THE PASSAGE OF DRUGS ACROSS THE PLACENTA

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A large number of drugs are nowadays available for the treatment of gynaecological, obstetrical and general medical disorders, but relatively little is known with regard to the transmission of therapeutic and toxic agents across the placenta at various stages of gestation and at term. In recent years an increasing amount of research on a scientific basis has been devoted to estimations of the amounts of drugs that reach the foetal blood and tissues and the amniotic fluid; previously the information was based almost entirely on clinical observations of the foetus or the newborn. For many drugs given during pregnancy or labour there is as yet no available information regarding their passage across the placenta and their effects on the foetus. Many statements in the older literature are no longer valid in the light of modern investigations. The whole subject is obviously of great importance in the choice of a drug of therapeutic value to the foetus, or for the avoidance of a drug that may be harmful to the foetus. Drugs, poisons and other noxious substances to which the mother was exposed before or during pregnancy have in certain instances been the cause of foetal malformations; e.g. the congenital malformations caused by rubella virus.

Information on the placental transmission of drugs is scattered in the literature, and a comprehensive account of the available details is obviously very desirable. Consideration has been given in the present article to the transfer of many substances across the placenta and their direct effects on the foetus; untoward effects on the mother have generally not been mentioned, nor has consideration been given to drugs which indirectly improve the prognosis for the foetus by ameliorating the condition of the mother.

Methods of Investigation

Many methods of assay have been used to determine the amount of drug that reaches the foetus after its administration to the mother, including chemical, biological, microbiological, and in recent years the use of radio-active isotopes. Details are given in many of the investigations cited in this article. In addition the following reports are mentioned for reference: A method of collecting placental blood similar to that employed in blood-donor centres is described by Siegel.[173] *In utero* investigation of the placental circulation, maternal and foetal, by means of injections of saline, air and latex is described by Earn and Nicholson.[53] McGaughey *et al.*[135] have studied placental transfer and equilibration in normal and toxic gestation by using antipyrine and sodium and comparing blood samples from the umbilical vein and the intervillous space (obtained by transabdominal aspiration). The comparative physiology of placental transfer based on studies with radio-active sodium is considered by Flexner and Gellhorn.[66] The basic structure of the human placenta with a summary of previous observations on placental structure is described by Hamilton and Boyd.[89] The structure of the placenta of the full-time and immature foetus is

described by Getzowa and Sadowsky[75] and the structure of placentas at various stages of gestation by Shanklin.[172] Attention is also drawn to studies on the histochemical analysis of the human placenta described by Holzaepfel and Barnes[103] and Wislocki and Dempsey.[204] The exchange of various molecules and ions across the isolated amniotic membrane has been studied by Garby.[72]

Placental Function

The placenta is not and can seldom function as a semi-permeable membrane. It appears at times to have a highly selective action. It is an incessantly active 'barrier', and the transfer of different kinds of substances depends upon the cytological and cytochemical structures of the organ as well as on simple diffusion and filtration. With certain exceptions, substances of small molecular weight under 1,000 such as oxygen, carbon dioxide, and perhaps glucose, pass through the placenta in either direction by simple diffusion, and tend to assume equal concentrations on both sides of the placenta. Substances of higher molecular weight either do not pass at all (e.g. sucrose) or are transferred in some special way in which numerous enzymes appear to be concerned.

Certain substances may also pass from the foetus to the mother (*diaplacental passage*), and Leinziger[126] has demonstrated that contrast material may pass from the placenta into the maternal circulation (see also below *re* foetal blood).

The constituents of the human foetus are derived from two sources, viz. transplacental absorption from the maternal circulation, and synthesis in the foetal tissues.[75] The mechanisms of transfer include the following:[106]

1. A pumping action of the placenta, serving as a foetal pump or accessory foetal heart by virtue of its smooth muscle fibres, causing fluids to flow to and from the foetus;

2. A pumping action of the uterus pushing fluids towards the decidual-placental junction, i.e. towards the foetal circulation;

3. A biochemical enzymatic 'pumping' system, with possibly adrenocortical hormones in the maternal circulation playing a role. Then also the trophoblastic epithelium with its cells and enzymes varying in function at various stages of gestation allows diffusion of certain substances and is highly selective in regard to others. A list of the enzymes of the human placenta is given by Page.[35]

A tentative classification of transport mechanisms across the human placenta, based on the primary physiological significance of the substance transferred, relative rates of transfer, and mechanisms of transport and distribution, has been proposed by Page.[147]

The functional role of the placenta, transport, and the comparative anatomy and histology, were discussed at a Conference on Gestation.[35]

PHYSIOLOGICAL ASPECTS

The physiological function of the placenta is to permit the exchange of respiratory gases, nutrients, electrolytes, and water for foetal growth. These substances and others must cross the barrier consisting anatomically of 3 layers: trophoblastic epithelium, chorionic connective tissue, and foetal endothelial capillary lining.

Fructose injected intravenously in women at the end of pregnancy raises both foetal and maternal blood glucose, but intravenous glucose raises the foetal fructose very little.

