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THE MORPHOLOGICAL BASIS OF PLACENTAL INSUFFICIENCY

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It is my intention in this paper to consider critically whether a morphological basis for the clinical syndrome of placental insufficiency can be established. If such a basis cannot be formulated then clearly the right of this syndrome to be considered an entity must be questioned.

However, the student of placental pathology is faced with several unique problems. Firstly, the terminology used to describe placental lesions has been, until quite recently, quaintly archaic; one may cite, for instance, the application of the terms "white infarct" and "red infarct" to a wide variety of unrelated lesions and the usage of "fibrin" and "fibrinoid" as synonyms. Most of this outdated nomenclature has now sunk into oblivion but traces of it still remain to pollute the obstetric literature.

Secondly, the placenta differs from most other organs in that its pathology is largely quantitative rather than qualitative; for example infarcts are common in placentas from normal pregnancies and hence their mere presence cannot strictly be considered as pathologic, a significance which they only assume if they are unduly large or numerous. It is therefore insufficient simply to enumerate placental abnormalities; all must be quantitated and their significance assessed in relation to the nature and outcome of the pregnancy, and any lesion, no matter how impressive pathologically, must be considered as of no importance if it does not interfere with fetal growth and maturation.

Thirdly, it would at first sight appear that pathological examination of placentas from cases of intrauterine fetal death would be of considerable value; this is not, however, necessarily the case, for following fetal death the placenta both survives and undergoes extensive histological changes. These changes are so marked that histological examination of placentas from all except very fresh stillbirths is of very little value and hence one of the most promising avenues for relating placental changes to fetal death is closed to the pathologist. Finally, the placenta is not histologically uniform and the villi normally vary considerably in appearances from one area to another; fortunately this variability is not totally random and can be overcome by taking in these as a point of reference.

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Macroscopic Abnormalities of the Placenta

These can be useful, though somewhat arbitrarily and artificially, divided into four groups between which there is, of course, some overlap:-

i. Developmental abnormalities.
ii. Lesions that reduce the population of functional villi.
iii. Lesions that obstruct or alter the blood flow through the placenta.
iv. Lesions that do not influence placental function.

Developmental Abnormalities

Some of these, e.g. the fenestrate placenta and the tripartite placenta, are so rare that their clinical significance cannot be estimated whilst others, such as bipartite placenta, accessory lobe, velamentous insertion of the cord and placenta accreta are primarily of obstetric interest and do not apparently influence either placental function or fetal development.

The commonest developmental anomaly of the placenta is placenta extrachorialis. This is found to some degree in about a quarter of all placentas and is characterized by the chorionic plate being smaller than the basal plate. The transition from villous to membranous chorion therefore takes place at some distance within the fetal margin of the placenta and if this transition is marked by an elevated ridge-like fold the placenta is classed as "circumvallate"; if the chorionic margin is flat the placenta is "circummarginate": either of these two anomalies may be complete or partial. The debate as to the clinical significance of this abnormality has been confused by the consideration of the extrachorial placenta as a single entity and by a failure to distinguish between the complete and the partial forms; studies which have avoided this pitfall have shown that the circummarginate placenta is of no clinical significance but that all forms of the circumvallate placenta are associated with an unduly high incidence of fetal growth retardation. The totally, but not the partially, circumvallate placenta is also linked with a relatively high incidence of fetal hypoxia and premature labour; nevertheless, circumvallate placentation is not accompanied by any increase in perinatal mortality and whether this type of placenta is functionally relatively inadequate or whether there is a common causal factor causing both the abnormal development of the placenta and the poor fetal growth is unknown.

Lesions Reducing Population of Functional Villi

Perivillous fibrin deposition: Deposition of fibrin around villi occurs in almost all placentas and in a proportion is sufficiently extensive to be macroscopically visible either as a firm white plaque or as an area of irregular whitish mottling. Such lesions consist histologically of widely separated villi embedded in fibrin which fills in the inter-villous space. The syncytiotrophoblast of the entrapped villi degenerates; and the stroma of the villi becomes markedly fibrotic and their fetal vessels undergo complete sclerosis.

