Feto-placental function: its nature and assessment

The histopathology of placental insufficiency

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Voltaire, regarded by some as a realist and by others as a cynic, remarked that 'if God did not exist it would be necessary to invent him'. One suspects that this comment is equally applicable to placental insufficiency, a concept that has similarly attracted not only faithful adherence but also bewildered agnosticism or defiant disbelief.

Placental insufficiency has been largely defined in clinical terms, principally by those who believe that the placenta is, during a normal pregnancy, extended to the full limit of its functional capacity. Adherence to this belief implies that any factor which adversely influences trophoblastic function, by no matter how limited an extent, will restrict the fetal supply of oxygen and nutrients, this resulting in fetal growth retardation, wasting, hypoxia or, in extreme cases, death. This clinical concept has been supported, to some extent, by placental function tests which, however, measure principally the biosynthetic and endocrinological activities of the trophoblast rather than its capacity for transferring oxygen and nutrients to the fetus. The final court of appeal for confirmation of a diagnosis of placental insufficiency is the pathologist who finds that the apparently inadequate placenta presented to him for appraisal may be large or small and can vary from being extensively infarcted and heavily calcified at one extreme to complete normality at the other. Many pathologists faced with this situation are forced into an attitude of diagnostic nihilism and are content not to pursue with any great degree of tenacity the question, to which this paper is directed, of whether a satisfactory pathological basis for placental insufficiency can be defined.

Clearly the syndrome of chronic fetal deprivation may have any one of three fundamental bases: (1) a deficient supply of oxygen or nutrients to the placenta either because of an abnormal constitution of the maternal blood or because of an inadequate maternal uteroplacental circulation; (2) a failure of the placenta to transfer adequately oxygen and nutrients from maternal to fetal blood; (3) a failure of the fetus either to take up, or to utilize adequately, nutrients and oxygen.

It is only the second of these possibilities which will be examined here in detail, for if the term 'placental insufficiency' has any meaning it must be that a placenta receiving an adequate supply of nutrients and oxygen is unable to transfer these to a normal fetus in quantities sufficient to ensure normal growth and development.

Placental Pathology in Fetal Deprivation

The functional unit of the placenta is the terminal villus and a placenta that is physiologically inadequate must have either (a) a decreased number of functioning villi or (b) a normal number of villi which are, however, functionally inefficient

A lesion which clearly reduces the total population of functioning villi is placental infarction (fig 1) in which a number of villi undergo ischaemic necrosis and become aggregated together to form an easily visible white plaque. Small infarcts are both common and unimportant but necrosis of more than 10 to 15 per cent of the placental parenchyma is associated with a very high incidence of fetal deprivation and death (Fox, 1967a); indeed, it has been this finding which has prompted the suggestion that the placenta has little or no functional reserve capacity. That this is too simplistic a view is, however, indicated by a consideration of two other lesions which cause a reduction not, it is true, in the total number of villi, but in the population of functioning villi, these being perivillous fibrin deposition and fetal artery thrombosis. In the former (fig 2) a portion of the intervillous space is obliterated by fibrin which is laid down around the villi as a consequence of eddy currents and stasis of maternal blood and forms an irregular white plaque that is often called an infarct. This is a regrettable misnomer but it has to be accepted that the villi embedded within the fibrinous mass might just as well be infarcted for they are no longer available to fulfil their transfer function. Similarly, following fetal artery thrombosis (fig 3), an event which usually occurs for no discernible reason, the avascular villi normally supplied by the occluded

Fig 1 A placental infarct: this is seen in the left half of the field and is characterized by aggregation of villi, obliteration of the intervillous space and necrotic changes in the villi (H & E $\times 56$).

vessel play no part in transferring oxygen or nutrients to the fetus. It is therefore surprising that neither of these lesions appears to affect adversely the fetus, this applying not only to small lesions but also to those in which as many as 30 per cent of the villi are rendered functionally inactive (Fox, 1967b). That the placenta can withstand the loss of nearly a third of its functional parenchyma without any fetal embarrassment bears eloquent witness to the fact that, far from being physiologically extended, it has a very considerable functional reserve capacity. Why then the paradox that a similar, or even much less substantial, loss of villi because of infarction is of such gloomy import for fetal growth and development? Placental infarction is due either to a retroplacental haematoma or thrombosis of a maternal utero-placental vessel; if those due to retroplacental bleeding are, for the moment, excluded it is clear that extensive infarcts are due to widespread thrombosis of maternal arterioles (Brosens and Renaer, 1972), a phenomenon that would not be expected to occur in a healthy vascular tree. Indeed, a significant degree of infarction is found only in placentae from women suffering from the hypertensive complications of pregnancy and these are precisely the conditions in which the utero-placental vessels are markedly abnormal (Robertson *et al*, 1975) and in which, as a consequence, maternal blood flow through the placenta is diminished. Extensive infarction is

usually therefore the visible hallmark, and only occurs as a complication, of a severely compromised utero-placental circulation and it is this, rather than the simple loss of villi, that is the true cause of the fetal complications.