Calcium utilization by the foetus is influenced by the vitamin-D intake of the mother, so that it is recommended that vitamin D and calcium should be administered in normal pregnancy. The developing foetus uses the dietary calcium of the mother about 5·1 times more than the dietary strontium.[34]

Fat appears to pass through the placenta to the foetal circulation. *Phospholipids* marked with ^{32}P and injected into the circulation of pregnant rabbits are taken up in large amounts by the placenta but they are not transmitted to the foetus.[16]

Amino acids injected into the mother increase the concentration in the foetal blood, which is at all times slightly higher than that of the mother. This is attributed to activity of the trophoblastic epithelium rather than the foetus.[136] There appears therefore to be an active transport mechanism for amino acids across the placenta. In healthy pregnant women at or near term it has been found that both unnatural D-histidine and natural L-histidine given intravenously cross the placenta by simple diffusion but the natural isomer, which crosses more rapidly, is assisted by an additional active transport mechanism.[148]

Radio-active isotopes, e.g. radio-active inorganic salts, have been used to study placental function and transmission, but need to be applied with caution. Pohl and Flexner[154] appear to have been the first to explore this field of investigation.

Radio-sodium is exchanged rapidly and always in excess of the metabolic demands of the foetus. It has been demonstrated that the permeability of the human placenta increases with gestation, the rate for sodium at 36 weeks being 70 times that at 9 weeks.[65,194] These studies as well as the data on the transference of deuterium oxide (heavy water)[97,194] have made it seem likely that the appearance time of radio-sodium in foetal blood is very short and peak concentrations are reached very rapidly—within 2 minutes in human pregnancy at term.[115] The rate of transfer of sodium per unit weight of placenta increases markedly as gestation proceeds.[74] The rate of passage of water and sodium from the maternal circulation to the amniotic fluid indicates, that the water of amniotic fluid is completely replaced, on average, every 2·9 hours, thus revealing that the amniotic fluid is not stagnant; the rate of transfer of water is about 5 times more rapid than that of sodium, indicating that the water is renewed about 5 times as rapidly as sodium.[194] It is of further interest that the exchange of radio-sodium at the placental site continues unimpaired during delivery until placental separation has taken place; thus, regardless of the major alterations in the uterus which accompany its evacuation at delivery, circulation in the intervillous spaces and exchange across the placenta are maintained.

In more recent studies it has been found by tracer methods that the quantity of sodium transferred across the human placenta is, on average, 450 times greater than is needed for the growth increase of the foetus at the particular gestation period.[38]

Radio-active sodium has been utilized for locating the placenta in the intact human uterus, chiefly to determine whether maternal blood can be obtained from the placenta *in situ* by aspiration.[22] Injection of radio-sodium into the mother has provided evidence of the more insidious types of placental ischaemia.[112] The method has also been used as a means of diagnosing foetal death.[31]

Radio-iron studies (see also pharmacological section) have shown that the accumulation of substances in the placental parenchyma is one of the features of foetal-maternal exchange.[195] From studies with radio-active isotopes of iron and phosphorus it was cautiously suggested that occasionally at the end of pregnancy there may be leakage of substances or blood corpuscles across the placenta from mother to foetus and *vice versa*.[145] Criticism, however, was made that such a placental lesion, when once it occurs in cases where the male parent is homozygous Rh-positive, should always recur in every subsequent pregnancy. Recently, by the use of a new technique, which is not dependent on the blood groups of the mother or foetus, it was demonstrated that the transplacental passage of foetal blood to the mother's blood is rather common.[209]

The *copper* content of foetal liver is unusually high, but it diminishes in the nursing period. The concentration in the liver at birth is 4-10 times higher than in the mother.[160] The ceruloplasmin (copper-globulin) content of the serum of women is elevated during the last trimester of normal pregnancy.[80]

PHARMACOLOGICAL INVESTIGATIONS

DEPRESSANTS OF THE CENTRAL NERVOUS SYSTEM

Alcohol passes through the placenta and can be found in the foetal circulation. The toxicity of alcohol for foetal rats is about the same as for adult rats.[30]

Volatile anaesthetics easily pass the placental barrier and tend to reach the same concentration in the foetal circulation as in the maternal blood. With *ether* the concentration in the blood of infants breathing immediately after birth is definitely less than that of infants with neonatal apnoea, which suggests that ether itself and not apnoea delays the onset of respiration.[80] The passage of ether into the foetus is rapid, and as anaesthesia progresses the foetal concentrations approximate to those of the mother;[32] in experiments on animals the concentration is almost the same in the brain and liver of the foetus as in the placenta, and much lower than in the arterial blood and brain of the mother.

