A HISTOLOGICAL STUDY OF THE DECIDUA.

A morphological study in normal pregnancy and in pregnancies associated with placental insufficiency with special reference to the placental bed.

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ABSTRACT.

The work in this thesis is concerned with the normal histological structures of the maternal side of the placenta ("Placental Bed") and its alterations in abnormal pregnancy.

The work of previous authors is critically reviewed and it is pointed out that because of lack of adequate material, no systematic study of the placental bed in late pregnancy has, to our knowledge, ever been performed.

The material for the present study consists of three uteri with placentae in situ and eleven uteri, all obtained by Caesarean hysterectomy and a series of placental bed biopsies from 260 patients.

The anatomy of the maternal blood supply to and drainage from the intervillous space has been studied with step serial sections of an in situ placenta. A model of the basal plate and septa with maternal channels of some two-fifths of an in situ placenta has been constructed and is described.

The normal histological appearances of the spiral arteries at the end of pregnancy, their development and their topographic distribution in the uterine wall have been investigated.

The observations by previous authors on vascular lesions in the placental bed in hypertensive pregnancies are extended. The differentiation between the physiological changes and the hypertensive lesions is described and the topographic distribution of the vascular lesions in the uterine wall has been studied.

The study concludes with an investigation of the lipid changes in the placental bed at the end of pregnancy. It refers to the arterial lipid changes and presents for the first time, evidence of changes in the placental bed in conditions other than hypertension which are known to be associated with placental insufficiency, namely postmaturity and maternal heart disease.

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INTRCDUCTION.

Antepartum and intrapartum asphyxia have been shown by the 1958 British Perinatal Mortality Survey to be responsible for the majority of perinatal deaths. Perinatal loss only represents the top of a pyramid covering an unknown number of cases of non-fatal morbidity. It is for this reason that modern obstetrics is greatly concerned with the understanding of clinical conditions likely to result in foetal damage or loss from antepartum or intrapartum asphyxia.

The present study deals with the morphological aspects of the maternal blood supply to the placenta in two clinical conditions, firstly the hypertensive states of pregnancy and secondly post-maturity. These are the two clinical complications associated with the majority of cases of antepartum and intrapartum asphyxia (BUTLER and BONHAM, 1963).

Maternal hypertension has been shown by BROWNE and VEALL (1953) to be associated with a reduction of the chorio-decidual (or intervillous) blood flow. A reduction of the maternal blood supply of the placenta could be produced either by a spasm of the utero-placental blood vessels or by organic changes of these vessels. One of the purposes of the present investigation is to study the organic changes, if any, of the utero-placental vessels, which may cause a reduced placental blood supply in the hypertensive complications of pregnancy.

BROWNE (1963) pointed out the increased perinatal mortality in postmaturity, and DIXON and his co-workers (1963) have shown that in a number of cases of postmaturity there is an apparent slowing of the choriodecidual blood flow. Furthermore, ELLIOTT and INMAN (1961) have demonstrated, on a quantitative basis, that in the normal pregnant woman the volume of liquor decreases

rapidly after 38 weeks, but as yet no convincing morphological changes have been demonstrated in the maternal side of the placenta past term. For the first time we are able in the present work to report microscopic abnormalities in the placental bed of postmature pregnancies.

During the course of the present study on pathological changes in the placental bed it was realized that our present concept of the anatomical structure of the maternal part of the placenta is incomplete and often not based on reality. Therefore we have reconstructed the maternal surface of some two-fifths of an "in situ" placenta with special reference to the siting of arterial and venous channels and placental septa.

The term "placental bed" was introduced to the British literature by DIXON and ROBERTSON (1958). The placental bed can be grossly described as that part of the decidua and adjoining myometrium, which underlies the placenta and whose primary function is the maintenance of an adequate blood supply to the intervillous space of the placenta. Certainly, there is no sharp anatomical demarcation line between the placental bed and the surrounding structures, but, as this part of the uterine wall has its own particular histological, functional and pathological aspects, it proves to be a most useful term for describing the maternal part of the placenta in contrast to the foetal portion.

REVIEW OF LITERATURE.

I. MORPHOLOGY.

A. The maternal Blood Supply to and Drainage from the intervillous space.

1. Anatomy.

Although the gross anatomy of the maternal blood supply to and drainage from the intervillous space was well described by W. HUNTER in 1774 (Fig. 1) a considerable degree of confusion arose later and it is only recently that the exact anatomy has been somewhat clarified.

Anatomically the utero-placental arteries can be defined as the radial and spiral arteries* which link the arcuate arteries in the outer third of the myometrium to the intervillous space of the placenta (Fig. 2). Before reaching the myometrio-decidual junction, the radial arteries usually split into two or three spiral arteries. Small arteries, the so called basal arterioles, branch off from the proximal part of the spiral arteries and vascularize the myometrio-decidual junction and the basal layer of the decidua. These vessels are, according to DARON (1936) insensitive to hormonal changes.

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* It must be stated that some confusion has arisen as to whether the spiral vessels of the placental bed should be called "arteries" as is commonly used in the German literature or "arterioles" as is more common in the English literature. In view of the size of the spiral vessels, which communicate with the intervillous space, the terminology of "spiral arteries" has been adopted for these vessels in order to distinguish them from the "spiral arterioles" of the decidua vera.

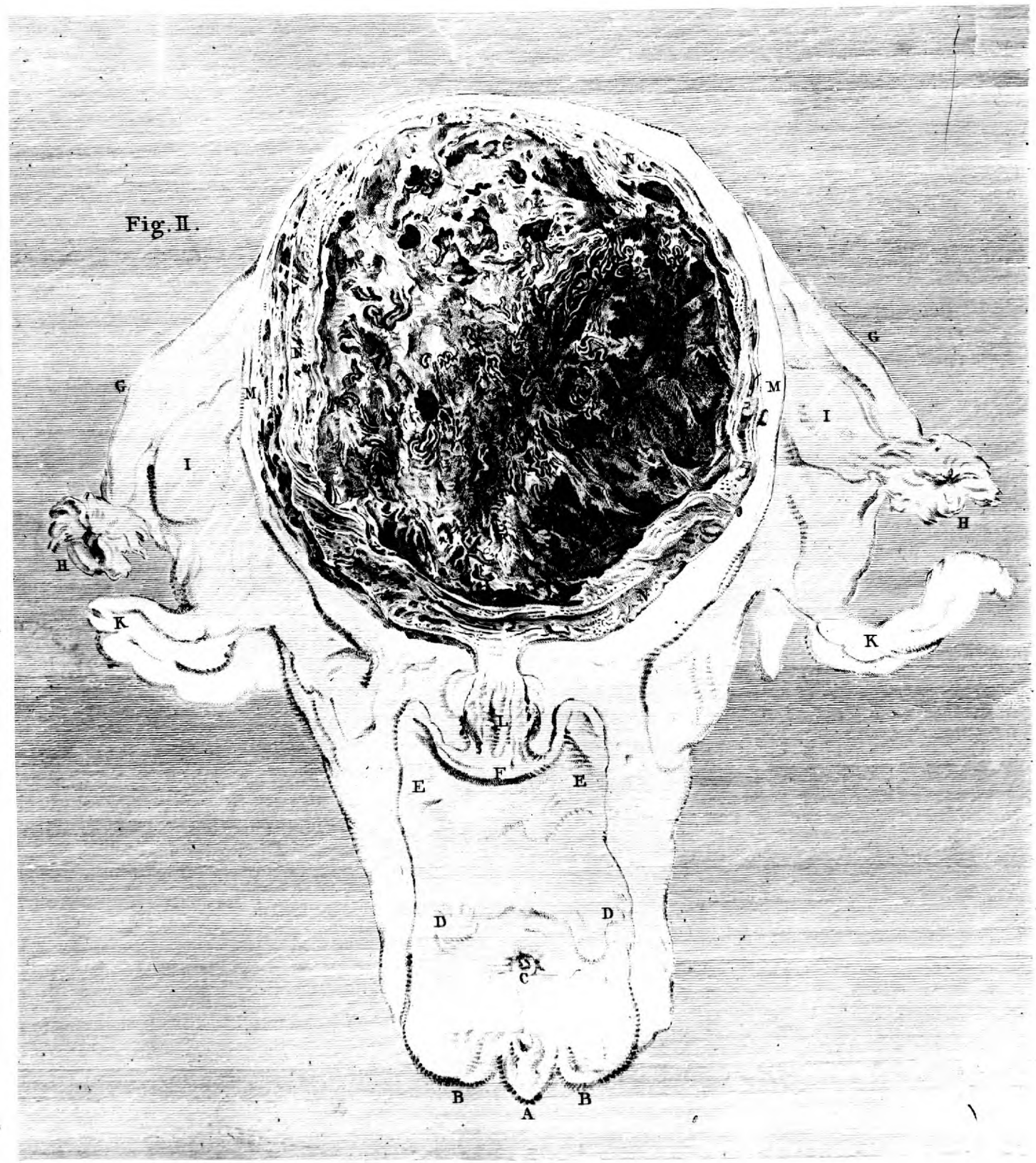


Fig 1. For text P. T. O.