As already mentioned, infarction may also be due to retroplacental bleeding. A sharp distinction has been drawn between the chronic condition of premature separation of the placenta and the acute catastrophe of abruptio placentae (Gruenwald *et al*, 1968); the former results in the formation of a retroplacental haematoma which indents the basal plate of the placenta and causes infarction of the overlying villi but does not usually produce any clinical symptoms whilst the latter produces a dramatic clinical picture, is usually followed rapidly by delivery of the fetus and may not leave any pathological imprint on the placenta. Retroplacental haematomata are found in about 5 per cent of pregnancies but the vast majority are small and of no importance; they are only associated with fetal deprivation if more than a third of the placental parenchyma is separated by the haematoma from the maternal utero-placental vessels or if the bleeding occurs in a pregnancy already complicated by a hypertensive condition.

It could, of course, be argued that the most obvious manner in which the villous population is diminished, namely, by the development of an

Fig 2 Perivillous fibrin deposition: the intervillous space is filled in by fibrin which completely envelops the widely separated villi (H & E $\times$ 350).

unusually small placenta, is often associated with poor fetal growth and that in such cases the inadequate growth of the fetus is a direct result of the small placental size. If, however, fetal growth were rigidly limited by placental size it would indicate that the placenta is functioning at the limit of its capacity, a view which appears to be incorrect. It is much more probable that the reverse situation is the case and that when the fetus is small the placenta, being a fetal organ, shares in the generally diminished growth of the fetus, the small placenta being thus a manifestation, rather than a cause, of poor fetal growth (Gruenwald, 1975).

Clearly, a very extensive loss of functioning villi, ie, of more than 30 per cent, will dissipate the reserve capacity of the placenta and thus be of considerable significance; extensive lesions of this type are, however, most rare and the vast majority of lesions that reduce the villous population are of little importance, the stress that has been placed upon them in the past being largely due to the fact that they

Fig 3 Avascular villi resulting from thrombosis of a fetal stem artery (H & E $\times$ 350).

are readily visible and thus serve as convenient pegs upon which to hang a diagnosis of placental inadequacy. This perhaps emphasizes that the macroscopic study of the placenta is not often of any great value to the pathologist concerned with defining placental insufficiency. It is true that this may reveal the crater marking the site of an old retroplacental haematoma or the very uncommon large haemangioma which may, possibly because it acts as an arteriovenous shunt and thus allows the return of unoxygenated blood to the placenta, be associated with fetal deprivation and that circumvallate placentation is accompanied unduly often by a minor degree of fetal growth retardation but most other visible lesions are quite banal. Thus subchorionic fibrin plaques, intervillous thrombi, small haemangiomas, septal cysts, marginal haematomata and calcification in no way influence trophoblastic function; it is perhaps necessary to stress that calcification, often thought of as a hallmark of placental degeneration or senescence, is of no clinical or pathological significance and, in particular, is no more common in placentae from prolonged pregnancies than in those from full-term gestations (Brandt, 1973).

If therefore neither the macroscopic pathology of the placenta nor a reduction of villous mass can be considered as offering a plausible basis for a diagnosis of placental insufficiency it must be postulated that the assumed functional inadequacy of the organ is due to an overall reduction in the ability of the trophoblast to fulfil its transfer role. Amongst the possible factors that have been variously suggested as influencing villous function in this manner are ischaemic, inflammatory or immune damage, deficient fetal perfusion, trophoblastic senescence, failure of villous maturation and inadequate trophoblastic differentiation.