Cyclopropane, like ether, crosses the placenta almost quantitatively. The average depression of infants receiving cyclopropane *via* the mother is said to be significantly greater than with regional or other inhalation anaesthesia.[6]

Nixtrous oxide passes over very readily into the foetal blood stream, where it is found in about 58% of the concentration in maternal blood.[32] Administration to the mother of 90%-10% nitrous oxide and oxygen promptly abolishes foetal respiratory movement, while a mixture of 85-15 has no depressant effects on the foetus for 40 minutes or longer.[80]

In addition to anaesthetic gases and vapours, the barbiturates, paraldehyde, chloral hydrate, morphine, and pethidine are all transferred from mother to foetus.[4] *Chloral hydrate*, administered orally in doses of 1·4 – 3·1 g., is soon demonstrable not only in the maternal but also in the foetal blood stream, and with no ill-effects produced;[20] large doses, however, may kill the foetus *in utero*.[113] After the administration of *paraldehyde* the concentration in the foetal blood is about the same as in the mother's blood.[73] *Tribromo-ethyl alcohol* has been employed in the second stage of labour, but depression of the foetal respiration sometimes occurs and the drug is not advised in obstetrics.

Barbiturates

Barbiturates readily cross the placenta and are distributed throughout the tissues of the foetus, so that doses for the mother should not exceed an amount which will produce sedation during labour. Some obstetricians shun their use because they regard them as liable to depress the foetal respiratory centre like morphine, but others have administered even large doses sufficient to produce basal anaesthesia. Observation of the effect of a barbiturate on the mother may give inadequate evidence of its effect on the child. It is clear, however, that marked depression of the baby's respiratory centre can occur if large doses are given to keep a restless mother quiet.

In experiments on cats, rabbits, and guinea-pigs with relatively large doses of *barbitone* and *amylobarbitone* the concentration of barbiturate in the foetus was found to be much higher than that in the mother's blood, the uterus, the placenta and the amniotic fluid.[47] Complete anaesthesia of pregnant cats with *pentobarbitone* profoundly narcotizes the foetus so that most die within 2 hours. Traces of barbiturate may be demonstrated in the amniotic fluid, placenta and foetus of rabbits receiving hypnotic doses of *barbitone sodium*.[48] Foetal respiration is particularly sensitive to the *thiobarbiturates*, as shown in rabbits, in which a dose that caused 50% decrease in the ventilation rate of the mother reduced the foetal respiratory rate by 85%, and this was not related to hypoxia.[50]

Thiopentone has been found in minimal amounts in the blood of the newborn infant up to 7 minutes after a single injection of the barbiturate, and equilibrium between maternal and foetal blood was reached within 10-12 minutes after the induction of anaesthesia, after which the foetal level was very low.[96] When this thiobarbiturate was administered 4-11 minutes before delivery it depressed the ability of the infant to gain normal adult oxygen saturation; at the end of 1 hour the average saturation was 80%, which was not significantly lower than in infants whose mother received no general anaesthetic.[156] From estimations of the maternal and placental concentrations of thiopentone it was found that 58% was transmitted across the placenta, with the foetal concentration only reaching 28% of the initial peak level attained in the mother;[33] the times of delivery of the infants in relation to the injection of thiopentone are unfortunately not given by these workers. Thiopentone given immediately before delivery by McKechnie and Converse[137] was found to cross the placenta rapidly, and in mixed umbilical-cord blood reached equilibrium with the maternal venous blood in 3 minutes; it was unusual for the babies to show respiratory depression. It has been suggested that thiopentone is distributed from maternal blood to the maternal tissues so rapidly that the actual amount reaching the infant is not enough to produce cerebral depression. On the other hand, Crawford[39] found that there was no appreciable placental barrier to thiopentone. Dundee[51] states that there is a delay of at least 5 minutes in the maximum transmission of barbiturates across the placenta; by the time equilibrium has been reached between maternal and foetal blood levels the peak of concentration of barbiturates in the mother will have passed.

Thioamytal injected intravenously in parturient women was found to be in equilibrium in the maternal and foetal blood within 4-5 minutes, and this equilibrium was maintained for at least 1 hour.[114] *Pentobarbitone sodium* crosses to the foetus almost immediately after intravenous injection in the mother, and reaches 74% of the maternal blood level.[62] *Amylobarbitone* and *phenobarbitone* administered intramuscularly, and *barbitone* orally, during the 4th to 7th months of human pregnancy, were demonstrated by spectrophotometric methods to reach equilibrium in maternal and foetal blood during the first 30 minutes, and the rate of elimination was about the same in mother and foetus.[152] The preparation *vinbarbital* in doses of 0·3 g. caused delay in respiration in the babies.[164]

More evidence is needed to support the view of certain workers that different barbiturates vary in their effects on respiration.

In fatal human poisoning (suicide) the level of barbiturate in the foetal blood was almost twice as high as in the mother's blood, owing to less effective detoxication and elimination.[134]

Bromides given during pregnancy may produce eruptions on the infant's face or body at birth (bromoderma).

