid development seems to be influenced by fetal rather than maternal thyroid stimulating hormone (TSH); there is no evidence that TSH crosses the placenta in biologically significant amount (81).

Human growth hormone (HGH), human placental lactogen (HPL), and human chorionic gonadotrophin (HCG).—Though HGH is present in

higher concentration in fetal than in maternal blood, it is not apparently transferred from mother to fetus or in the reverse direction (92), nor does HPL, a hormone synthesized by the trophoblastic cells and with similar immunochemical and metabolic properties to HGH enter the fetal circulation (93). Similarly there is no evidence of HCG transfer from trophoblast to fetal or of transplacental passage to the fetus of other protein hormones such as erythropoietin or angiotensin.

Steroid hormones.—Iatrogenic masculinization of a female fetus as a result of maternal ingestion of male hormones (e.g. testosterone) or even after synthetic progestins (e.g. norethindrone) is well recognized clinically and indicates that sex hormones may cross the placenta in a form enabling them to exert significant influence on fetal development. Depression of neonatal adrenal function after maternal corticosteroid administration suggests that cortisone and related compounds are similarly transferred across the placenta in significant amounts. Quantitative data in respect of individual steroids are, however, scanty.

Administration of ^{14}C labelled cortisol to pregnant women has shown that cortisol crosses the placenta with ease, probably in both directions (94–96); the steroid may also reach the amniotic sac by other routes, possibly across the amnion or chorion. Rapid placental transfer is essentially a property of the free steroid; conjugation of cortisol or of its congeners limits placental transfer, probably in consequence of formation of highly water-soluble compounds. Placental transhydrogenation of cortisol to cortisone with transfer of the latter to the fetus has been suggested in explanation of the higher cortisone/cortisol ratio in fetal than in maternal blood (97).

Placental steroid transfer may also be influenced by the increased blood levels of estrogens and progesterone in pregnancy. The latter result from a collaborative synthetic venture between the fetus, placenta, and maternal organism (15, 98). For estrogen synthesis, certain precursers must be provided both by fetus and mother. The fetus and the placenta are incomplete steroid-forming systems and each complements the other in forming estrogens, the different reactions being dependent on the presence or absence of enzymes required for specific metabolic pathways in either the fetal adrenal or placenta. Estrogen production involves, first, placental synthesis from cholesterol or small molecules, of pregnenolone and progesterone, their conversion to androgens in the fetal adrenal or liver, and finally placental conversion of the 16-hydroxy-androgens to oestrogen. Additionally, steroid conjugation with sulphuric acid can occur in the fetal adrenal or liver, and the placenta may then hydrolyse the sulphated conjugated steroid. On the other hand, all the enzymes required for progesterone bio-synthesis are present in the placenta.

Thus the enzyme systems involved in the different metabolic pathways concerned in steroid synthesis are distributed between placenta and fetus so that certain reactions are carried out exclusively or predominantly in one or

other part of the feto-placental unit. In consequence, steroids shuttle to and fro from placenta to fetus and back again for the different chemical reactions. Endogenous placental steroid transfer has considerable biological significance but whether synthetic steroids would be transferred at similar rates and their potential influence on fetal and placental mechanisms requires investigation.

Anti-Thyroid Drugs

Thiouracil readily crosses the placenta and influences fetal thyroxine synthesis; quantitative aspects have been studied in the rat and rabbit (99, 100) and have shown rapid and facile transfer throughout pregnancy, with rates comparable to those of the natural amino acids glycine and phenylalinine, and suggestive of active placental intervention. No marked difference in overall intellectual level or in various psychological tests was found in 18 children born to mothers treated with propylthiouracil in pregnancy compared with a control group (101), though a goiter was present in three of the children exposed to thiouracil antenatally. No data is yet available in respect of carbimazole transfer, but clinical observation suggests no significant alteration of neonatal function after carbimazole administration in pregnancy; a prospective study is, however, required.

Cholinesterase Inhibitors

Not surprisingly, since these drugs are rarely indicated in pregnancy, there is scanty information on their transplacental passage. From the fact that neostigmine, edrophonium, and pyridostigmine contain a quaternary ammonium group, one would expect such drugs to cross only slowly and in limited amounts. Neonatal myasthenia gravis resulting from prenatal transfer of pyridostigmine has been described (102) and transient muscular weakness reported in up to 20 percent of infants born to women receiving cholinesterase inhibitors for myasthenia gravis in pregnancy (103). These compounds may therefore cross more readily than has hitherto been suspected.

Environmental Contamination and Food Additives

Pesticides.—Environmental pollution is a major problem of modern civilization. It is therefore not surprising, though somewhat disquietening, that significant amounts of chlorinated hydrocarbon pesticides such as DDT and its metabolite DDE have been found in newborn infants in America (104). Evidence that this may reflect prenatal exposure resulting from the transplacental passage of DDT has recently been provided (105), DDT and DDE were found in amniotic fluid at or near term in normal pregnancy and in cord blood at delivery, the levels in both cord blood and aminotic fluid being less than in maternal blood. Considerably greater amounts of both DDT and DDE were found in the vernix caseosa and significant amounts were also found in products of conception at four weeks' gestation.

The presence of DDT in blood or tissues is thought to reflect recent exposure to the pesticide, while the levels of DDE may relate to more chronic exposure. The fact that DDT levels in cord blood were much less than in maternal blood (105) may suggest some placental block to DDT transfer, but since DDE levels were much greater in the vernix caseosa, rapid turnover of the pesticide with subsequent deposition in the vernix has been suggested. The relation of these findings to the influence of DDT and other pesticides on fetal development, placental function, and the metabolism of steroids such as progesterone in man requires urgent investigation.