Changes secondary to utero-placental ischaemia are certainly seen in a fairly high proportion of placentae from deprived fetuses. The most obvious histological evidence of this (fig 4) is hyperplasia and proliferation

Fig 4 An undue prominence and increased number of villous cytotrophoblastic (Langerhans) cell in a placenta from a woman with preeclampsia. One of these cells is arrowed (P.A.S. $\times 560$).

of the villous cytotrophoblastic cells (Wigglesworth, 1962); these are the stem cells from which the syncytiotrophoblast is derived and they form what can be considered as a regenerative zone which is,

in the mature placenta, normally quiescent but which becomes activated when the syncytium suffers ischaemic damage. The cytotrophoblastic proliferation represents an attempt to repair and replace damaged syncytium, and, as such, the degree of proliferative activity provides an approximate guide to the severity of the ischaemia to which the placenta has been subjected. This repair activity appears to be strikingly successful, for at both light and electron microscopic level the ischaemic syncytium shows remarkably little evidence of structural change. This being so, it is difficult to believe that the functional capacity of the placenta is severely restricted under such circumstances and the evident ability of the trophoblast to repair itself indicates that in conditions of ischaemia the placenta is probably working as efficiently as the diminished maternal blood flow will allow; thus any failure of fetal nutrition in these cases is probably not due to placental inadequacy but to the diminished maternal supply of nutrients and oxygen.

The reverse situation, inadequate fetal perfusion, is seen in, but is not confined to, placentae from prolonged pregnancies in which there is, for reasons that are presently obscure, an apparent collapse of the fetal circulation through the placenta, with the villous capillaries, instead of being sinusoidally dilated, appearing small and inconspicuous. Under these circumstances, and in all others in which fetal villous blood flow is restricted, eg, fetal artery thrombosis, the underperfused villi show excessive stromal fibrosis and a markedly increased formation of syncytial knots (Fox, 1969). These villous changes may be, but often are not, associated with fetal deprivation but there is no convincing evidence that either a diminished fetal blood flow or the resulting villous abnormalities impair placental function, and, indeed, ultrahistochemical studies show that trophoblastic enzymatic activity is either unimpaired or increased in placentae from prolonged pregnancies (Jones and Fox, in preparation). It seems highly probable therefore that any fetal deprivation which does occur in association with fetal underperfusion of the placenta is due not to trophoblastic inadequacy but to a diminished ability of the fetus to take up oxygen and nutrients from the placenta; an alternative explanation that must be kept in mind is, of course, that the decreased fetal circulation through the placenta is a consequence, rather than a cause, of fetal deprivation.

The question of whether the placenta can suffer immune-mediated damage is a moot one but it is sufficient to note here that there is no evidence, even of the most tentative nature, that immune damage to the trophoblast is a cause of placental insufficiency; thus the lesion which is often quoted as being a

hallmark of immune attack, namely, villous fibrinoid necrosis, involves too few villi to be of any possible functional significance whilst a prolonged ultrastructural search for deposition of immune complexes in placentae from deprived fetuses has proved unrewarding (Jones and Fox, unpublished observations). It is also perhaps worth noting that under experimental conditions increasing degrees of materno-fetal incompatibility with regard to H loci lead, not to a small fetus, but to increasingly large placentae and fetuses, presumably as a result of hybrid vigour (Lanman, 1975; Beer, 1975).

It has been claimed that inflammatory damage to the placenta as a result of bacterial or viral infection can produce a functional inadequacy, this claim being based on the finding that placentae showing villitis are commonly associated with an infant of low birth weight (Altshuler *et al*, 1975). The effects of villous inflammation on placental physiology are not known but it is difficult to accept that the functional capacity of the trophoblast is seriously impaired by a villitis for the affected villi are both few and scattered. It could be postulated that the villitis is a red herring and that the real brunt of the inflammatory damage falls on the maternal vasculature, for in certain veterinary infections, eg, aspergillosis of the ungulate placenta, there may be a widespread necrotizing vasculitis of the utero-placental vessels with, of course, dire consequences for the fetus; there is, however, no evidence that an inflammatory lesion of this type ever occurs in the human placenta. In considering the effects of placental infection it must be borne in mind that the organ presents a very easily breached barrier and that in most, probably all, cases of villitis the fetus is also infected; almost certainly it is the direct effect of such infection on the fetus that is responsible for the retarded growth rather than the inflammatory damage to the placenta. To this rule one apparent exception must be noted, for heavy malarial infestation of the placenta, without fetal involvement, is often associated with an unduly small baby (Jelliffe, 1967); the malarial parasites do not, however, cause any damage to, or destruction of, placental tissue and the inadequate nutrition of the fetus appears to be due to the massive histiocytic infiltration of the intervillous space which is found in such cases and which acts as a barrier to separate the trophoblast from the maternal blood.