This lesion is found in about a quarter of placentas from uncomplicated mature pregnancies; its incidence is not increased in prolonged pregnancy and is unduly low in pre-eclamptic toxaemia.

The villi embedded in fibrin are not infarcted but nevertheless are of no functional value to the fetus as they are obviously incapable of participating in any transfer activity. However, macro-

scopically visible perivillous fibrin deposition, whilst clearly decreasing the total population of functional villi, not only lacks any clinical significance but tends to be associated with an unduly low incidence of fetal hypoxia; this applies not only to small lesions but also to those in which as many as 20 per cent of the villi are entrapped in fibrin. The clinical triviality of this lesion is, however, explicable in terms of its pathogenesis. There is no doubt that the fibrin is formed by thrombosis of maternal blood in the intervillous space; as the villous syncytiotrophoblast is in direct contact with this blood and can thus be considered as playing an endothelial-like role it was in the past thought that thrombosis occurred as a consequence of syncytial "degeneration". Electron microscopy has, however, shown that the initial stage in the development of this lesion is deposition of platelets on healthy syncytiotrophoblast and it is almost certain that this occurs as a result of eddy currents and stasis of maternal blood in the intervillous space; the entrapped villi are thus only accidently included within the thrombus and the syncytial damage is a secondary phenomenon. The low incidence of perivillous fibrin deposition in placentas from toxaemic women and the inverse relationship between this lesion and fetal hypoxia suggests that it tends to develop particularly in placentas with a good maternal blood supply; clearly, the greater the blood flow through the closed irregular intervillous space the greater is the possibility of turbulence, stasis and fibrin deposition.

The banality of this lesion indicates that the placenta is, in the presence of a good maternal blood supply, unaffected by the functional loss of a considerable proportion of its villous population and thus bears eloquent witness to the considerable reserve capacity of this organ.

Infarction

Placental infarcts, when fresh, are well demarcated, dark red and moderately firm; as they age they become converted into hard white structureless plaques. Histologically, the villi in a fresh infarct are closely packed and the intervillous space is narrowed or obliterated; the villous capillaries are widely dilated and markedly congested whilst the trophoblast shows early necrotic changes. As the infarct ages the villi undergo a progressive coagulative necrobiosis so that the well established lesion is formed solely of crowded "ghost" villi.

Small areas of infarction, involving less than 5 per cent of the parenchyma, are found in almost a quarter of placentas from normal pregnancies and are of no clinical significance. Extensive infarction, that is involving more than 10 per cent of the villous substance, is associated with a high incidence of fetal hypoxia, low birth weight and fetal death and is virtually confined to placentas from patients suffering either from the hypertensive complications of pregnancy or from large retroplacental haematomas. It is tempting to attribute the fetal complications simply to the loss of viable villous tissue but, as discussed previously, a similar loss of villi due to entrappment in fibrin is of no consequence to the fetus. This is an apparent paradox unless it is borne in mind that the villi are oxygenated by the maternal blood and that although many maternal vessels open into the intervillous space there is little or no mixing of the streams from individual arterioles; these vessels can therefore be considered as end arteries and an infarct is due to a localized obstruction to the utero-

placental circulation either by a retroplacental haematoma or by occlusion of a maternal arteriole. If one excludes those infarcts which are a consequence of retroplacental bleeding it follows that extensive infarction is due to occlusion of multiple maternal arterioles; the usual occluding lesion is a thrombus. It would not be expected that multiple thrombi would occur in a healthy vascular tree and, indeed, it has been clearly shown that the hypertensive complications of pregnancy, i.e. those conditions specifically associated with a significant degree of placental infarction, are regularly accompanied by marked abnormalities of the utero-placental vessels. Thus extensive infarction only occurs against a background of an inadequate maternal circulation through the placenta and it is this, rather than the simple loss of placental villi, that is the cause of the fetal complications. Although the loss of the infarcted villi will clearly further deplete the functional capacity of the placenta the principal significance of placental infarcts is that they are, when extensive, a visible indication of a severely comprised uteroplacental circulation.