Chlorpromazine given orally or intramuscularly for nausea and vomiting and hyperemesis gravidarum in doses up to 50 mg. 3 times daily produced no harmful effects on mother or child;[17] also when given intramuscularly every 4-6 hours during labour, alone or with analgesics and hypnotics, there were no significant effects on the newborn.[118] When given with pethidine and hyoscine in varying proportions to 1,881 patients delivered of 1,887 infants, active resuscitation was required in 2·6%, there was moderate respiratory depression in 11·9%, and 1·6% were stillborn.[128]

'*Trilafon*' given together with tuinal, pethidine, and scopolamine, or alone, in a double-blind study, produced no harmful effects in the child.[99]

Reserpine appears to be transferred to the infant *in utero*.[85] *Rauwolfia* (alseroxylon fraction), 1 mg. combined with amphetamine sulphate 3 times daily, later twice daily, produced no adverse effects on the foetus or the mother.[23]

Analgesics

The peculiar sensitivity of the foetus to the depressant effects of analgesic drugs is recognized and respiratory movements may be abolished in the foetus at a level of analgesia which does not impair maternal respiration.

Morphine readily crosses the placenta and is detectable in the foetus both chemically and by its pharmacological effects. It has caused death of the foetus in utero,[113] and distinct tolerance is found in the newborn of animals habituated to morphine.[161] Morphine has been in the main replaced by pethidine in normal labour because of its depressant effect on the foetal respiratory centre.

Dihydrocodeine given with hyoscine in repeated doses produced analgesic effects comparable to those of pethidine, with little respiratory depression of the baby.[164] One or more injections of 30 mg. subcutaneously, with one dose of 100-200 mg. of seconal orally at the beginning, produced no depressant effect on the foetus *in utero*.[144]

Pethidine has negligible effect on the respiratory centre of the foetus unless large doses are administered late in the second stage of labour. About 60-70% crosses the placenta. Less than 1% of a total dose of 100 or 200 mg. given during labour was found in the urine of the infants.[197] With doses that produce satisfactory analgesia in the mother there is not necessarily significant depression in the newborn baby. The plasma concentration in the infant may vary from 45 to 106% (average 77) of the levels measured

simultaneously in the maternal blood.[6] A mixture of 100 mg. of pethidine, 0·3 mg. of hyoscine and 10 mg. of nalorphine given in divided doses on demand by the patient for relief of pain during labour (the maximum amount of pethidine given was 200 mg.) caused no marked depression in the infants and none died.[91]

Alphaprodine (nisentil), 40 mg. subcutaneously, does not produce serious depression of the foetus, but when administered 5 times at 2-hourly intervals it produces foetal respiratory depression.[88] Doses of 30 mg. or less given subcutaneously caused somewhat less foetal depression than morphine and methadone.[177] This analgesic produces moderate or marked depression of the foetal respiration, varying from 5%[117] to 16%.[156] No foetal deaths have been recorded.

Methadone produces depression of foetal respiration intermediate in degree between that produced by morphine and by pethidine. The subcutaneous injection of 10 mg. caused severe foetal depression.[177]

Levorphanol (dromoran) in analgesic doses depresses and delays the respiration of the newborn infant.[87]

Nalorphine, injected about 10 minutes before delivery, or in the newborn infant, has been used in the prevention and treatment of neonatal depression due to analgesics used for sedation of the mother.[55,56,26,12]

Salicylate readily crosses the placenta. In rabbits and rats it passes into the foetal blood in the same concentration as that in the maternal blood.[110] Abortion and foetal death occur only with doses that are fatal to the mother.

OTHER DRUGS

Stimulants of the Central Nervous System

Caffeine administered in fairly large doses to dogs was found in the foetal blood and liver in as high a concentration as in the maternal tissues.[61] Stieve[155] a Berlin anatomist, found that when small doses of caffeine were given to black rabbits during pregnancy the offspring generally died and anatomical changes were demonstrable in the placenta and in the offspring.[193]

Amiphenazole given intramuscularly to the mother in doses of 30 mg. reduces the depressant effect of morphine on foetal respiration and reduces but does not completely eliminate neonatal apnoea caused by morphine.[102]

Autonomic Drugs

Amphetamine sulphate in 5 mg. doses combined with rauwolfia (alseroxylon fraction) produced no adverse effect on the foetus or the mother.[23]

Hydergine given intravenously produced a small decrease in the foetal heart rate.[179] Orally or sublingually it caused no foetal or maternal complications.[111]

Hydralazine has not been shown to have any effects on the infant.

Neostigmine administered during pregnancy produced no ill-effects on the foetus.[99]

Atropine readily crosses the placenta and enters the foetal circulation.

Ganglion-blocking Agents

These are best avoided during pregnancy because they can cross the placenta and may cause paralysis of the intestine of infants.

Hexamethonium passes freely across the placenta in rabbits and can soon be detected in the liquor.[206,207] The possibility of aspiration of amniotic fluid by the human foetus with harmful effects (ileus) was suggested by Morris.[139] Large doses administered for pregnancy toxaemia may cause ileus or bladder distension in the infant; the bladder and stomach of the newborn should be emptied since the amniotic fluid may have had a high concentration of hexamethonium.[163] Submammary drip infusion given after an intramuscular dose in severe toxaemia caused no apparent harm to the foetus.[13]

Mecamylamine appears to have caused fatal ileus in a premature infant.[3] Because of this danger it is recommended that mecamylamine should never be administered to pregnant women within 48 hours of the onset of labour. Repeated or big doses given to the mother may produce effects on the foetal intestine that may last for many days after birth.