Cyclamate transfer.—Using ^{14}C cyclamate, cyclamate transfer has been studied in pregnant monkeys with the amniotic sac intact and with catheters chronically implanted into a peripheral maternal vein, the inferior vena cava, and amniotic and intraplacental veins (106). Transplacental passage of cyclamate itself was rapid though limited, with a maternal-fetal gradient of 4:1; but cyclohexylamine, a compound to which 20 percent of humans metabolize the parent sweetener, cyclamate, was freely diffusible with a gradient of 1:1. Similar studies are obviously required in respect of the sweetener sodium saccharin.

Diuretic Transfer

Thiazides are widely used in obstetric practice but there is little data on their transfer across the placenta. Chlorothiazide crosses without difficulty (107) but fetal effects have been disputed.

Preferential placental transfer from mother to fetus of certain substances is well established but the possibility that passage might be accelerated in the reverse direction i.e., from fetal to maternal circulation, has not generally been considered. Studies in ewes in late pregnancy have, however, provided evidence of selective fetal to maternal transfer of triamterine, a diuretic compound normally secreted into the urine (108). The more rapid transplacental transfer of triamterine from fetus to mother than the reverse, could not be explained by greater availability of the unbound nonionized form of the drug in fetal plasma, though the different transplacental rates could be partly attributed to the lower concentration of fetal plasma proteins. Whether other compounds may be similarly treated thereby explaining their relative distribution between fetal and maternal compartments and differential effects on fetal and maternal activity requires investigation. Suggestive evidence of more rapid transport of T_3 from fetus to mother than in the reverse direction has already been provided (87).

General Comments

The foregoing examples of placental drug transfer illustrate the fragmentary state of our knowledge on this subject and emphasize that the results of experimental studies in respect to any particular drug should only be applied to the clinical situation—the administration of drugs to pregnant

women—with certain reservations. Thus the extent of placental drug transfer is conventionally considered in relation to concentrations in cord blood at delivery, despite the evidence that such levels may be a poor indication of drug transfer in utero. Drug levels in fetal tissues are of equal, if not greater importance, as are the concentration of metabolites that influence fetal activity and may even be toxic and whose transfer across the placenta may be accelerated compared with that of the parent drug. Metabolism by fetal tissues after transfer is of particular importance in this respect; incubation of fetal tissues, for example, with norethindrone acetate, a progestogen whose use was advocated in pregnancy in place of norethindrone, a known androgen, resulted nevertheless in liberation of significant amounts of free norethindrone (109).

The circulatory characteristics of the placental vascular bed play a major determinant role in transfer mechanisms; alterations in supply pressure and volume of blood perfusing the placenta affect placental transfer activity (4). Additionally, vaso-active compounds that alter vascular caliber influence transfer independent of the extent of their own passage across the barrier. Thus 5-hydroxytryptamine, angiotensin, and bradykinin alter vascular caliber both in peripheral and placental vessels and at the same time affect the rate of sodium transfer from mother to fetus in the rodent (110). Different physio-pathological conditions in which altered release of these amines occur, must therefore influence drug transfer. Similarly, though the deterioration in fetal state when the vasopressor, methoxamine, was given to correct hypotension after spinal anesthesia in the ewe, was attributed to constriction of the uterine vascular bed and decreased placental flow induced by methoxamine (111), it could also result from interference with transfer mechanisms.

Genetic and environmental factors also influence drug metabolism. Genetic differences have been demonstrated in the metabolism of tranquilizers and other drugs sufficient to explain the fact that effects of a fixed dose of a drug may vary widely, some patients having only a slight therapeutic effect and others experiencing adverse effects (112, 113).[1] Concommitant administration of other drugs also affects drug metabolism in maternal tissues. That similar influences may be exerted on the placenta is suggested by the increase observed in placental enzymic demethylation after chronic phenobarbital administration in pregnant rats (114). The effects of analgesics and other drugs taken over long periods of time thus requires similar study. Such studies should include investigation in human tissue, for though, in tissues such as the liver and brain, metabolic processes in rodents have been taken as indicating at least qualitatively the response in the corresponding human organ, the marked anatomical difference between human and rodent placentae and the presence of a functional yolk sac in the latter, limits the

[1] Little is known, however, about genetic influences on placental transfer mechanisms.

inference for human placental function that can be drawn from rodent studies. Furthermore investigation of carbohydrate metabolism and responses to anoxia in rat placentae have demonstrated qualitative as well as quantitative differences between the two species (30, 115). Extrapolation of results from rodent studies to human pregnancy cannot therefore be made without at least some confirmatory studies in man.

The functional characteristics of the human placenta also change during gestation. Lactate production and glycogon content decrease towards term (10, 31). Ribose formation and nucleic acid turnover are also much higher earlier in gestation than at term (116). The pattern of intermediary metabolism in the human placenta can be altered by hypoxia and by the influence of hormones such as estrogen and cortisone (10). The potential effects of drugs on the pattern of placental metabolism has rarely been considered though it undoubtedly merits investigation. In studies of the action of epinephrine on metabolic processes in the isolated human placenta, it was found that epinephrine evoked a marked increase in lactate production, both early in gestation and at term, the effect being proportional to the dose of catecholamine added; glucose uptake and glycogon breakdown were also affected in these circumstances (29, 31). Since the fetus is entirely dependent on its placenta, changes in the metabolic potential of this organ must affect fetal development in utero. Indeed such changes may have greater fetal consequences than direct transplacental drug passage. Therefore in order fully to evaluate the effects of drugs given to pregnant women, their influence on human placental metabolic processes must also be considered.

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