Small Placenta

Not uncommonly a low fetal birth weight is attributed to an unduly small placenta, the assumption being in such cases that the placenta has an abnormally small villous population and is therefore unable to fulfill adequately the nutritional demands of the fetus. It has already been pointed out that the placenta has a considerable functional reserve and that a simple reduction in villous population is, unless extreme, unlikely to interfere with fetal nutrition or growth. It is therefore not surprising that extensive surveys have been unable to correlate changes in placental weight with fetal hypoxia and we are forced to the conclusion that weight is a poor indicator of placental adequacy. That a rough correlation between placental weight and fetal birth weight exists however is almost certainly true, especially if the true blood-free weight of the placenta is measured rather than the extremely inaccurate (and uninformative) gross weight. This does not, however, necessarily mean that the fetus is small because the placenta is small; indeed, the reverse is more probably the case and the placenta, being a fetal organ, is small because the fetus is, for unrelated reasons small. In this respect it may be noted that the placenta/fetal weight ratio is often normal, or even slightly increased, in infants of low birth weight.

Fetal Artery Thrombosis

Thrombosis of a fetal stem artery produces a roughly triangular area of pallor in the placental substance; histologically there is a sharply localized group of avascular fibrotic villi which contrast markedly with the surrounding fully vascularized villi. An organising thrombus in a fetal stem artery can always be found at the apex of the lesion.

Single lesions of this type are found in 3-4 per cent of placentas from live births but are rather more common in placentas from diabetic women; these, though reducing the population of functional villi, are of no clinical significance. Occasionally, however, there may be thrombosis of multiple stem arteries and this may cause fetal death, though this does not occur until about 40 per cent of the villi have been rendered avascular.

The thrombosis usually occurs in otherwise morphologically normal arteries and its etiology is unknown.

Lesions That Obstruct or Alter Blood Flow Through the Placenta Retroplacental haematoma

This is apparent on the maternal aspect of the placenta and bulges up towards the fetal surface thus compressing the overlying placental substance which is often, though not invariably, infarcted.

Retroplacental haematoma are found in 4 to 5 per cent of all placentas and their incidence is therefore much higher than is that of clinically detectable abruptio placentae. A high proportion of those haematomas which are only detectable pathologically are, however, small and of little or no clinical significance. Large retroplacental haematomas are associated with a high incidence of fetal hypoxia and death, largely because a very considerable proportion of the villi are acutely separated from the maternal uteroplacental circulation. Despite its reserve capacity the placenta cannot compensate for an abrupt loss of 40-50 per cent of its functioning villi.

The retroplacental haemorrhage probably comes from a ruptured maternal arteriole but the pathogenesis of this vascular accident is far from clear.

Chorangioma

Hemangiomas are present in about 1 per cent of placentas; although usually solitary they may be multiple and occasionally there is a diffuse hemangiomatosis of the placenta. The vast majority of hemangiomas are small, firm, apparently encapsulated, intraplacental nodules; a minority are large (more than 5 cm in diameter) and form obvious tumours on the fetal or maternal surface of the placenta.

Small hemangiomas are of no clinical importance but the larger ones are sometimes associated with polyhydramnios or antepartum bleeding; even more importantly they are accompanied by a relatively high incidence of fetal hypoxia and low birth weight, this being particularly the case when there are multiple or diffuse lesions. These fetal complications have been attributed to fetal blood being shunted through the hemangioma rather than through the placenta and thus being returned to the fetus in an unoxygenated state. A large hemangioma can also be considered as a peripheral arteriovenous shunt and this may be the cause of the transitory cardiomegaly that is sometimes seen in neonates whose placentas have contained such a lesion.