Skeletal Muscle Relaxants

When quaternary ammonium muscle relaxants are present in the maternal blood of animals the foetal blood does not contain paralysing concentrations. Small amounts probably pass through the rabbit placenta but the foetal neuromuscular junction is less sensitive than that of the adult.[207]

Tubocurarine does not appear to cross the placenta in significant amounts.[116,40] Injection into the uterine artery of dogs near term was followed by placental transmission of the drug in non-dangerous amounts; in human babies delivered with the aid of therapeutic doses of the relaxant, clinical curarization was not observed.[150] *Tubadil*, a long-acting tubocurarine preparation, given intramuscularly also produced no ill-effects on mother or child.[198]

Gallamine enters the foetal circulation more readily than tubocurarine. However, in a large series of forceps deliveries and Caesarian sections, 100 mg. caused no depression of the baby.[191] It has been demonstrated in the foetal serum, often in readily detectable and apparently significant amounts.[40] In dogs it crosses the placenta after injection into the uterine artery.[151]

Decamethonium crosses the placenta when given intravenously in large doses just before delivery,[58] but did not do so when it was injected into the uterine artery in dogs.[151]

Suxamethonium was found to cross the placenta by Little *et al.*,[129] but not so by Thesleff.[187] After injection into the uterine artery in dogs it was found to pass through the placenta.[151]

Drugs Acting on the Cardiovascular System

Digitoxin, in radio-labelled form, and possibly its metabolic products, were shown to pass through the placenta of rats and guinea-pigs; on a tissue weight basis the concentration in the foetal heart is higher than in the maternal heart.[146] It would appear that as the gestation period increases there is a corresponding increase in the rate of transfer of digitoxin across the placenta.

Drugs Affecting the Urine

Mersalyl does not pass into the amniotic fluid.[176]

Drugs Acting on Blood Vessels

Ganglion-blocking agents, reserpine, hydralazine and other drugs used in hypertension have already been considered.

Protoveratrine given orally or intravenously in toxaemia of pregnancy produced no foetal death, no pooling of secretions in the respiratory tree, and no respiratory depression.[125]

Antihistaminic Drugs

Promethazine (phenergan) given with pethidine to patients in active labour had no apparent effect on the condition of the babies at birth.[63]

Buclizine hydrochloride given in relatively large doses over a long period for nausea and vomiting of pregnancy was unassociated with foetal, or maternal, complications.[36]

The Respiratory System

Carbon dioxide 7·5% in oxygen has little or no effect on foetal respiration, in contrast to marked stimulation produced in the mother.

Carbon monoxide was not found in the foetus in fatal poisoning of a pregnant woman; the mother's blood was cherry-red in colour but the blood of the foetus was dark in colour and contained no carboxyhaemoglobin. These findings were adduced as an indication that there is no transfer of red blood corpuscles across the intact placenta, since CO is fixed in the red cells.[134] Caesarian section might therefore be advisable to save a foetus near term. However, in an analysis of the literature Curtis *et al.*,[42] found that most authors have reported actual passage of CO from maternal to foetal circulation, with several foetal deaths, but some authors have stated that this does not occur. Recently Friberg *et al.*[79] demonstrated that CO is transmitted, slowly, from maternal to foetal blood. In animal experiments it has been found that the percentage saturation of foetal haemoglobin with CO depends on the percentage saturation of the mother's haemoglobin and the length of exposure to the gas.

Salts

Magnesium sulphate injected intravenously and intramuscularly in toxaemia of pregnancy produced no signs of significant foetal depression although the degree of hypermagnesaemia in the foetus closely paralleled that in the mother.[158]

Sodium fluoride passes freely across the placenta to the foetus[142,94] but, while high concentrations in the mother mean high blood levels in the baby, this is not in direct proportion. This has also

been demonstrated in mice and, in the newborn mice, abnormalities were observed in the jaw bones, enamel, and dental pulp.[64] The possibility that fluorine may cause mitotic disturbances and teratism in the foetus is emphasized by Steyn.[184] Many workers believe that the ingestion of fluoride by the mother during pregnancy has no effect on the newborn child since it is only available in small amount to the foetus, and some regard its deliberate administration during pregnancy and lactation as beneficial in reducing the incidence of caries in the child.

Drugs Acting on the Blood and Blood-forming Tissues

Cyanocobalamin crosses the placenta from mother to foetus.[80,130,166] Attempts to influence foetal blood formation by the administration of liver extract during pregnancy have not been successful; this is not surprising since in pernicious anaemia the administration of the haematinic principle in excess of the amount necessary to produce a maximum response brings about no added effect. Cyanocobalamin and folic acid in the mother's serum decrease during pregnancy, owing presumably to their transfer to the foetus.[8] In some cases the serum levels in the infant at birth are more than 4 times as high as in the mother.