Not only villitis, which is caused by a haematogenous infection, but also chorioamnionitis, which is due to an ascending infection, is often found to be associated with a baby of low birth weight. There can be little doubt, despite intermittent claims to the contrary, that the dominant aetiological factor in chorioamnionitis is prolonged rupture of the

membranes (Fox and Langley, 1971) and thus it is of interest that Lind and Hytten (1969) have shown that the lower the weight of the fetus the longer is the average time interval between membrane rupture and delivery, possibly because the strength of the myometrial contractions is related to the bulk of the uterine contents. Hence the chorioamnionitis often found in placentae from small babies is probably a result, rather than a cause, of the low birth weight.

The question of whether the placenta ages during its short life span is extraordinarily difficult to answer. Certainly, the villi, during the course of pregnancy, undergo a series of morphological changes which have been interpreted by some as an aging phenomenon but which should more correctly be considered as a progressive maturation (Vorherr, 1975). One cannot define with any degree of assurance changes in the placental villi that could be considered as morphological evidence of senescence though it has been maintained that the abnormality usually known as villous fibrinoid necrosis is actually a form of senile amyloidosis, the amyloid being deposited as a result of immune attack on trophoblastic cells with misspecified protein synthesis (Burststein *et al*, 1973); this is a hypothesis that is open to some considerable doubt but even if it were true the villi involved are insufficiently numerous for their loss to be of any real functional significance. At the ultrastructural level changes of an apparently aging nature have been observed in trophoblastic nuclei and nucleoli and these have been thought to be indicative of impaired protein biosynthesis in late pregnancy as a result of a programmed senescence (Martin and Spicer, 1973). Whether this interpretation of the rather subtle electron-optical abnormalities which have been observed is fully justified is a question to which, at the moment, no firm answer can be given.

Irrespective of whether or not the trophoblast ages as pregnancy progresses there can be no doubt that the villi undergo a progressive morphological maturation; they decrease progressively in diameter and their vessels, which in early pregnancy are small and centrally placed, become sinusoidally dilated and eventually come to occupy most of the cross-sectional area. It is assumed that these changes tend to facilitate materno-fetal transfer and it has been suggested that they are of the type which would be expected if the organ was changing from one in which active transfer dominated to one in which simple diffusion was of prime importance. Placental maturation is not, however, simply a reflexion of fetal maturation, for an asynchrony between the two maturation rates can occur, and it is by no means unknown for an undoubtedly full-term fetus to have a placenta in which most of the villi have failed to

mature beyond the stage expected for a gestational age of 24 to 28 weeks (fig 5). Such fetuses are, though mature, very often unduly small and it is thought that this is because the incomplete villous maturation leads to a functional inadequacy during late pregnancy (Becker, 1975).

Fig 5 A placenta from a pregnancy of 40 weeks in which the fetus was of low birth weight. The villi are uniformly immature (H & E $\times$ 56).

It is not always fully appreciated that villous maturation appears to be accompanied by a progressive topographic differentiation of the trophoblast, the two processes being intertwined though probably independent of each other. The villous trophoblast has both a synthetic and transfer function and it would be reasonable to assume that different areas become adapted for one or other of these two roles. This assumption has received support from electron optical studies of first trimester villous trophoblast which have shown that despite the apparent morphological homogeneity of this tissue at light microscopic level there is considerable ultrastructural evidence of regional functional differentiation (Dempsey and Luse, 1971). In the mature placenta the villous syncytiotrophoblast is

clearly not morphologically homogeneous for there are, in many villi, thinned anuclear areas of trophoblast which directly overlie and, on light microscopy, appear to fuse with the wall of a dilated fetal capillary (fig 6). These attenuated areas have been

Fig 6 A vasculo-syncytial membrane (arrowed) in a mature placenta (H & E $\times$ 560).

called 'vasculo-syncytial membranes' (Getzowa and Sadowsky, 1950) and although electron microscopy shows that there is no real fusion between trophoblast and vessel wall it is clear that they differ markedly from the non-thinned nucleated areas of the trophoblast. The membranous areas bulge into the intervillous space and they are not simply due to mechanical stretching of the trophoblast by dilated fetal vessels, for scanning electron microscopy shows that they are randomly sited and very localized, often occurring along the course of a vessel as a dome-shaped swelling protruding from the lateral wall of a villus (Fox and Agrofojo-Blanco, 1974); this pattern of distribution argues strongly against a mechanical explanation for their formation and it has been suggested that they are specialized areas of trophoblast for the facilitation of gas transfer across the placenta. This suggestion has been principally

based on the fact that where the trophoblast is focally thinned the fetal and maternal circulations come into their closest approximation to each other; this would, however, only facilitate gas transfer across the placenta if membrane resistance were an important limiting factor in this process and there is considerable evidence that this is not the case (Longo, 1972). The trophoblastic thinning is, however, only one indication of the specialized nature of the membranous areas for not only do they differ both histochemically (Amstutz, 1960) and ultra-structurally (Burgos and Rodriguez, 1966) from the non-membranous areas of the trophoblast but scanning electron microscopy shows that there is a sharply localized loss of microvilli over their surface. It thus appears that the functional segregation which is discernible in the trophoblast during the first trimester becomes more blatant in the mature placenta and the view that trophoblastic transfer function is largely confined to the membranous areas and synthetic activity to the non-membranous areas would appear to be a reasonable one.