Lesions of no Clinical Significance

These include septal cysts, subchorionic fibrin plaques, marginal haematomata and intervillous thrombi; the latter often contain nucleated red blood cells and mark the site of fetal bleeding, presumably from a ruptured villous capillary, into the intervillous space but are otherwise of no importance. Macroscopically visible calcification, often in the past thought to be a feature of either placental degeneration or senescence, is of no clinical or pathological significance; it is no more common or extreme in placentas from prolonged pregnancies or from pregnancies complicated by pre-eclamptic toxaemia than in those from normal term pregnancies and is not associated with any fetal complications. The cause of the calcification is unknown but it occurs most commonly in first pregnancies and its incidence is related directly to low maternal age, high maternal socio-economic status and delivery during the summer months; local factors within the placenta must, however, also play some role for the placentas of bichorionic twins may

show significantly different degrees of calcification.

Histological Abnormalities of the Placenta

Villous Lesions

It is preferable to classify villous abnormalities on a functional rather than a purely morphologic basis. Thus, they may be grouped into:

i. Changes secondary to a reduced maternal uteroplacental blood flow.

ii. Changes secondary to a reduced fetal blood flow through the villi.

iii. Abnormalities of maturation and differentiation.

iv. Abnormalities of unknown, but possibly immunologic origin.

Changes Secondary to a Reduced Maternal Uteroplacental Blood Flow

The villi depend on the maternal blood for their oxygen supply and the villous response to a uteroplacental blood flow which, though reduced, is sufficient to maintain viability is characterized by cytotrophoblastic hyperplasia and thickening of the trophoblastic basement membrane.

Cytotrophoblastic hyperplasia is seen most strikingly in placentas from women suffering from pre-eclamptic toxaemia or essential hypertension and its presence can be correlated with a high incidence of fetal hypoxia and intrauterine death. These findings suggest that cytotrophoblastic hyperplasia is a response to villous ischaemia and this concept has been reinforced by studies which have shown that this change can be specifically induced under *in vitro* conditions by subjecting cultured villi to a low oxygen tension.

There is now no doubt that the cytotrophoblastic cells are the stem cells of the villous trophoblast and thus function as a germinative zone from which the syncytiotrophoblast is formed by a process of cell fusion and dissolution of cell membranes. Although the villous cytotrophoblastic cells, so prominent in the first trimester placenta, become progressively smaller and fewer as pregnancy proceeds they are nevertheless still present in many of the villi of the normal mature placenta, though admittedly rather inconspicuous and easily overlooked. If the syncytiotrophoblast suffers ischaemic damage (and there is no convincing evidence that any other factor does produce syncytial damage) the cytotrophoblast will proliferate in an attempt to replace the damaged tissue. Cytotrophoblastic hyperplasia is thus a repair phenomenon and under ischaemic conditions these cells are both numerous and prominent; mitotic figures can often be seen.

It will be clear that the degree of cytotrophoblastic hyperplasia is related to the extent of the syncytial damage and thus serves, by inference, as a rough quantitative index of the severity of the ischaemia to which the villi have been subjected.

Thickening of the villous trophoblastic basement membrane is also commonly seen in placentas from women suffering from hypertensive complications of pregnancy and this change can also be reproduced *in vitro* by subjecting cultured villi to hypoxia. It thus seems certain that thickening of the basement membrane can be a consequence of uteroplacental ischaemia but this change is seen also in other conditions in which there is no suggestion of a reduced maternal blood flow through the placenta and is. therefore, unlike cytotrophoblastic hyperplasia, a non-specific change.