Iron is transferred from mother to foetus in considerable amounts during pregnancy, 400 mg. to the foetus and 150 mg. to the placenta, and large iron reserves protect the new born infant against anaemia for a time if it is kept on a milk diet.[105] The concentration of foetal serum iron at birth is almost double that in the mother's serum. The transport of iron across the placenta in rabbits has been studied by Bothwell *et al.*[21] Potassium ferrocyanide or iron ammonium citrate injected into the mother does not pass into the foetus, but with simultaneous administration of ascorbic acid the ferric citrate is enabled to pass.[170] Saccharated iron oxide injected intravenously is rapidly transferred to the foetus and converted into physiological iron compounds.[157]

Radio-active iron given orally in a single dose to pregnant women near the end of gestation appears in the foetal circulation within 40 minutes. It becomes widely disseminated in the foetal tissues, with the highest concentration in the red blood corpuscles and the largest quantity in the liver.[155] Red cells tagged with radio-iron and injected into pregnant women produced significant amounts of radio-activity in the blood of the foetuses in 25 out of 29 patients.[138] Other investigations with radio-iron are considered in the section dealing with physiological studies.

In women, red blood corpuscles have been shown to cross the placenta from foetus to mother[209] (see above); and sickle-trait cells have been shown experimentally to cross the placenta to the foetal circulation in a small percentage of subjects.[132]

Dicoumarol has been given to women before, during and after labour, with beneficial effect on phlebothrombosis, thrombophlebitis, and pulmonary embolism; prothrombin estimations are then absolutely essential. The anticoagulant crosses the placenta and may produce harmful effects on the foetus; cerebral haemorrhage may occur in the newborn infant. Intra-uterine death from haemorrhage occurred in one foetus on the 53rd hospital day, and it was delivered stillborn and macerated on the 74th day.[165] In pregnant rabbits large doses caused death of the foetuses *in utero*; although 'safe' prothrombin levels were maintained in the mother the prothrombin activity was found to be markedly decreased in the infant rabbits at birth.[124]

Drugs from Endocrine Glands

Oestrogens and *androgens* given in large doses to women in early pregnancy appear to produce no adverse effect on the foetal reproductive system.[45] However, when large doses of oestrogens are given to pregnant rats they produce feminized male offspring.[83] and androgens cause the production of masculinized female offspring.[82]

Cortisone was given by Wells[200] for hyperemesis gravidarum and 24 out of 27 infants were apparently normal at birth, but 3 had abnormalities (coarctation, club foot, undescended testes), and another baby was later found to have cataract in one eye. Katzenstein and Morris[119] could find no evidence of damage to a baby from cortisone and corticotrophin therapy given to the mother. They also cite reports of other cases where steroid therapy in pregnant women produced no damage in the babies. On the other hand it has been demonstrated experimentally that cortisone and corticotrophin may damage the foetus *in utero* in mice[67,68,77,162] and in rabbits.[37]

Thyroid hormone normally crosses the placenta and controls the development of the foetal thyroid gland.[25]

Thyroxine and *tri-iodothyronine* (labelled with ^{131}I) given by injection have been studied in women with regard to their passage from mother to foetus;[143] the concentration of organic ^{131}I in the foetal serum was approximately 1/10th that in the maternal serum. The passage of thyroxine across the placenta in guinea-pigs and rabbits is very slow. The rat placenta is slightly permeable to thyroxine.[104]

Iodine administered during pregnancy for at least the last 4 weeks decreased the incidence of goitre in newborn infants in Switzerland from 38% untreated to 8·4% treated.[201] Hundreds of thousands of pregnant women have taken about 100 μg. of iodide every day without harmful effects on mother or child.[57] Studies with *radio-active iodine* have shown that in the human foetal thyroid localization occurs at the time of appearance of discrete thyroid follicles in the 14th-32nd weeks; concentration of radio-iodine occurs only if the mother is injected after the thyroid follicles develop.[27] The human foetal thyroid can accumulate demonstrable amounts of ^{131}I by the 12th week of gestation.[100] In a case treated with radio-iodine during the 6th month of pregnancy there was no detectable effect on the infant.[28]

Sodium radio-iodide (radio-active iodine) is considered to be contra-indicated in pregnancy and lactation because it crosses the placenta freely and is stored in the foetal thyroid after the 3rd month.

(*Thiouracil* compounds cross the placenta from mother to foetus in animals,[149] leading to thyroid hyperplasia and cretinism in the young; this has also occurred in human pregnancy.[60,140] This drug-induced congenital goitre regresses progressively to normal.[1] Thiouracil compounds can be used effectively for hyperthyroidism in pregnancy, but the procedure is not without risk to the infant.)

Insulin apparently does not cross the human placenta, but investigations are still being made on this problem. The hormone appears to pass across the placenta in the rat at full term, also in rabbits and sheep.[183] *Alloxan*, which has been much used experimentally, is found within one or two minutes in the cord blood of rats following its injection into the mother.[71]

Vitamins

Ascorbic acid is always at a higher level in the foetal plasma than in the maternal plasma. After administration of the vitamin both the foetal and maternal plasma levels rise, followed by a fall, which is slower in the foetal plasma.[10] A detailed report on the placental transfer of ascorbic acid in guinea-pigs and human beings is given by Raiha.[159]

Riboflavine is also in higher concentration in human foetal blood than in the maternal blood. The placenta probably effects the transfer by taking flavin adenine nucleotide from the maternal blood and splitting it to free riboflavine.[131]

Vitamin A and carotene in the foetus are both increased when there is an increase in maternal carotene, but an increase in maternal vitamin A is not followed by a similar response in the foetal circulation.[11] It has been concluded that the principal transfer to the foetus takes place in the form of carotene and the foetal system converts the carotene to vitamin A. A period of several weeks is required for these transplacental changes to occur.

