SOME ASPECTS OF PLACENTAL FUNCTION

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THE PERINATAL Mortality Survey has shown that deaths due to anoxia during and before labour account for 10.5 in every 1,000 deliveries (Butler and Bonham, 1963). It is believed that the majority of these intrauterine deaths are due to an abnormality of the placenta (Potter, 1961). Although in some such cases an anatomical lesion of the placenta may be found, as for example, in retroplacental haemorrhage, placental infarction and massive thrombosis of the placental blood vessels, in most cases there is no anatomical lesion in the face of obvious physiological failure. It is because of this that an important obstetrical research problem at the present time is the development of a placental function test (Corner, 1964). Such a study must be based on an understanding of the constitution of normal placental activity, and the following discusses some of the present-day knowledge of those aspects of the structure and function of the placenta which are related to transport of naturally occurring substances.

Whilst many instructive data have resulted from observations made on humans, the possible risk to mother and foetus precludes the employment of a number of useful experimental techniques, and so much information has been gained from the use of other animals. From such studies it is possible to conclude that the foetus is a highly independent organism physiologically. This is probably mediated in the placenta whose cells are not passively equilibrating with those of the mother, but are metabolically very active. However, there still remains doubt as to the actual anatomical location of the placental barrier.

Morphology

Basically the placenta represents the juxtaposition of foetal and maternal tissue for the exchange of materials. But the actual arrangement is variable within the Mammalia. In some animals, e.g. the Ungulates and Cetaceans, connection between mother and foetus is quite superficial, the two layers of tissue begin little

more than interdigitating. In others, e.g. Carnivores and Rodents, the foetal tissue becomes deeply embedded in the uterine epithelium and fused with it, so that at parturition the maternal portion is shed along with the foetal elements. This is a deciduate placenta.

As in other organs where the exchange of substances is effected, the surface area is increased, in this case by projections or villi. In labyrinthine placenta, as found for example in Rodents, these are interconnected by a complicated system of labyrinths. In placenta of the villous type, however, they retain their individual form, as in the Ungulates.

The gross morphology of the placenta is dependent upon the distribution of villi over the surface of the chorion. The pig and horse have a diffuse placenta with the villi present over the entire area. Where the villi arise in tufts scattered over the chorion, a placenta of the cotyledonous type is produced as in cattle. In Rodents, Insectivores and Man the villous area is disc shaped forming a discoid placenta and in Carnivores there is a zonary placenta with the villi arranged as a band around the chorion.

The actual foetal membranes involved in the formation of the placenta are variable. In all mammals, from the Insectivores upwards, there is a chorioallantoic placenta formed from the avascular chorionic membrane and blood vessels from the allantois. However, during development, a transitory stage may occur when either of two more primitive states, chorionic or yolk sac placentation, may predominate.

The fine structure of the placenta leads to yet another means of classification. Such a scheme was devised by Grosser as long ago as 1909, and remains intact today, although its shortcomings are recognised. Grosser found that within the Mammalia there was a basic difference in the numbers of layers of tissue separating the maternal and foetal blood, and postulated that this variation is brought about by the degree of erosion of the uterine epithelium by the invasive foetal tissues. He proposed four main types and named them in

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such a way that it is apparent which maternal and foetal tissue layers are opposed. In the group designated epitheliochorial which includes pig, horse, cow and deer, all the maternal tissue is present and the chorion lies against the endothelium. Erosion of the outer epithelium of the uterus so that the chorion contacts the connective tissue gives the syndesmochorial type found in sheep and goats. Further erosion leads to the formation of the endotheliochorial state where only the maternal blood vessels remain. This occurs in some Insectivores, bats and Carnivores. Finally, the haemochorial stage is reached in most Rodents and higher Primates, including Man; there the chorion is directly bathed by maternal blood. Later, Mossman (1926) added a haemendothelial state found in certain Rodents where the foetal blood vessels themselves are bathed by maternal blood.

Grosser also suggested that the placenta with the least layers of tissue separating maternal and foetal blood would allow larger and more molecules through to the foetus than one with a greater number of tissue layers, thus making a haemendothelial placenta more efficient than an epitheliochorial one.

Grosser's classification can be criticised because it has been found that the structure of any one placenta is not uniform throughout and in some areas of an epitheliochorial placenta there is as close an apposition of maternal and foetal blood vessels as is found in a haemochorial placenta. In addition, it is now appreciated that the overall arrangement of the tissues is of less importance than the actual constituent cells and their possible activities.

Today, although the anatomical aspect is being pursued with the aid of the electron microscope, studies incline towards the physiological implications of the placenta.