Changes Secondary to a Reduced Fetal Blood Flow Through the Villi

These are seen in their purest form in

the localized group of villi which, whilst fully oxygenated by the maternal blood, have been rendered avascular by a fetal artery thrombosis. Such villi show a marked fibrosis of their stroma and a strikingly excessive number of syncytial knots; the latter are formed of syncytial nuclei which are focally clumped to form a multinucleated protrusion from the villous surface and it is by no means clear how they are formed.

These characteristic changes of stromal fibrosis and excess syncytial knot formation occur in generalized form whenever the fetal circulation through the villi appears to be reduced. Thus, they are seen most strikingly in placentas from prolonged pregnancies in some of which, but by no means all, there is a marked hypovascularity of the villi, the fetal villous capillaries being small and inconspicuous instead of sinusoidally dilated, as is the norm. As the fetal stem arteries are usually normal in prolonged pregnancy the cause of this reduction in villous perfusion is unclear though it could be due to the accumulation of a vasoconstrictor substance, possibly a prostaglandin. A reduced fetal perfusion also occurs when the fetal stem arteries are partially occluded by an "obliterative endarteritis" as is the case of some placentas from patients with pre-eclamptic toxaemia, maternal diabetes mellitus or materno-fetal rhesus incompatibility.

Irrespective of the mechanism which is responsible for reducing fetal blood flow through the villi the inevitable result is stromal fibrosis and excess syncytial knot formation both of which are good indices of the degrees of reduction in villous perfusion. Why these particular changes should result from an impairment of fetal blood flow through the villi is unknown, but a reduction of fetal blood flow through the placenta does not in itself appear to be of any great consequence as far as fetal well-being is concerned for neither stromal fibrosis nor excess syncytial knot formation are associated with any excess incidence of fetal hypoxia, death or growth retardation.

Abnormalities of Maturation and Differentiation

Placental and fetal maturation are not always synchronous and a proportion of prematurely delivered babies, normally developed for their gestational age, have placentas in which the villi are morphologically fully mature whilst a persistent morphological immaturity of the villi may have serious consequence for the continued growth of the fetus.

The factors controlling placental maturation are unknown but those cases in which placental and fetal maturation are disassociated indicate that there must be some intrinsic mechanism within the placenta itself. Possibly, villous maturation may be dependent upon the fetal circulatory system through the placenta. Unduly immature villi contain, as one of their defining morphological features, small non-dilated fetal capillaries which are often at some distance from the trophoblast; it is usually thought that this failure to attain full vascularization of the villi is due to villous immaturity but the reverse may be the case and the failure to reach full villous maturity may be due to a relative failure of villous vascularization. It must be stressed, however, that this is a purely speculative hypothesis.

It is not always fully appreciated that villous maturation appears to be accompanied by a progressive differentiation of the trophoblast, the two processes being intertwined though probably independent of each other. The villous syncytiotropho-

blast has both a synthetic and a transfer function and it would be reasonable to assume that this tissue shows topographic functional differentiation so that different areas become adapted for one or other of these two roles; recently, this assumption has received support from electronoptical studies of the first trimester villous syncytiotrophoblast which have shown that despite the apparent morphological homogenity of this tissue at light microscopic level there is considerable ultrastructural evidence of functional regional differentiation. 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. These attenuated areas have been called "vasculo-syncytial membranes" 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 tend to 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 villus; 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 was an important limiting factor in this process and recent work suggests that this is not the case. The trophoblastic thinning is, however, only one indication of the specialized nature of the membranous areas for not only do they differ both histochemically and ultrastructurally 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 present in the trophoblast during the first trimester becomes accentuated 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 supported by the finding that a deficiency of vasculo-syncytial membranes in the mature placenta, i.e. present on less than 5 per cent of the villi, is associated with a high incidence of fetal hypoxia; this paucity of membranous areas can be considered as a failure of trophoblastic differentiation—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 associated failure of differentiation that lends to villous immaturity its serious import. In some placentas which lack vasculo-syncytial membranes the villi are, however, fully mature and here there appears to be solely a defect in trophoblastic differentiation. If the fetal vessels within the villi become small and inconspicuous, as is the case in some placentas from prolonged pregnancies, the vasculo-syncytial

membranes will no longer be clearly apparent; whether this morphological regression is also accompanied by a functional decline in the transfer activity of the membranous areas is as yet unknown.