Fig. 1.

"The inside of the womb after the placenta has been separated. - The centre of the circular surface at the forepart of the womb, to which the placenta in this case, adhered. It was full of arteries and veins, which had passed between the womb and placenta, and which we broke through in separating these two parts : the arteries were small, and convoluted, and of a lighter colour, as at the letter P; the broken veins had the appearance of dark spots, or holes, of some considerable size, as at the letter Q."

HUNTER, W. (1774), The Anatomy of the gravid Uterus exhibited in Figures. Birmingham. Plate XXVIII, Fig. II.

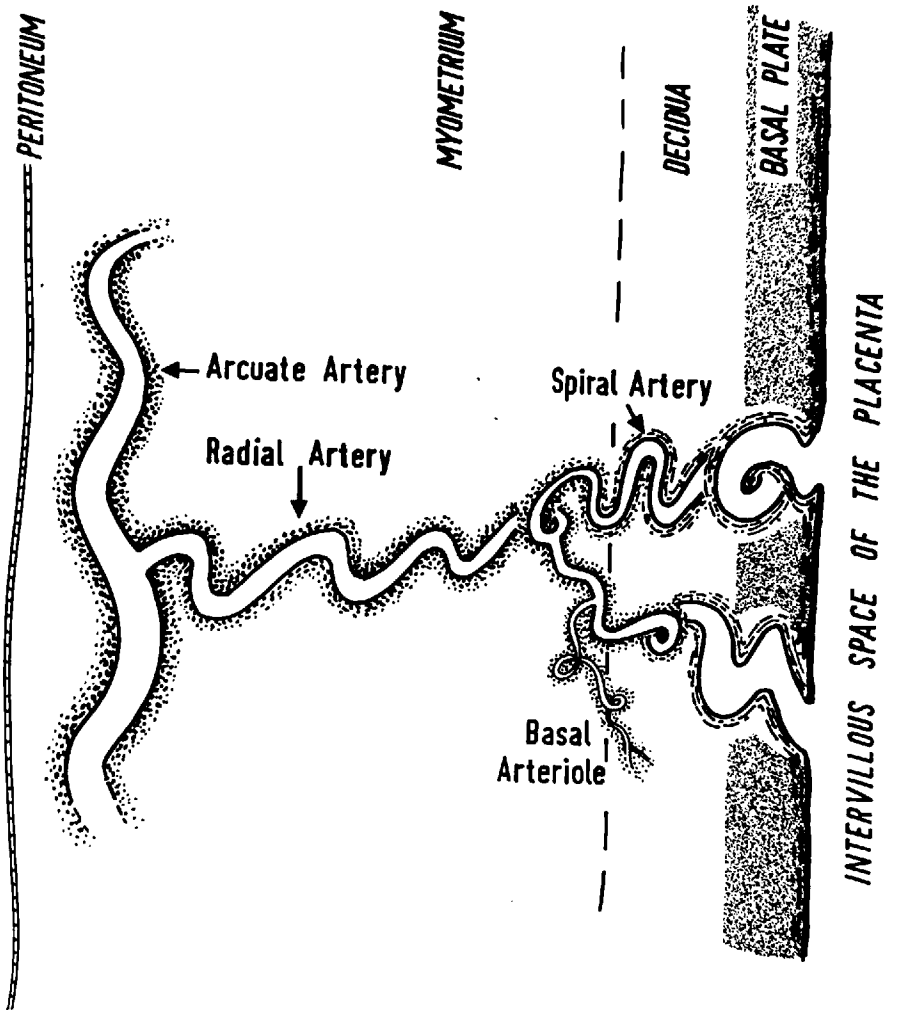


Fig. 2. Diagrammatic representation of the arterial circulation in the placental bed.

KOELLICKER (1867), WALDEYER (1890), BUMM (1893) and many others have given descriptions of the spiral course of these arteries. KOELLICKER in 1879 first described an increase of these vessels in length as well as in number during pregnancy. The utero-placental vessels are greatly hypertrophied at the site of the placenta as compared with the corresponding arteries elsewhere in the uterus (BEKER and VAN STEENIS, 1927, ARTS 1958 1961) According to BEKER (1948), however, the uterus of the primigravida is vascularized to a far lesser extent than that of the multigravida.

BLOCH in 1889 suggested that in the human the terminal part of the spiral artery is no longer spiral or corkscrew-like (korkzieherartiger Verlauf). A more undulating course of this vessel was also postulated by REYNOLDS (1949, 1954) as a result of the "conversion" occuring in the uterine growth during pregnancy. This undulating and not spiral course has been demonstrated in the Rhesus monkey (Macaca Mulatta) by RAMSEY(1949, 1954 a and b, 1955).

Attempts to count the number of spiral arteries communicating with the intervillous space have been made by KLEIN (1890), SPANNER (1936) and BOYD (1956). KLEIN counted in one separated placenta 15 maternal cotyledons with 87 arteries and 39 veins and in a second 10 cotyledons with 45 arteries and 27 veins. SPANNER working with a corrosion preparation of about 6 months gestation found 94 arteries and a total of 488 openings. BOYD on the basis of partial counts calculated 180, 310 and 320 openings in three different term placentae. On the other hand, RAMSEY (1959) has shown in the Rhesus monkey the uneven distribution of arterial communications with the intervillous space. If in the human there

is a similar uneven distribution of spiral arteries, the partial counts may have introduced error in calculations. BØE (1953, 1954) on the separated placenta found several arteries in the larger, maternal cotyledons and usually one artery in the smaller ones.

The situation of the openings of the spiral arteries in the basal plate has been the subject of great controversy. BUMM in 1893 pointed out that "the arteries are mainly lying in the decidual projections and septa, and eject their blood from the side of the cotyledon inwards to the intervillous space" (Fig. 3). As the septa were thought by some to be structures standing up in the intervillous space from the basal plate and reaching the chorionic plate, BUMM's statement has been quoted as implying that the arteries open in the intervillous space near the chorionic plate. This, however, is not exactly what BUMM has shown in his work, as he obviously regarded the subchorionic blood as somewhat venous in nature. KOELLICKER (1879) and HINSELMANN (1958) have confirmed the septal opening of the spiral arteries. WIELOCH (1923) and STIEVE (1941) have corrected BUMM's observations in that they specified that the spiral arteries mainly open at the base of the septa. However, ever since BUMM, this point has been controversial. WEBSTER in 1901 pointed out: "His (BUMM's) beautiful figured artery coiled outward in a decidual hillock and then sending jets of red paint outward among the villi must be regarded only as a pretty fancy.... Afferent as well as efferent vessels open indiscriminantly on the decidual surface between the decidual elevations as well as on them, as FARRE long ago pointed out. ... It (the intervillous