Transport Mechanisms

Since the placenta consists of a thin layer of cells separating the maternal and foetal blood streams, the permeability of the placenta may depend upon the function of the membranes of these cells. In many cases there is only the capillary wall dividing the maternal and foetal environment, but Crawford (1962) warns against attributing absorptive and excretory regulation solely to this. From the work of Davson and Danielli (1952) and Robertson (1959) it is known that the cell membrane consists of a bimolecular lipid layer covered on its inner and outer surfaces by a layer of protein. The actual mode of transport through such a protein-lipid membrane still remains

a source of speculation. Pores are present, and Schanker (1962) has suggested that these allow water and ions to pass through whilst larger molecules are transferred by a carrier mechanism. Moya and Thorndike (1962) have suggested four possible transport mechanisms, ultrafiltration, diffusion, active transport and pinocytosis. The first of these received much support fifty years ago but is not nowadays seriously considered. Diffusion, the process by which substances move down the concentration gradient and establish equilibrium across a membrane, and more especially facilitated diffusion, where the equilibrium is reached more quickly than can be explained on physico-chemical grounds, may account for the transport of gases. But Huggett (1959) suggests that all other substances are transferred by active transport. This is a process whereby substances are moved against the chemical potential and concentration gradients (Ussing, 1949) and depends on some special activity on the part of the cells (Mudge, 1949) which involves expenditure of metabolic energy. Some form of carrier system is envisaged and Siekevitz (1959) has postulated one such for the transport of glucose in and out of a cell. Glucose enters the cell by pinocytosis and is phosphorylated onto the endoplasmic reticulum by hexokinase. Glucose-6-phosphatase then transfers the glucose into the vesicles of the endoplasmic reticulum, whence it will pass out of the cell. Certainly, deprivation of oxygen decreases the rate of placental transport, and the placenta has a rate of oxidative phosphorylation similar to the adult liver and kidney and contains at least as great a range of enzymes as these organs (Villée, 1962), which suggests that these membrane components may be involved.

Finally, the possibility that pinocytosis is a means of transport cannot be totally excluded since there is increasing evidence from electron microscope studies that this is a common phenomenon in certain mammalian cells. In the placenta this may involve minute invaginations in the endothelial cells of the villi, engulfing portions of the maternal plasma and transporting these droplets to the foetal blood.

Transfer of Physiological Substances

Studies on the passage of substances through the placenta have been greatly enhanced by the work of Flexner and Pohl who, in 1941, introduced the use of radioactive isotopes in this field. By administering labelled substances to the mother and measuring the rate of

accumulation in the foetus the actual rate of flow across the placenta can be estimated.

The tissues of the embryo are composed of a high percentage of water, although during the course of pregnancy this progressively decreases (Dickerson and Widdowson, 1960). However, Gellhorn and Flexner (1942) found in the guinea pig that the foetus does not merely absorb the amount of water necessary for growth, but carries out a continuous exchange with the mother at a very rapid rate. This exchange rate is not constant throughout gestation. In the human foetus at 14 weeks, 700 times the amount of water incorporated into the growing tissues enters the foetus, and by the 31st week this has risen to 3,800 times. At the 35th week, water traverses the placenta at such a speed that the amniotic fluid is renewed twice each hour. By the end of gestation, however, this has decreased so that the amniotic fluid is changed only once in 2.9 hours (Flexner, Cowie, Hellman, Wilde and Vosburgh, 1948).

Taking into account this very rapid transport of water across the placenta, and experimental evidence from sheep and goats, Meschia, Battaglia and Barron (1957) conclude that the placenta is freely permeable to water. Such a passive behaviour of the placental barrier would explain the rapid attainment of osmolarity between foetal and maternal circulations demonstrated by Dancis, Worth and Schneidau (1957) in the rabbit. Paul, Enns, Reynolds and Chinard (1956) have further shown that in the rabbit not only the placenta is involved, but the membranes play an integral part. They suggest that as much as 50% of water exchange occurs between the amniotic fluid and the maternal circulation through the foetal membranes.

Nevertheless, Seller (1963b) has presented evidence that in the rat transplacental flow of water is not merely an expression of passive transport. For when the maternal blood was overhydrated by intravenous injection of water, there was no concomitant dilution in the foetus; instead, the foetal blood showed a dehydration. Further, the rest of the foetal tissues also resisted hydration (Seller, 1963a). It appears therefore that foetal homeostasis is being maintained against an osmotic gradient by some process at the foetal/maternal barrier. This suggests that energy is being expended whilst actively extruding water or ions from the foetus. In the same experiments, when a very large volume of water was introduced into the mother, the water content of the whole foetus did rise, when a maximal rate of ion extrusion is

suggesting that there may be a threshold effect obtained, and at osmotic gradients higher than this level ions could flow into the foetus. Adolph and Hoy (1963) have also found the rat foetus very resistant to a gain in water content.