Abnormalities of Unknown But Possibly Immunologic Origin

Amongst these the most interesting is fibrinoid necrosis of placental villi. The first stage in the evolution of this villous abnormality is the appearance of a small nodule of homogeneous, strongly P.A.S.—positive material at one point in the deep part of the trophoblastic layer. This nodule progressively enlarges to form a mass which gradually bulges into and replaces the villous stroma. The syncytio-trophoblast of the affected villus is normal in the early stages of the development of this lesion but later undergoes a progressive atrophy and near total degeneration. The eventual appearance is therefore that of a villus which has been totally replaced by fibrinoid material but which still retains a few degenerate syncytial nuclei around its perimeter.

It has been thought that this lesion is due to deposition in the villus of fibrin derived either from the maternal blood in the intervillous space or from the fetal blood in the villous capillaries. This concept is, however, incompatible with the observation that the fibrinoid change appears initially in the trophoblast and electronoptical studies have confirmed that the fibrinoid material accumulates first in villous cytotrophoblastic cells and only later appears extracellularly. Recently it has been suggested that the fibrinoid material has many of the characteristics of amyloid but this remains to be proven.

Villi that have undergone fibrinoid necrosis are seen in many placentas from uncomplicated pregnancies but usually the proportion of such villi does not exceed 3 per cent and an incidence in excess of this is abnormal; an unduly high incidence is found in placentas from diabetic women, from cases of materno-fetal rhesus incompatibility, from cases of pre-eclamptic toxaemia and in some placentas from cases of idiopathic premature onset of labour. The etiology of villous fibrinoid necrosis is obscure but the possibility that it is due to an immunologic reaction within the villous cytotrophoblast is worthy of consideration. Thus, fibrinoid necrosis is well recognized as one of the hallmarks of immune damage, the fibrinoid material in the affected villi contains a considerable quantity of immunoglobulins and anti-D anti-bodies localize to villi showing fibrinoid change in placentas from cases of materno-fetal rhesus incompatibility; those who consider the fibrinoid material to be amyloid postulate that this substance is comparable to senile amyloid and due to immune attack on trophoblastic cells with misspecified proteins. All these observations are, of course, open to varying interpretations and are, in themselves, inconclusive whilst it is recognized that the whole question of immune-mediated placental damage is highly controversial; nevertheless, villous fibrinoid necrosis merits further study as a possible index of an immunological attack on cytotrophoblast.

General Comments

It will be clear from the preceding account that most macroscopic abnormalities of the placenta are of little importance. In the past these have received undue attention, partly because they are easily noted and thus serve as a convenient peg upon which to hang the facile diagnosis of "placental insufficiency" and partly because the reserve capacity of the

placenta was underestimated thus allowing for the elevation to an undeserved status of those lesions which simply reduce the total villous population. It is true that very large or multiple lesions, such as extensive infarction, thrombotic occlusion of multiple fetal arteries, large hemangiomas or large retroplacental haematomas can seriously affect fetal nutrition and oxygenation but these are found in only a small proportion of placentas from fetuses that have failed to thrive.

Most of the villous abnormalities encountered in the placenta represent a response to events occurring outside the placenta—usually in either the maternal or the fetal circulation—and very few, with the exception of failure of villous maturation or trophoblastic differentiation, can be considered as evidence of intrinsic placental disease.

The available evidence suggests that the placenta is rarely insufficient: it is a vigorous, energetic, resourceful organ which in most cases of "placental insufficiency" is showing compensatory changes in response to an unfavourable maternal milieu. The term "placental insufficiency" should probably be abandoned for, in most cases, its use reflects attention away from the true cause of failure of fetal growth.