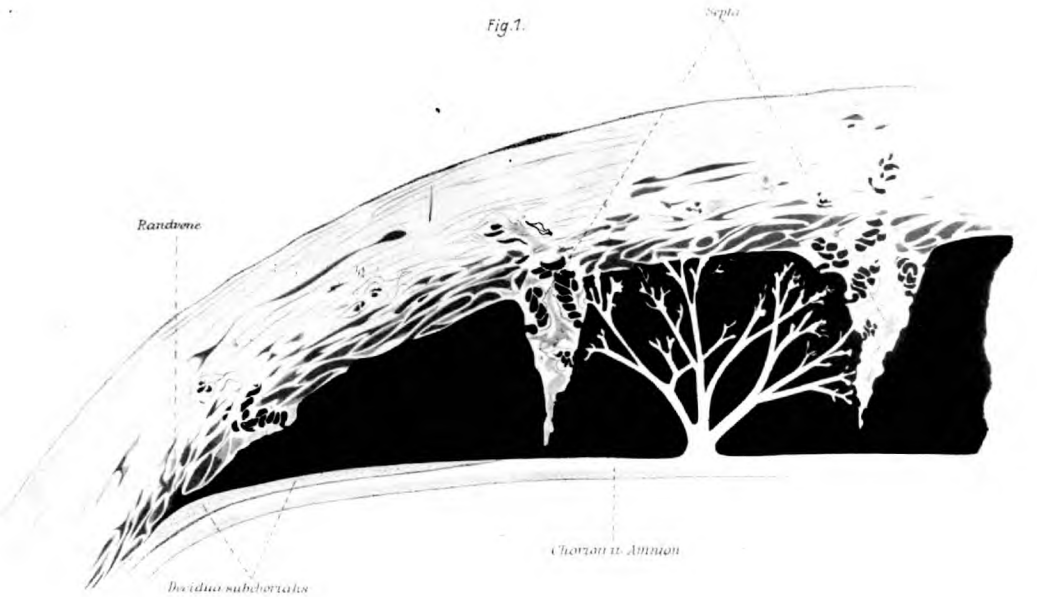


Fig. 3. - Diagrammatic representation of the circulation in the intervillous space of the placenta. (After BUMM, 1893).

space circulation) is probable not a swift-flowing, pulsating stream but a readily-moving mass of blood." WIELOCH (1923) and also RAMSEY (1956 a) wonder whether the structures considered by BUMM as septal arteries were in fact artefacts of tissue fissures. HAMILTON and BOYD (1960) found the arteries opening at variable situations in the basal plate, whereas SPANNER (1936) and BØE (1954) describe them as opening in the area underlying the central part of the foetal cotyledon.

The anatomy of the venous drainage has been the subject of quite as much discussion. It was KOELLICKER in 1879 who first stressed the role of a marginal sinus, partly lying in the placenta and partly in the decidua vera. According to his description maternal blood enters into the intervillous space at the basal plate, joins the subchorial meshes and is drained off through the marginal sinus. It is surprising that SPANNER, who is 1936 revived this theory did not quote KOELLICKERS's work.Since SPANNER, however, the absence of venous drainage other than the marginal sinus has been believed by many (McKELVEY, 1939, EARN and NICHOLSON, 1952). On the other hand, anatomical work by many early authors and repeated by recent authors on placentae in situ (BLOCH, 1889, WALDEYER, 1890, WEBSTER, 1901, STIEVE, 1942, RAMSEY, 1959, HAMILTON and BOYD, 1960, ARTS, 1961) and on the separated placenta (BUMM, 1893, KLEIN 1890, KERMAUNER, 1912, BØE 1953, 1954, MARAIS, 1962 a) has shown that venous drainage occurs all over the basal plate. The unlikelihood of an exclusive marginal drainage was also shown by the haemodynamic studies of BROWNE (1954). Both STIEVE and BØE hold the view that, although venous drainage occurs over

the entire basal plate, venous openings are mainly situated at the margin of the maternal cotyledon. The veins fuse beneath the basal plate to form the so called "venous lakes" (RAMSEY, 1956 a). The term "sinusoid" has also been applied to these vessels. This term has caused much confusion in the literature, since in some instances the intervillous space has been called the "sinusoidal space" and in other instances this term is applied to designate any dilated, arterial or venous, vessel in the placental bed. The venous lakes, as described by RAMSEY (1956 a) are the "distended portions of the wreath of endometrial veins which circles beneath the placenta and shows localized dilatations. These are the strictly maternal veins which may or may not communicate with the intervillous space."

The question of the existence of arteriovenous anastomoses in the decidua arose when HERTIG and ROCK (1941, 1945, 1949) described extensive anastomoses in the decidua. SCHLEGEL (1946) and DALGAARD (1946) confirmed the presence of such anastomoses in the endometrium. BARTELMEZ (1956), however, after re-examination of the original histological sections of HERTIG and ROCK cast doubt on the drawings published by these authors in 1941. WILKIN (1955) only describes anastomoses in the most superficial layer of the endometrium and BOYD (1956) states that no such shunts were found during the latter stages of pregnancy.

2. Histology.

The morphological changes which occur in the vessels of the pregnant uterus were extensively studied, mainly by German investigators, around the turn of this century.

The earliest work was concerned with the study of the mechanism preventing the uterus from bleeding during the postpartum period. In these studies, carried out on material from late pregnancy and the postpartum period, no special attention was paid to the topographic situation of the arteries and in the gravid specimens no distinction was made between vessels communicating with the intervillous space and vessels limited to the non-placental part of the uterus. Subsequent studies were devoted more to the vessel changes occurring in the placental area and a broad spectrum of such changes was described. Hence, the literature on the vessel changes in the normal uterus - which we shall call physiological changes - will be reviewed and summarized.

a) The myometrial Arteries.

Almost all authors before 1925 (BALIN 1880, WESTPHALEN 1886, DITTRICH, 1888, FRANKL and STOLPER, 1910, BUETTNER, 1911, WOLFKE, 1900, PICK, 1900, PANKOW 1906, SCHWARTZ and McNALLEY, 1923, WERMBTER, 1925) agree that thickening of the intima occurs in myometrial arteries as a result of gestation. WERMBTER in an extensive study showed that this change is not specific for pregnancy, but is also related to some degree with age. The importance attached by these authors to this intimal thickening was that under the influence of contractions the vessel becomes occluded and that the projections caused by this intimal proliferation could act as

supports for the formation of thrombi in causing primary occlusion of the vessel in the postpartum period.

The elastic tissue of the arteries is also reported to increase wi th parity. Many authors have described an increase of elastic tissue in the wall of the arteries of the parous uterus (PICK, 1900, GRUBE, 1902, WITTEK, 1906, PANKOW, 1906, GOODALL, 1910) and in the pregnant uterus (WERMBTER, 1925). The large myometrial arteries of the multigravida are characterized by an abundance of elastic and collagenous tissue in the adventitia, although the amount of increase in elastic tissue does not necessarily correlate with the number of gestations.

b) The spiral Arteries.

While most authors seem to be agreed on the presence of parity and age changes in the larger, myometrial arteries, much confusion and discussion has arisen in respect of vessel changes in the placental bed.

FRIEDLÄNDER first described in 1870 an outstanding vessel change in the placental bed, which was wrongly described by LEOPOLD (1877 a and b) as "Die Spontane Venenthrombose." FRIEDLÄNDER's description is as follows : "One finds....that many of these blood spaces are surrounded by a moderately thick coat e.g. for a sinus of 0.5 mm. diameter a coat as thick as 0.04 mm., which contains many apparently large cells with prominent nuclei and a clear, nearly homogenous ground substance staining intensively with Carmin stain.... The next remarkable phenomenon is that the content of the sinus is no

longer made up of red and white blood cells, but contains, in a more or less great number, very dark, large and granulated cells..... These cells are sometimes lying singly in the centre of the sinus, sometimes adherent to and lining, as a continuous epithelium, a part of the wall, and, at last, can become so numerous that they completely block the sinus only leaving here and there gaps for an occasional red blood cell."

In 1904 SCHICKELE drew attention to the fact that the vessel changes described by FRIEDLÄNDER (1870) and LEOPOLD (1877) occurred mainly in arteries and only occasionally in veins. FRIEDLÄNDER and LEOPOLD were also incorrect in thinking that the cells in the arterial lumen were most marked in late pregnancy. In fact, their description includes two different changes, which, although they may be related to each other, appear in the spiral artery at a different time during the course of pregnancy. The intrusive cells in the arterial lumen are present in early and mid-pregnancy, but have almost completely disappeared at 28 weeks, whereas the changes in the arterial wall are the prominent feature of the spiral artery at the end of pregnancy.