Interest in the transport of carbohydrates is centred on the fact that the placentae of mammals may be separated into two categories with regard to the transfer of these materials. The first group includes Rodents, Carnivores and Primates where the placenta contains much stored glycogen and the circulating sugar is glucose. The second is seen in the Ungulates where the placenta contains little glycogen, but the foetus has in addition to glucose, a second monosaccharide sugar—fructose. In these animals maternal glucose is converted to fructose, and fructose production is constant in any one animal and is independent of both maternal and foetal glucose levels. (Alexander, Huggett, Nixon and Widdas, 1955).

In the Rodent and Primate series, fructose is present but in very low concentrations. It does cross the placenta but is transferred at an extremely slow rate. When it reaches the foetus, it is not incorporated into the foetal tissues as is glucose, but remains in the plasma and is slowly converted to glucose, possibly by the liver (Davies, 1954). Glucose rapidly crosses the placenta but the amount of glucose in the foetal blood is less than in the maternal blood. This is not due to a more rapid utilisation by the foetus, but is maintained by the active process of the placenta (Davies, 1955). In the rat, after intravenous infusion of glucose to the mother, this situation still exists, but the difference between the two levels is reduced somewhat (Seller, 1964a). This suggests that the placenta, while allowing transport of glucose, does not altogether permit its free passage. This implies some form of carrier system, and although Widdas (1952) has calculated the kinetics of a possible system, this remains a theoretical proposition.

There is conflicting evidence as to whether insulin is transferred. But the discrepancies may be explained by other observations for it appears that in the rat and the human, insulin accumulates in the placenta and is degraded (Freinkel and Goodner, 1962; Buse, Roberts and Buse, 1962). It is also questionable whether the foetal tissues are mature enough to respond to insulin. Foetal sheep, goats and dogs give little or no hypoglycaemic reaction to massive doses of insulin (Passmore and Schlossman, 1938; Schlossman, 1938). Davies and Lacy (1957) found the same to be true for rabbits.

Further, Stimmler, Brazie and O'Brien (1964) have demonstrated that although the blood of newborn infants of diabetic mothers has a raised insulin level it also has a high glucose level. It is not until one hour after birth that the insulin has a hypoglycaemic effect.

Sodium, like water, is continually being exchanged across the placenta but at a rate fifty times less rapid than that of water. (Gellhorn and Flexner, 1942). In the rat they observed that the relative permeability increases during the first nine tenths of pregnancy. In humans at 36 weeks' gestation the permeability has increased seventy times from that which existed in the ninth week. Cox and Chalmers (1953) have calculated that this amount is 450 times that required for foetal growth. During the last few weeks of pregnancy, the permeability to sodium decreases. This increased facility for sodium transport as gestation progresses has been attributed to an increase in the number of villi with proliferation of the blood vessels. The sudden decrease in transfer has been correlated with the appearance of thrombi and other vascular changes associated with hyaline degeneration which occurs in the placenta in the later stages of pregnancy (Dancis, 1962).

D'Silver and Harrison (1953) have found that the cells of the placenta of rats and guinea-pigs are fast exchangers of potassium, and that transport does not take place between mother and foetus. No dynamic studies have been carried out on the placental transport of the chloride ion. While most investigators agree that the concentration of potassium is markedly higher in the foetal than the maternal blood plasma, there appears to be a species variation in the relative concentrations of sodium and chloride in the maternal and foetal plasma. The potassium level in the foetal plasma may be nearly twice that occurring in the mother in the rat. (Christianson and Chester-Jones, 1957; Seller, in preparation). It has been suggested that this is due to the effects of hypoxia (Barker, 1961), although McCance and Widdowson (1961) have excluded this possibility in the pig. Kerpel-Fronius, Nagy and Bata (1962) have shown that premature babies have a high potassium level, but the more premature the baby is, the higher the concentration of potassium. These babies show no symptoms of hyperkalaemia which suggests that such a high potassium concentration is a true physiological state. All these observations indicate that active transport against a concentration gradient must have occurred in the placenta.

Calcium, too, is present in higher concen-

trations in the foetus than the mother (Needham, 1931). Strontium crosses the placenta but at a rate slower than calcium, and both in the rat and rabbit the placenta will select calcium in favour of strontium (Wasserman, Comar, Nold and Lengeman, 1957). It is not known whether this is so in humans. Wilkinson and Hoeker (1953) have demonstrated that barium is transported but at a rate still slower than strontium.

There appears to be no placental transport of molybdenum in swine (Shirley, Jeter, Feaster, McCall, Outler and Davies, 1954), chromium in the rat between the fifteenth and twentieth day of gestation (Visek, Whitney, Kuhn and Comar, 1953) and radium. Martland and Martland (1950) studied the children of women who had been subjected to accidental radium poisoning in pregnancy and found that they were healthy and completely unaffected.