This concept is strengthened by the finding that a deficiency of vasculo-syncytial membranes in the mature placenta is associated with a high incidence of fetal deprivation (Fox, 1967c); such a paucity of membranous areas can be considered as a failure of trophoblastic maturation—a failure that appears to subject the fetus to considerable risk. A lack of trophoblastic differentiation may be simply one facet of villous immaturity and it is possibly this failure of differentiation that lends to villous immaturity its serious import. In some placentae which lack vasculo-syncytial membranes the villi are, however, fully mature and here there appears to be solely a defect in trophoblastic differentiation.

The Nature of Placental Insufficiency

Does an acceptable pathological basis for the syndrome of placental insufficiency emerge from a critical review of the morphological changes found in placentae from deprived fetuses? Certainly, most of the lesions often thought to account for placental inadequacy are either of no clinical importance or are secondary to events occurring outside the placenta, either in the fetus or in the mother. The only lesions capable of serving as a basis for a primary failure of placental function are inadequate villous maturation and defective trophoblastic differentiation. Changes of this type are, however, found in only a relatively small proportion of placentae from deprived fetuses and it must be concluded that in most cases no abnormality can be found within the placenta which could serve to explain its apparent inadequacy. Three possible

explanations could be proposed to resolve this dilemma:—

1 Placental insufficiency is usually secondary to an external factor, such as utero-placental ischaemia.

2 The changes occurring in the insufficient placenta are too subtle to be observed by the relatively crude techniques of conventional microscopy.

3 Placental insufficiency is a very uncommon condition and is grossly overdiagnosed.

It is certainly tempting to consider that placental insufficiency is often secondary to a maternal factor. There is, however, much to suggest that the placenta, when faced with an unfavourable maternal environment, far from being inadequate, may be functioning more efficiently than normal in an attempt to overcome the disadvantage at which the fetus is placed. Thus, for instance, the placenta is often larger than normal in severe pregnancy anaemia (Beischer *et al*, 1970; Agboola, 1975), in pregnancy at high altitude (McLung, 1969), and in pregnancies complicated by decompensated maternal heart disease (Clavero and Botella Llusia, 1963), all conditions often associated with a fetus of low birth weight. In the hypertensive complications of pregnancy the placenta appears fully able to repair any damage resulting from utero-placental ischaemia and it appears highly likely that the placenta is functioning reasonably adequately; indeed it is worthy of note that in preeclampsia the placental/fetal weight ratio is often increased (Hözl *et al*, 1974) and that women with essential hypertension not uncommonly give birth to unusually large babies (Gruenwald, 1966).

The possibility that placental insufficiency may be due to changes not detectable on ordinary microscopy merits some attention. Jones and Fox (1976), using an ultrahistochemical technique, have recently shown that in some mature placentae from underweight babies there is a phosphatase-dependent transfer system similar to that normally found in the first trimester placenta. Whether this is due to a failure of functional maturation or is indicative of a compensatory mechanism is unknown but it is certainly possible that relatively subtle changes of this type may be of greater importance than is now thought to be the case.

Currently, however, the conclusion must be that placental insufficiency, occurring as either a primary or a secondary phenomenon, is a relatively rare, and much overdiagnosed, condition. Assali *et al* (1975) have, although mixing their metaphors, stated the position succinctly . . . 'the term (ie placental insufficiency) has become an umbrella to cover our ignorance of the aetiology and pathogenesis of chronic utero-placental-fetal disturbances; it has also

served as a waste basket to dump a variety of disorders interfering with maternal supply of nutrients to the fetus or with fetal metabolism or with disorders related to abnormal placental function.'

In most cases of fetal deprivation the fault lies outside the placenta which, being a vigorous, versatile and energetic organ having a considerable reserve capacity, is usually functioning with optimal efficiency. The great danger of an insufficiently critical acceptance of a diagnosis of placental inadequacy is that it promotes a false feeling of having solved, or at least localized, the problem and that in this lulled state attention is diverted away from the true causes of fetal deprivation and new avenues of investigation remain unexplored.

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