(1) The intrusive Cells in the Lumen.

Several different terms have been advanced to describe this vessel change : Verstopfung der Uterussinus (occluded uterine sinus) by FRIEDLÄNDER (1870, 1876), spontane Venenthrombose (spontaneous venous thrombosis) by LEOPOLD (1977 b) and physiologische Thrombose der Uterusgefässe (physiological thrombosis of the vessels of the uterus) by PATENKO (1879).

BLOCH in 1889 had already noted that these cells are usually absent in term placentae and HAMILTON and BOYD (1960) in a series of in situ placentae have shown that they appear in the enlarged terminal part of the spiral artery about 40 days after conception and are rarely found in the lumen at the end of pregnancy.

The origin of these cells has been widely discussed. Some authors (PATENKO, 1879, HINSELMANN, 1913, WISLOCKI, 1956, MARAIS, 1962 b) consider them as maternal, whilst others (LEOPOLD, 1877 b, WEBSTER, 1901, PINTO, 1905, MEYER, 1906) regard them as foetal SCHICKELE (1906 and 1911) and later HAMILTON and BOYD (1960) have demonstrated on "in situ" placentae the continuity of these cells with the cytotrophoblastic cells of the basal plate of the placenta. WISLOCKI and STREETER (1938) and RAMSEY (1956 a) describe similar cells in the spiral arteries in the Rhesus monkey, but regard them as maternal.

The function and role of these cells in the lumen of the spiral arteries remains obscure. HAMILTON and BOYD (1960) speculate that they may play some role in the chorio-decidual haemodynamics in early pregnancy by cutting down the pressure of the blood reaching the intervillous space.

(2) The Changes of the Wall.

A confusing terminology has been used to describe the changes which occur in the walls of the spiral arteries comm - unicating with the intervillous space, such as : physiologische regressive Metamorphose (physiological, regressive meta-morphosis) by SCHICKELE (1904), hyalin Rohr mit grossen

Zellen (hyalin tube with large cells) by FRANKL and STOLPER (1910), fibrinoid and hyalin structures of bizarre outline in collapsed vessels by WILLIAMS (1931) and diffuse thickening of the entire wall by SCHWARTZ and McNALLEY (1923).

This vessel change is usually fully developed in the term placenta. The features of this vessel change are the disappearance of the muscular and elastic coat of the artery and the deposition of a thick fibrinoid layer in the wall. KOELLICKER in 1879 described the absence of an elastic membrane in the spiral arteries of the pregnant uterus and this observation was confirmed by many others at that time (BLOCH, 1889, WEBSTER, 1901).

Many authors have also described the presence of large basophilic cells with single prominent nuclei in the wall of these arteries. Some authors (FRIEDLÄNDER, 1870, PINTO, 1905, SCHICKELE, 1906 and 1911, MEYER, 1906) have suggested the ability of the giant cells to invade and even to perforate the arterial wall. There is, however, as yet, no proof as to which cells these large basophilic cells in the altered wall are related. On the other hand, some authors have suggested that placental bed giant cells originate from cells of the arterial wall (DURANTE and LEMELAND, 1928, LE LORIER, DURANTE and MAYER, 1932, DEELMAN, 1933 BRETTNER, 1964).

Although BRETTNER (1964) has shown that, in the presence of a male embryo, sex-chromatin material can be found in some giant cells, he has not actually shown any transitional form between the muscular cells of the artery and the multinucleated giant cells in the vicinity of the spiral arteries.

Early authors have related these physiological vessel changes to the involution of the uterus after delivery. As several authors (BALIN, 1830, BROERS, 1895, PANKOW, 1906) had described fatty changes in the media of the arteries during the postpartum period, WERMBTER (1925) examined a large series of uteri during pregnancy for the presence of lipids using Sudan red and Scharlach red techniques, but failed to find any appreciable amount of lipid in the vessel wall during pregnancy.

B. The giant Cells.

KOELLICKER in 1879 first described the giant cells - "Riesenzellen" - in the placental bed and he indicated that these cells are restricted to the decidua basalis. His observation has since been confirmed by others. In the basal plate of the placenta many of these cells are mononucleated and often form a continuous layer with the cytotrophoblastic basal shell of the intervillous space. In the basal decidual stroma and myometrium the giant cells are mainly multinucleated, although some of them may be mononucleated.

Opinions are, however, much less uniform on the origin of the cells. A number of investigators, notably KASTSCHENKO (1885), WEBSTER (1901), MEYER (1906), SCHILLER (1922), McKAY and collaborators (1953), BOYD and HAMILTON (1960) and SCHRAMM (1962) have studied the giant cells in the later stages of pregnancy and consider them to be trophoblastic in origin. There are, on the other hand, a number of publications

(LEOPOLD, 1877, KEIFFER, 1928, DURANTE and LEMELAND, 1928, MASSON, 1956, PARK, 1959, BRETTNER, 1964) in which a maternal origin is suggested or specifically stated.

In the human several morphological aspects point to the foetal origin of the giant cells in the placental bed. HAMILTON and BOYD (1960) examined placentae at closely spaced time intervals during pregnancy and observed a continuity in the outgrowth of foetal syncytial elements into the maternal tissue. McKAY and collaborators (1958) showed histochemical similarity between the giant cells and the trophoblastic cells of the basal plate and SCHRAMM (1962) observed that in pregnancies with male embryos the nuclei of the giant cells, in contrast to the nuclei of decidual cells, possessed no sex chromatin. BRETTNER (1964) has, however, shown that in the presence of male embryos sex chromatin can be found in some multinucleated cells of the decidua. It remains to be seen whether the chromosome structure of trophoblastic cells is diploid of polyploid.

As to the function of the giant cells in late pregnancy little or no information is as yet available. Suggested functions for the giant cells are the production of enzymes, possibly to "soften up" the maternal tissue, and the elaboration of hormones.

BOYD and HAMILTON (1960) had the impression that there is no marked effect, cytolytic or otherwise, of the giant cells on the maternal tissue. These cells seem to push aside the maternal cells and to dissolve the surrounding reticulin and collagen, but there is no appearance of any very active destructive effect on the adjacent maternal cells.

The possibility of hormone production by the giant cells in the human has been suggested by their histological and

histochemical appearance (KEIFFER, 1928, LATTA and BEBER, 1957), but no exact information is as yet available. It is only recently that the study of the ultrastructure of the deciduo-trophoblastic junction in the guinea pig has shown evidence of intense metabolic activity in this area (WYNN, 1964).

II. FUNCTIONAL ASPECTS.

The primary function of the placental bed is the maintenance of an adequate choriodecidual or intervillous circulation throughout pregnancy.

In recent years several haemodynamic aspects of the maternal circulation of the placenta have been investigated using different techniques, such as determinations of the ^{24}Na clearance time in the intervillous space (BROWNE and VEALL, 1950, 1953, 1954, DIXON, BROWNE and DAVEY, 1963) and myometrium (MORRIS, OSBORN and PAYLING WRIGHT, 1955, 1956) and the ^{133}Xenon clearance time in the myometrium (MUNCK, LYSGAARD, PONTONNIER, LEFEVRE and LASSEN, 1964), cineradiographic visualization of the utero-placental circulation in the monkey (RAMSEY, 1963 a and b, MARTIN, McGAUGHEY, KAISER, DONNER and RAMSEY, 1964) and in the human (FERNSTRÖM, 1955, BOREL, FERNSTRÖM and WESTMAN, 1958) and finally the determinations of the pressure in the intervillous space (ALVAREZ and CALDEYRO, 1950, HELLMAN, TRICOMI and GUPTA, 1957, HENDRICKS, 1958, 1959, CORNER, RAMSEY and STRAN, 1963).