Iron crosses the rabbit placenta against a concentration gradient (Bothwell, Pribilla, Mebust and Finch, 1958) and its passage has been confirmed in several other species including Man (Widmer, 1948). Laurell (1947) found that iron is transported in serum in combination with a specific iron-binding protein, and Nylander (1953) showed that this substance, ferritin, is involved in iron transport in the rat placenta. There is experimental evidence that most other inorganic ions are transferred with relative ease in at least one species, and the same is true for most anions. Inorganic phosphate crosses the placenta, but only in amounts approximating to that required for growth. (Wilde, Cowie and Flexner, 1946).

Under normal circumstances the foetal pH is lower than that of the mother (Young, 1952). This factor has been attributed either to a delay in the exchange of carbon dioxide across the placenta, or to the presence of an anion in the foetus which is relatively non-diffusible (Kaiser and Cummings, 1958). In all animals the P_{CO_2} is higher in the foetal plasma (Dancis, Worth and Schneidau, 1957). This is necessary as it ensures the elimination of carbon dioxide from the foetal blood stream into the maternal circulation. Seller, (1964b) induced a metabolic acidosis in the pregnant rat, and while the pH of the foetus decreased to the same extent as that of the mother, the standard bicarbonate, which in the mother dropped markedly, decreased only slightly and was maintained above that of the mother. This suggests that the foetus may possess buffering substances other than bicarbonate. Haemoglobin may be involved as Young (1952) claims that foetal haemoglobin

has more efficient buffering properties than maternal haemoglobin. Blechner, Meschia and Barron (1960) suggest that there is a restriction in placental transport of bicarbonate, but Seller (1964b) found that when the bicarbonate level in the mother is increased that of the foetus increases to the same extent, suggesting free placental transport in at least one direction.

Proteins are not transported through the placenta very readily. However, component amino-acids are rapidly transferred from the mother and then used in protein synthesis by the foetus (Dancis and Shafran, 1958). This transfer is an active process for the amino-acid concentration in the foetal blood is higher than in the maternal (Clemetson and Churchman, 1954) and there is isomeric differentiation in the ease of transport; the naturally occurring L-isomer of amino acid is transferred at a much faster rate than the corresponding D-form (Page, Glendening, Margolis and Harper, 1957).

Antibodies are transferred across the placenta albeit very slowly whilst in many animals antibodies reach the foetus by other routes. For instance, in rabbit and guinea-pig they are absorbed from the uterine cavity by the yoke sac splanchnopleure (Hemmings and Brambell, 1961). Freda (1962) states that there is good evidence that in man, antibodies are transferred across the placenta.

The placenta is freely permeable to urea. The levels of urea and uric acid in maternal and foetal blood are equal (McGaughey, Corey, Scoggin, Bobbit and Thornton, 1959).

Hormones on the whole are transferred slowly and in small amounts. Cortisol is found to cross the placenta fairly easily in rats (Jones, Lloyd and Wyatt, 1953), while there is little transfer of cortisone (Lanman, 1953) and there is no doubt that the steroid sex hormones are successfully transmitted. It is now almost proven that some cases of female pseudohermaphroditism have been induced by the administration of sex hormones to the mother during early pregnancy (Grumbach and Ducharme, 1960).

All vitamins are transferred, but the fat soluble A, D and E seem to cross more slowly than those which are water soluble (Hagerman and Vilee, 1960).

Fats are synthesised in the foetus from simple components which are transported across the placenta (Goldwater and Stetten, 1947). In rabbits, phospholipids enter the placenta from the maternal circulation and are hydrolysed before being released into the foetus (Popjak and Beekmans, 1950).

Other Placental Functions

It becomes increasingly evident that the placenta carries out a wide spectrum of activity. Apart from its nutritional function, it is an endocrine organ producing chorionic gonadotropin, oestrogens and progesterone (Ryan, 1962), hormones important for the maintenance of pregnancy, and also has the capacity to degrade and conjugate steroids (Vilee, 1962). It is a storage organ especially important for holding reserves of glycogen. In addition, since the foetus differs genetically from the mother, the placenta must hold within its boundaries some form of barrier which usually (but not invariably) isolates foetal antigens.

Compared with other organs the placenta has a short life cycle. At the beginning of gestation, it must rapidly establish itself in order to supply the needs of the developing embryo. It must then continue to expand so as to support the growing foetus. It is not unexpected that this rapid growth cannot be maintained and towards the end of pregnancy it begins to show signs of aging and decline as is evidenced by the appearance of fibrinous deposits and by a decrease in efficiency of transport of certain substances. Then, after parturition, the life of this versatile organ, of such basic but transient importance to the survival of the Mammalia, is over.

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