Menaphthone crosses the placenta, and used prophylactically it produces marked reduction in infant mortality and haemorrhages (hypoprothrombinaemia of the newborn).[95]

Alpha-tocopherol concentration in the umbilical venous blood is generally higher than in the maternal blood when the latter tocopherol value is high, and 3-4 times higher than that of the umbilical arterial blood.[7]

Metals

Copper (see above).

Mercurials cross the placenta. Congenital syphilis was at one time treated by mercurial inunction of the mother, and the concentration in the amniotic fluid was found to be 0·2 – 0·6 mg. per litre.[178]

Lead administered to rabbits injured the chorionic epithelium and caused coagulation necrosis and haemorrhages, with death of the foetus.[44] Rats are resistant to this effect. The quantity of lead in the newborn animal (rats, dogs) is proportional to the amount ingested by the mother.[24,141] The exposure of either parent to lead is believed to decrease fertility, probably by interfering with implantation or early development of the zygote.

Lead-mining districts in Europe are stated to have an abnormally high incidence of malformed and defective children.

Arsenic when given intravenously in the form of arsphenamine and neoarsphenamine passes through the human placenta; traces reach the foetus, not by simple diffusion but by some other mechanism, and it is constantly present in the meconium of newborn infants.[54] In rats, arsenic crosses the placenta when arsenic trioxide is included in the diet.[141]

Bismuth passes freely across the placenta to be distributed in the foetal tissues, including the bones. It has also been found in the amniotic fluid of the human foetus.[123] In rabbits the distribution in the tissues is the same as in the adult.[127]

Lithium salts exert a direct toxic effect on embryonic tissue, and reduce the percentage of deliveries in pregnant mice.[15]

Selenium passes through the placenta of animals into the foetus.[175] In stock poisoning the foetus may be born without hoofs. The first evidence of the placental transmission of selenium in human beings was recently reported.[86]

Thallium passes into the foetus.[69]

Boric acid (boron) passes through the rat placenta to the foetus.[105]

Chemotherapeutic Agents

Sulphonamides readily pass through the placenta into the foetal circulation and tissues. The blood levels are 50-90% of those in the maternal blood. The drug appears more slowly in the amniotic fluid than in the foetal blood. Sulphanilamide crosses freely,[150] and so do sulphathiazole and sulphadiazine,[182] and sulphamethoxypyridazine.[208]

As regards toxic effects from sulphonamides the following reports are cited. In rabbits sulphanilamide was found to increase the neonatal mortality[2] and large doses given to rats throughout pregnancy also caused increased mortality.[181] In pregnant mice sulphadiazine and sulphamerazine decrease the number of deliveries.[15] There is evidence of possible injury (anaemia and jaundice) to the human foetus from sulphanilamide therapy,[93] and acute liver atrophy and acute haemolytic anaemia resulted from administration of sulphanilamide to the mother.[76] It has been found that the administration of sulphonamides to rats during the latter part of gestation produces almost complete absence of calcification in the foetus; this is attributed to inhibition of phosphatase.[19] The continued administration of sulphaguanidine to pregnant rats delays the development of the foetus.

There are rarely indications for prolonged administration of sulphonamides during pregnancy. In view of the above findings the continued administration of big doses may be hazardous.

Penicillin injected into the mother is transmitted through the placenta, appearing in significant amounts in the foetal blood, but usually much below that in the maternal blood; the antibiotic is found also in the amniotic fluid. Bacteriostatic levels are reached in the foetal circulation.[98,84,107,205,29] Thus adequate treatment in pregnancy is almost 100% effective in the prevention of congenital syphilis or in curing an already infected foetus *in utero*.[196,171,41] Procaine penicillin and the penicillin ester penethamate hydriodide given intramuscularly during labour cross the placenta and satisfactory cord levels are maintained over a 24-hour period.[14]

Streptomycin passes through the placenta but the concentrations found in the foetal blood and tissues and in the amniotic fluid are 50% or less of the concentration in the maternal plasma.[120,81,29]

Tetracyclines readily enter the foetal circulation in antibacterial concentrations,[29] the levels usually being only ¼ - ⅔ of those in the maternal blood. When oxytetracycline (2 g.) is administered during labour some crosses the placenta and is present in cord blood; it appears to have no harmful effects on the newborn.[49] In pregnant rats which ingested chlortetracycline the drug could be demonstrated in foetal tissues.[59]

Chloramphenicol is found in the foetal blood at a level about ¾ that in maternal blood.[168] After the administration of 2 g. orally no toxic reactions occur in mother or infant, and the concentration in foetal cord blood is generally at a therapeutic level.[169,29]

Erythromycin crosses the placenta when a total multiple dose of 0·6 – 1·0 g. is administered within 18 hours of delivery.[122]

Quinine passes through the placenta and may cause congenital blindness and deafness in the offspring from damage to the ganglion cells of the retina or the internal ear. This view has been challenged. It is strange that cases were not reported more frequently in the past. Also to be considered is the fact that the effects of rubella on the foetus have only been appreciated in recent years. In malaria, quinine and more recently introduced compounds have been used to prevent congenital infection which may occur with *P. falciparum* infection of the mother.