It is now generally accepted that arterial blood enters the intervillous space as a more or less constant stream through the irregularly scattered orifices of the spiral vessels in the decidua,

and forms funnel shaped streamsof blood at a relatively high pressure. This not only baths the villi with oxygenated blood, but drives out the blood already in the space through the venous drainage openings which lie scattered in the decidua in proximity to the arteries (Fig. 4). It is, therefore, as WIELOCH suggested in 1943, not the difference in level or distance between arterial and venous openings, but the pressure in the maternal arterial vessels which, in the first instance, provides an adequate blood flow through the intervillous space.

As would be expected, uterine contractions cause closure of the venous channels followed by the arterioles and the pressure in the intervillous space rises. It is also known that between subsequent contractions not all the arterial openings into the space are open at the same time in the normal placenta. This implies an intermittent functional patency of the spiral arteries. MARTIN and his co-workers (1964) suggest "that this intermittent closure seems to be related to active vasomotion rather than to passive compression by the surrounding myometrium".

Determinations of the amount of maternal blood flowing through the uterus and the intervillous space have been carried out by BROWNE and VEALL (1953) and also by ASSALI and co-workers (1953). These authors agree that the maternal blood flow through the uterus is at the rate of approximately 750 ml./ minute and of this 600 ml./minute is through the placenta.

Recent work by HENDRICKS and his co-workers (1959) has shown that the intra-uterine pressure is identical whether one measures it in the choriodecidual or intra-amniotic space, thus

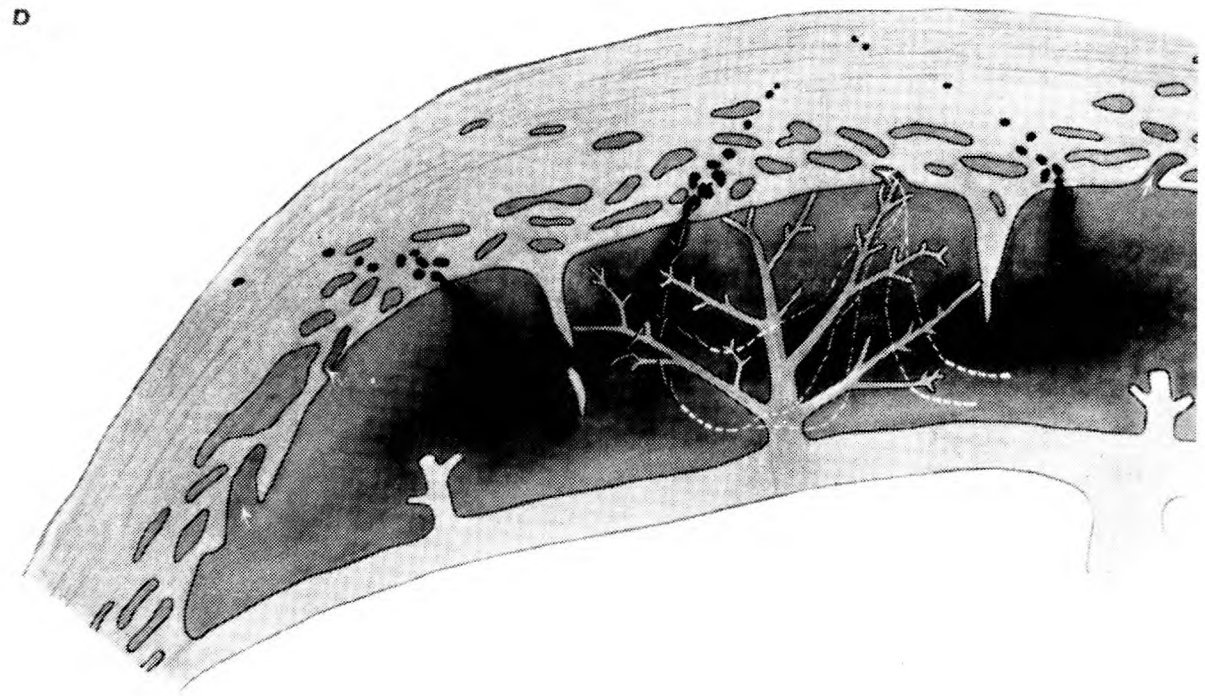


Fig. 4. - Diagrammatic representation of the course of the circulation through the intervillous space of the placenta. (After RAMSEY, 1958).

suggesting a regulating mechanism governing both inflow and outflow of the intervillous space.

Determinations of the choriodecidual flow rate using the method devised by BROWNE and VEALL (1953) have been carried out by DIXON and his co-workers (1963) in late pregnancy, and have shown a slight but progressive slowing of the flow up to term. This normal slowing is even aggravated past term, although a few patients show a marked slowing and some an apparent acceleration. DIXON and co-workers suggested that, if the assessment of maturity in this last group is correct, it is possible that the acceleration in flow represents a protective mechanism for a failure of placental function. In hypertension a considerable decrease of flow rate is found and the extent of this change appears to be related to the severity of maternal hypertension. (BROWNE and VEALL, 1953, DIXON, BROWNE and DAVEY, 1963).

III. PATHOLOGY OF THE PLACENTAL BED VESSELS.

Since the beginning of this century authors have described vascular changes in the placental bed which are found wholly or almost wholly in abnormal pregnancies. Many of these authors have used a different terminology such as : end- and mesarteriitis (SEITZ, 1903), degenerative arterial changes (WILLIAMS, 1915), acute degenerative arteriolitis (HERTIG, 1945) and acute atherosis (ZEEK and ASSALI, 1950).

End- and Mesarteriitis (SEITZ 1903)

In a remarkable study of two uteri with the placenta 'in situ' from patients dying from eclampsia SEITZ describes severe changes in the vessels directly underlying an infarcted area of the placenta. The elements of the arterial lesion he describes are "small cell" infiltration around the vessel, concentric narrowing of the lumen, thrombosis of the lumen by a uniform, homogeneous, sometimes fibrillar substance, and the presence of cells in the wall showing some similarity with decidual cells. Unfortunately, the lack of micophotographs makes uncertain the exact nature of the lesions SEITZ was describing.

Degenerative arterial Changes. (WILLIAMS, 1915)

Whithridge WILLIAMS in 1915 described vascular lesions in two uteri obtained by Caesarean hysterectomy from patients with premature separation of the placenta, one with toxaemia, the other without. The lesions occurred in the smaller arteries : "The endothelium was unchanged, but the tissue beneath it was increased in thickness, took a peculiar bluish color with haematoxylin and suggested a mucoid change. Here and there it contained peculiarly shaped refractile bodies..".

Acute degenerative Arteriolitis (HERTIG, 1945).

HERTIG in 1945 gave a clearer description of what was apparently the same lesion and of its development : "In its early stage, there appears beneath the intima of the spiral arterioles a collection of foamy, fat-laden, mononuclear leucocytes or phagocytes. This phase is soon followed by a fibrinoid

degeneration of the media which is in turn superseded by a fibroblastic proliferation of the intima that soon results in a nearly complete obliteration of the lumen."

Acute Atherosis (ZEEK and ASSALI,1950)

The lesion described by HERTIG was named acute atherosis of the decidual vessels by ZEEK and ASSALI. They described it as occurring in "endometrial spiral arterioles, their decidual termini and in endometrial venous lakes". ZEEK and ASSALI observed that, whenever present, acute atherosis was a diffuse lesion in the decidua, but seemed to be most marked in the decidua basalis near areas of ischaemic necrosis of decidua and of overlying placental infarcts.

Hypertensive vascular Changes. (DIXON and ROBERTSON, 1958, 1961).

DIXON and ROBERTSON described in the placental bed a range of hypertensive vascular changes, such as hyalinization, intimal and medial hyperplasia, and fibrinoid necrosis. The authors disagreed with HERTIG's interpretation and with the term acute atherosis in that it suggested that infiltration of the vessel with foam cells is the primary factor. According to DIXON and ROBERTSON the first stage of the development of this particular vessel lesion in pre-eclampsia is an acute fibrinoid necrosis. Later the damaged vessel becomes dilated, presumably as a result of its inability to withstand the continuing hypertension and finally, as a curious feature which has no counterpart in malignant hypertension, an infiltration of lipophages into the damaged wall occurs.

Arteriosclerosis (MARAIS, 1962 c)

Seven types of arteriosclerosis are distinguished by MARAIS (1962 c)

- (a) Fibrin and red blood cell intimal flakes;

- (b) Pure intimal or connective tissue proliferation;

- (c) The above (b) in association with fibrin, red blood cell and clot incorporation in the vessel wall;

- (d) Purely fibrinous or thrombotic deposition;

- (e) Mainly an "insudation" of a homogeneous, waxlike material. This type is particularly associated with foam cells.

- (f) Foam cell infiltration and disintegration;

- (g) Acute damage with solid or layered thrombosis.

The decidual spiral arterioles are according to MARAIS especially susceptible to injury due to their construction (acute spiralling, successive lengths of narrow and wide lumen in the same arteriole, shelves projecting into the lumen), made worse by the absence of muscular and elastic layers. MARAIS considers that the described types of arteriosclerosis in the spiral arterioles are due to the versatility of the intima. Absence of endothelium in many with its sequel of fibrin flakes, layered thrombosis, proliferation of the intima with incorporation of the hyalin material or fibrin in the wall, all finally result in a "hard" lesion with sclerosis of the wall and narrowing of the effective lumen.

The versatile intimal cells of the spiral arterioles are thought be MARAIS to be the most likely source of the peculiar cells, which, during most of the first and second trimester, irregularly fill nearly the entire lumen. By their irregularity they maintain turbulence and by their protection of the vessel

wall they allow normal development to full capacity. At about 24 to 27 weeks the spiral arterioles are fully developed. These cells are then washed away and the arteriosclerotic process described above takes over (MARAIS, 1962 b).

In the more severe types of arteriosclerosis the lesion appears to be "soft". A waxlike, homogeneous material - apparently liquid in its early stage - insudates into the wall and surrounding tissue, but also sometimes plugs the vascular lumen. This soft material constitutes a keen attraction for lipophages and in fact MARAIS notes an "absolute obsessive attraction" of the lipophages for fibrinoid material. He also thinks the lipophages are intimal cells, which become actively phagocytic, ingesting the soft fibrinoid material and rapidly growing larger to become foam cells. They are incorporated in the wall by overgrowth or they become mobile. These phagocytic cells show on the other hand little interest in the "hard" lesion of layered thrombotic intimal deposits. The sudanophilic material in the vessel wall is derived from foam cell disintegration or fine granular deposits which also are incorporated in the wall by connective tissue overgrowth or fibrin deposition. MARAIS considers this "soft" lesion with lipophages as the most acute human atherosclerotic lesion.

IV. CLINICO-PATHOLOGICAL CORRELATION.

From the previous chapter it is clear that a diverse terminology has been used to describe the vascular changes in the placental bed. As a result, the reports of studies on the association of clinical complications with particular changes in

the utero-placental vessels are often very confusing. In this chapter, the literature will be reviewed with special reference to the material used, the histopathological criteria adopted and the clinical assessment of the patient.

1. Studies based on the delivered Placenta and foetal Membranes.

For many years this has been by far the commonest method of obtaining material for the study of the spiral arteriole pathology. Its value for a careful study is doubtful. First, because the separated placenta has been subjected to gross mechanical distortion during delivery and, second, because identification of vessels in the basal plate of the placenta may often prove to be impossible or dubious. WEBSTER pointed out in 1901 : "There can be no doubt that in normal cases it is rare to find a vessel worthy of the name of artery or vein in the superficial part of the mucosa", and in spite of the efforts of modern investigators this anatomical fact still holds true. Since BUMM in 1890 first used the separated placenta for studying the anatomy of the spiral arteries, discussion has raged as to whether a particular vessel is an artery or a vein.

Studies on the separated placenta and membranes have been carried out by McKELVEY (1939), ZEEK and ASSALI (1950), SEXTON, HERTIG, and collaborators (1950), PAINE (1954), BURSTEIN and collaborators (1957), SHANKLIN (1958), BØE (1959), HUBER and collaborators (1961) and MARAIS (1962, 1963).

There exists great discrepancy between the findings of these authors: McKELVEY (1939) and BURSTEIN and collaborators (1957) and SHANKLIN (1958) observed no vessel changes

in association with toxaemic conditions, PAINE (1954) found occasional thickening of the medial coat in essential hypertension and in pre-eclampsia, if present for several weeks, and ZEEK and ASSALI (1950) found acute atherosis in pre-eclamptic toxaemia and hyperplastic arteriolar sclerosis in essential hypertension. HERTIG (1945) thought that acute degenerative arteriolitis of the spiral arterioles is a pathognomonic lesion of toxic separation of the placenta, but in a subsequent article in association with SEXTON (1950) he correlated this lesion rather with previous vascular and renal diseases. Recently, in a series of papers MARAIS (1962, 1963) found that a certain degree of spiral arteriosclerosis is present in normal pregnancies, but that the changes are much accentuated in the "toxaemic" group.

2. Studies on placental Bed Biopsies and uterine Curettings.

In 1958 DIXON and ROBERTSON drew attention to a new and simple technique for obtaining tissue from the human placental bed suitable for histological examination. This technique has since been used by several authors. DUPARC (1960), on the other hand, obtained material by curetting the uterine cavity immediately following the third stage of labour. Both techniques have permitted observations on decidual and myometrial vessels in a number of clinical conditions, such as toxaemia, diabetes and postmaturity.

Observations in hypertensive complications of pregnancy have been made by DIXON and ROBERTSON (1958, 1961), DUPARC (1960), PINKERTON (1963), and JONAS and REWELL (1963). DIXON and ROBERTSON found in the placental bed

vessels of patients suffering from essential hypertension changes which showed the characteristic features of vessels exposed to a systemic hypertension, i.e. hyalinization of the true arterioles and intimal hyperplasia with medial degeneration and proliferative fibrosis of the small arteries. In pre-eclampsia and eclampsia they observed acute fibrinoid necrosis with or without infiltration of lipophages into the damaged wall, while in pre-eclampsia superimposed on essential hypertension the arteriolonecrosis occurred in conjuction with arteriolosclerosis. In renal disease these authors observed a peculiar degenerative lesion of the media which appears oedematous with disappearance of the muscle accompanied by a cellular, presumably endothelial, proliferation. No such changes were found in normotensive patients. DUPARC concluded that the decidual arteries in normal pregnancies show some degree of arteriosclerosis and found in toxaemic pregnancies a more severe and more frequent lesion which he described as stenotic sclerosis. PINKERTON noted in some severe cases of pre-eclampsia superimposed on essential hypertension the presence of a vessel change, which he called "arteriolar narrowing", but unfortunately did not characterise this lesion. Great caution must be exercised in drawing conclusions about the blood flow through vessels apparently stenosed in histological sections. The pitfalls of artifacts in tissue which has been killed by removal and fixation are many, particularly in making dynamic interpretations. JONAS and REWELL reported complete failure to confirm the findings of DIXON and ROBERTSON. They suggested an ethnographic factor in decidual vascular lesions.

In a large series of biopsies from diabetic patients, PINKERTON (1963) was unable to show any spiral artery pathology associated with diabetes.

Changes in biopsies from postmature pregnancies were reported by DUPARC (1960) as being identical with the findings in toxaemia, but this finding was not corroborated by DIXON and ROBERTSON (1961), who were unable to demonstrate any histological evidence of vascular changes in the placental bed in postmaturity.

3. Studies based on Uteri obtained by Necropsy or by Caesarean Hysterectomy.

SCHMORL in 1893 reported on the necropsy findings in 18 cases dying from eclampsia without mentioning vascular changes in the uteri which were examined. KWORCSTANSKY (1903) in a report on 20 uteri including those from one eclamptic and four nephritic patients found hyalinization and narrowing of all decidual vessels in one of the nephritics. SEITZ (1903) described the intact uteri with placentae from two eclamptic patients with abruptio placentae and noted a proliferative and degenerative lesion in the spiral arteries, with narrowing and even occlusion of the vascular lumen. He found occluded arteries underlying an infarcted area of the 'in situ' placenta, and related the vascular and decidual degeneration to the toxaemic state. In later literature this excellent report on the utero-placental pathology in eclampsia has been completely ignored, probably because at that time most authors were mainly interested in the presence of inflammatory cells in the decidua as a possible cause of eclampsia.