Mepacrine crosses the placenta.[80]

Vaccines, Toxins, and Antitoxins

Diphtheria and pertussis and tetanus vaccines injected into pregnant women produce a high titre of antibodies in more than 80% of the mothers and their infants;[32] that is to say, transplacental protection against these diseases can be increased by active immunization of the mother during pregnancy. Diphtheria and tetanus antitoxins pass the placenta and also the immune bodies opposing the viruses of measles, smallpox, mumps, poliomyelitis, and the ordinary upper respiratory infections.

Allergens and antigens, viral as well as others, may cross the placenta. The transplacental passage of important allergens rarely results in clinical manifestations of immediate postnatal hypersensitivity and can seldom if ever be demonstrated by skin tests at the time.[85] The passage of the Rh antigen from foetus to mother and the return of anti-Rh antibodies into the foetus show that unchanged protein is able to cross the placenta. Immunization of an Rh-negative mother with Rh-positive blood produces antibodies that enter the foetal circulation and destroy the foetal cells, and similar phenomena may occur with other antigens (e.g. in ABO incompatibility of the mother and foetus). Glutinins (univalent antibodies) traverse the placenta more readily than agglutinins (bivalent antibodies), as shown in studies on two cases of erythroblastosis foetalis.[202]

The transfer of antibodies from mother to young before and after birth has been studied in many laboratory animals and in women. The transmission may be directly *via* the placenta or *via* the amniotic fluid with selection of gamma globulins occurring at the enterodermal lining of the foetal gut. The transfer of other serum proteins from mother to foetus needs more study. The selective placental transmission of whole homologous serum proteins (albumin and gamma globulin) from mother to foetus has been demonstrated in the near-term rhesus monkey; in this animal the placenta resembles the human placenta very closely in the later stages of pregnancy. The amniotic fluid appears to play an unimportant role in the transfer of these proteins.[9] The placental transfer of albumin is reviewed by Winkler *et al.*,[203] who also report on the placental passage of radio-active iodinated rabbit albumin; this transfer is slow so that protein nutrition of the foetus is dependent rather on the passage of simple amino acids than the transfer of the larger protein fractions.

Drugs used in Neoplastic Diseases

Nitrogen mustard injected into pregnant mice in a single dose at the 10th–12th day of gestation had no apparent effect on the mother but induced profound changes in the foetuses, some being killed and others showing teratological anomalies.[43] In pregnant rats nitrogen mustard has produced foetal abnormalities or foetal resorption.[92]

Urethane has been administered to a woman suffering from chronic myeloid leukaemia; the baby showed no evidence of leukaemia.[109] In pregnant mice this drug may cause less young to be produced per litter[101] and embryos may suffer malformations or death.[174]

Mercaptopurine has been administered in acute leukaemia complicating late pregnancy without producing ill effects in the foetus.[147]

Folic acid antagonists, e.g. aminopterin and methotrexate, seriously interfere with embryogenesis through an action on the embryonic mesenchyme. Decidual tissue and placental tissue are unaffected by doses of the drugs which cause foetal death. These drugs should not be administered during pregnancy.[190] In the human subject 6–12 mg. of aminopterin administered in the first trimester of pregnancy induced foetal death and spontaneous delivery in 10 out of 12 cases. In young foetuses there was depression of haemopoeiesis and necrosis of tissues; in 3 older foetuses malformation of the cranium was present.[188] In a recent series of publications Thiersch[189] has reported on compounds with anti-neoplastic properties which produce lethal effects on rat foetuses *in utero*.

Sodium radio-iodine has been considered above in connection with thyroid disorders. When ^{131}I was administered to a woman with carcinoma of the thyroid the foetus delivered 6 days later

by abdominal hysterotomy was found to contain enough radio-iodine in its thyroid to ensure a dose of at least 80,000 rads.[78]

Strontium (radio-active) passes into the foetus of pregnant rabbits; retention in the mother and foetus is greater when the diet is low in calcium.[121,192,133]

The Hiroshima atomic bomb explosion caused 7 out of 11 children exposed during the first half of intra-uterine life, within 1,200 meters of the bomb hypo-centre, to develop microcephaly with mental retardation. Radiation produced an interruption of pregnancy in a number of cases.[153]

Malignant tumours have been found in 4 instances to have crossed the placenta from mother to foetus—from bronchial carcinoma, from lymphosarcoma, and in 2 cases from melanosarcoma. The presence of tumour tissue in the placenta is rare, but not in the foetus.[199] Metastasis of maternal tumour (carcinoma) to the placenta has been reported, with the babies and the umbilical cords unaffected.[18]

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