Whitridge . WILLIAMS in 1915 described two cases of abruptio placentae. Although no blood pressure readings are given one of the cases presented with albuminuria and probably had nephritis, while in the other the urine was normal both before and after the accident. Both presented identical and striking arterial changes. As the lesions in the second case could not be attributed to nephritis, WILLIAMS prefered to believe that the lesions in both cases were due to some common cause, which he assumed to be "toxaemic" in character, but distinct from the usual "toxaemia" of pregnancy. FRANKL and HIESS (1921) were unable to find histological abnormalities in a series of 8 uteri with toxaemic and non-toxaemic accidental haemorrhage, but SCHWARTZ and McNALLEY (1923) reported that in toxaemia the normal vessel changes were more frequently present and more advanced. ZEEK and ASSALI (1950) included in their report on the separated placentae and foetal membranes a necropsy study of 30 pregnant and postpartum cases, of which 13 were toxaemic and 17 non-toxaemic. Atherosis of decidual vessels was found in 11 of the former and in only one of the latter group. The non-toxaemic case with acute atherosis of the decidual vessels had a history of syphilis and multiple miscarriages and died of generalized miliary tuberculosis. Similar early atheromatous lesions were found in extragenital regions in this case. On the other hand it is noteworthy that in the 11 toxaemic cases with acute atherosis of decidual vessels no lesions of a similar nature were found in sections from other organs.

SCOPE OF THE PRESENT STUDY.

The confusion that exists in the literature regarding the spiral arteries of the placental bed and their pathology at the end of pregnancy can be largely ascribed to two difficulties.

The first is the lack of adequate material. The separated placenta and the foetal membranes are, of course, easily available, but their value for such work is very limited. The technique of placental bed biopsy permits the study of a large number of cases with excellent and well preserved material, but only of a very limited area of the implantation site. The histological examination of the entire uterus makes an extensive examination of the changes in the placental and non-placental area possible, but no detailed study of such material has ever been performed.

The second difficulty is the correct assessment and differentiation of physiological and pathological changes in the spiral arteries. In an organ subjected to so many changes as the pregnant uterus, it is not easy to delineate between normality and disease and no author has ever tried to make a clear distinction between physiological changes and pathological lesions in the spiral arteries.

The present study comprises placental bed biopsies from 260 cases and 14 Caesarean hysterectomy specimens, three of which had the placenta 'in situ'. The topographic distribution of the spiral arteries and their communication with the intervillous space at the end of gestation have been investigated and a model of some 2/5 of the maternal surface of the placenta has been constructed.

The extensive examination of the hysterectomy specimens has allowed investigations of the normal histological appearances of the spiral arteries at the end of pregnancy and assessment of the pathological changes in hypertensive complications of pregnancy.

The study also includes an investigation of the lipid changes in the placental bed at the end of pregnancy with particular reference to arterial lipid changes and the distribution of lipid in the other tissues of the placental bed in normal and abnormal pregnancies.

MATERIALS AND METHODS.

I. HISTOLOGICAL MATERIAL AND METHODS.

The material for the present study consists of placental bed biopsies and Caesarean hysterectomy specimens.

A. Placental Bed Biopsies.

1. Biopsies obtained vaginally (50 cases)

In a group of 50 patients two large biopsies were taken from the placental bed after vaginal delivery of the baby under spinal or general anaesthesia. The implantation site of the placenta was first manually localized and after removal of the placenta the uterine wall was biopsied by means of an ovum forceps. The ovum forceps, which is an instrument currently used for the evacuation of the uterus in abortions, had for this purpose the edges of both its spoons sharpened. This instrument was selected because with the large spoons excessive crushing of the biopsy by the forceps could be avoided. To avoid any traction on the biopsy the surrounding tissue was digitally dissociated from the forceps. In each of these cases two biopsies were taken and fixed in Bouin's fixative. In none of the 50 cases has any subsequent harmful effect been noted. Mainly decidua and only a few millimeters of myometrium is gripped with the forceps. The size of the biopsies is approximately 1.5 x 1 x 0.5 cm. each.

Histopathological studies of small arteries in other organs have shown serial sections to be essential for a fair evaluation of vascular lesions (MORITZ and OLDT, 1937).

Therefore, in all 50 cases in which large biopsies were taken by the vaginal route with the ovum forceps, at least one biopsy was completely examined with the step serial section technique, one section being stained for every five, ten or twenty sections cut. Consequently, in every case, between 100 and 200 sections were examined microscopically. The total number of sections examined was approximately 6500.

Apart from routine staining with haematoxylin and eosin and Masson's trichrome techniques, the following staining procedures were used, where indicated : Verhoeff's and Weigert's elastic stain, Periodic acid Schiff's for mucopolysaccharides, and Perl's reaction for free iron. These techniques were employed as described in the standard textbooks of histological methods.

2. Biopsies taken at Caesarean Section (210 cases)

In a group of 210 patients one, or more frequently, two biopsies were taken from the placental bed at the time of Caesarean section using the biopsy forceps devised for this purpose by DIXON and ROBERTSON (1958). In a number of cases a biopsy was also deliberately taken from the non-placental area of the uterine wall as a control.

The biopsies were fixed in 10% neutral formalin-saline. They were thoroughly washed in running tap water before freezing by immersion in liquid nitrogen (-170^{o}C). From each biopsy six to ten sections were cut at different levels on a cryostat (PEARSE model) at -20^{o}C and stained with Oil Red O in isopropyl alcohol. Details of this staining technique are given in Appendix I.

When two biopsies were taken from the placental bed the second biopsy was embedded in paraffin and 10 sections were cut at different levels of the biopsy. Sections were stained with haematoxylin and eosin, Masson's trichrome and Weigert's elastic stain.

3. Caesarean Hysterectomy Specimens.

The entire uterus was obtained at the time of Caesarean hysterectomy in 14 women. A technique for preserving the placenta 'in situ' during Caesarean hysterectomy was developed and a successful attempt was made in three cases. This technique consists of packing the uterine cavity with gauze packs immediately following delivery of the baby (RENAER, 1962) and making a large incision through the peritoneum and myometrium overlying the placental area (SCHOCKAERT, 1962).

Each uterus was partially fixed in 10% formalin-saline for one or two days. The specimen was then sliced in blocks one centimeter thick, these comprising sagittal sections of the complete placental bed and entire thickness of the uterine wall or in the three cases complete sagittal sections of the placenta and underlying uterine wall.

Further fixation in 10% formalin-saline for one week or longer was allowed. After fixation, blocks were embedded in paraffin by special technique as described in Appendix II. From these paraffin blocks serial sections were cut at 8 microns on a M. S. E. sledge microtome adapted with a Moore stage measuring 135 by 90 mm.. One in every twenty or thirty serial sections was mounted so that totals of between 10 and 100 sections were obtained from the blocks.

These large sections were stained by haematoxylin-eosin and Masson's trichrome techniques and Weigert's elastic stain. The sections were then used to follow individual arteries in their course through myometrium and decidua. In each specimen 10 to 25 arteries in the placental bed and a similar number in the non-placental area were examined.

II. CRITERIA FOR HISTOLOGICAL IDENTIFICATION OF THE ORIGIN OF THE "PLACENTAL BED BIOPSY"

On those uteri in which the placenta was still attached to the uterine wall, it was found that the decidua basalis could be identified in three ways :

1) by the presence and distribution of giant cells in the decidua and myometrium;

2) by the presence of villi attached to the decidua;

3) by the presence of "physiological vessel changes" which will be described later.

Using these criteria it was possible, on the one hand, to identify the placental bed origin of the biopsies and, on the other hand, to identify in the large sections of the hysterectomy specimens with separated placenta the implantation site of the placenta.

By applying these criteria to the "biopsies from the placental bed" it was surprising to find that only 60% of the biopsies fulfilled one or more of the three criteria. Although it is possible that some of the other biopsies did in fact originate from the very edge of the placental bed, every biopsy which did not satisfy at least one of these histological criteria of the placental bed was excluded from the present study.

III. CLINICAL CRITERIA WITH SUBDIVISION OF CASES.

The patients are grouped according to the techniques by which material was obtained for histological examinations.

1) The first group, consisting of the 50 patients from whom placental bed biopsies were taken vaginally after normal delivery, is classified according to the standards adopted by the American Committee on Maternal Welfare (See Appendix III).

The subdivision of the hypertensive group is as follows :

	Number of cases.
Pre-eclampsia : mild	5
severe	4
Eclampsia	5
Essential hypertension with superimposed pre-eclampsia	4
Hypertensive vascular diseases	7

The normotensive group includes 25 cases.

2) The second group consists of the 210 patients from whom biopsies were taken from the placental and non-placental areas at the time of Caesarean ection. In only 121 cases one or more biopsies satisfied the histological criteria of "placental bed origin".

The hypertensive group is subdivided according to the more stringent criteria used by DIXON and ROBERTSON (See Appendix IV). This was done because the use of Oil Red O staining enabled the very early vessel lesions due to hyper - tension to be demonstrated. The subdivision of the hypertensive

group is as follows :

	Number of cases.
Essential hypertension :	
borderline	9
mild	19
Episodic hypertension	5
Terminal hypertension	22
Pre-eclampsia	5
Essential hypertension with pre-eclampsia	4

The normotensive group consists of 57 cases.

The duration of gestation was calculated from the first day of the last menstrual period (Nägele's rule). Due allowance was made for obvious errors revealed by examination throughout pregnancy. The duration of gestation is given in completed weeks.

"Small for dates babies" are babies that are abnormally small by weight for the duration of gestation, i.e. less than two standard deviations of the mean birth weight by week of gestation. The standards are those of DAWKINS from the Second Report of the British Perinatal Mortality Survey (See Appendix V).

3) The third group consists of 14 patients who underwent a Caesarean hysterectomy. This group consists of 8 normotensive and 6 hypertensive cases according to the standards adopted by the American Committee on Maternal Welfare (See Appendix III).

IV. CONSTRUCTION OF A MODEL OF THE MATERNAL SIDE OF THE PLACENTA.

A model has been constructed to show the maternal side of some two fifths of a placenta enlarged six times. For this purpose one of the uteri with the placenta in situ obtained by Caesarean hysterectomy was used. Two fifths of the specimen was entirely cut in 8 micron sections, one section being collected and mounted for every thirty cut. In this way sections were collected through the entire two fifths of the specimen at approximately 250 micron intervals. In total about 200 sections were collected and all sections were stained with haematoxylin and eosin.

With these sections a model was constructed in three steps:

1) The first step consisted in examining the sections under a Zeiss binocular colposcope on a transilluminating box and in tracing directly from the transilluminated sections the outline of the basal plate, septa and decidual arteries and veins on to tracing paper.

2) From these tracings a contoured map of the basal plate including the septa and vascular openings was made and then reproduced on a six times enlarged plan.

3) Using this map as a base plate and with frequent reference to both tracings and original sections, the decidual plate and septa were fashioned in modelling paste (Barbola). The positions of maternal arterial and venous openings were then marked.

RESULTS

I. THE NORMAL ANATOMY.

A. Architecture.

Figure 5 shows the model referred to on p. 51 of the maternal site of some two fifths of a placenta.

The model shows the irregularly and apparently haphazard distribution of the septa and the free intercommunication of every part of the intervillous space.

The distribution of both the arterial and venous openings is irregular (Fig. 6) and the arteries occasionally tend to occur in groups of two or three. Veins drain all over the basal plate, but the great majority of the spiral arteries open at the base or in the lower third of a septum (Fig. 7, 8). A few spiral arteries were found to open more than 1 cm. up a septum (Fig. 9).

Forty-eight spiral arteries were counted in these two fifths of a placenta and therefore the total calculated number for the entire placenta would be of the order of 120 arteries, i.e. approximately one artery for every two square centimeter of basal plate.

All arteries in this placenta were found to communicate by only one opening with the intervillous space. On the other hand, the so called venous lakes in the decidua drain blood from the intervillous space through multiple openings spread over the entire basal plate (Fig. 10).

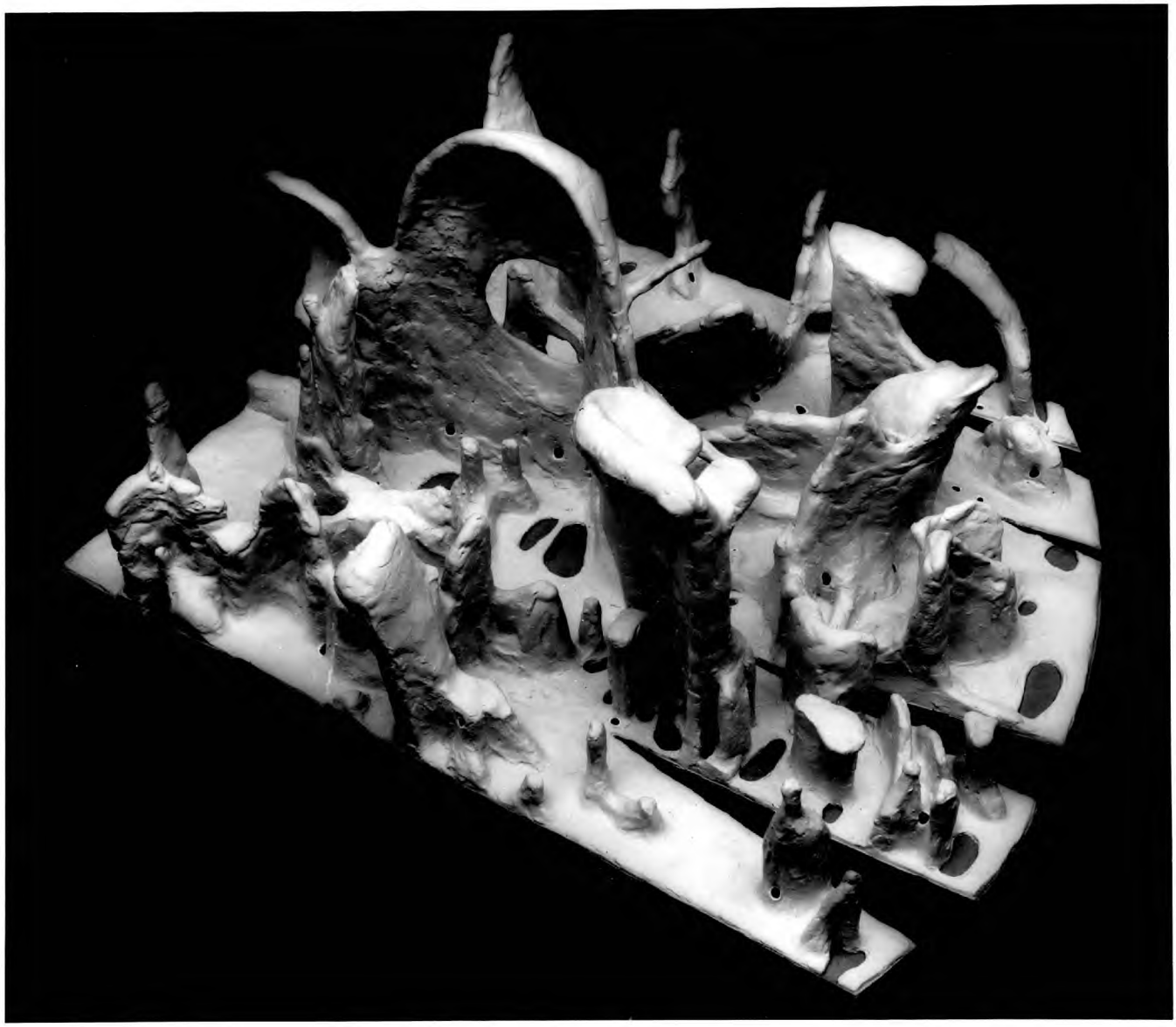


Fig. 5. - Model representing the basal plate and the septa of a placenta with indication of the site of opening of arteries (small openings) and veins (large openings). The inlets on the margin are due to the artificial flattening of the surface.

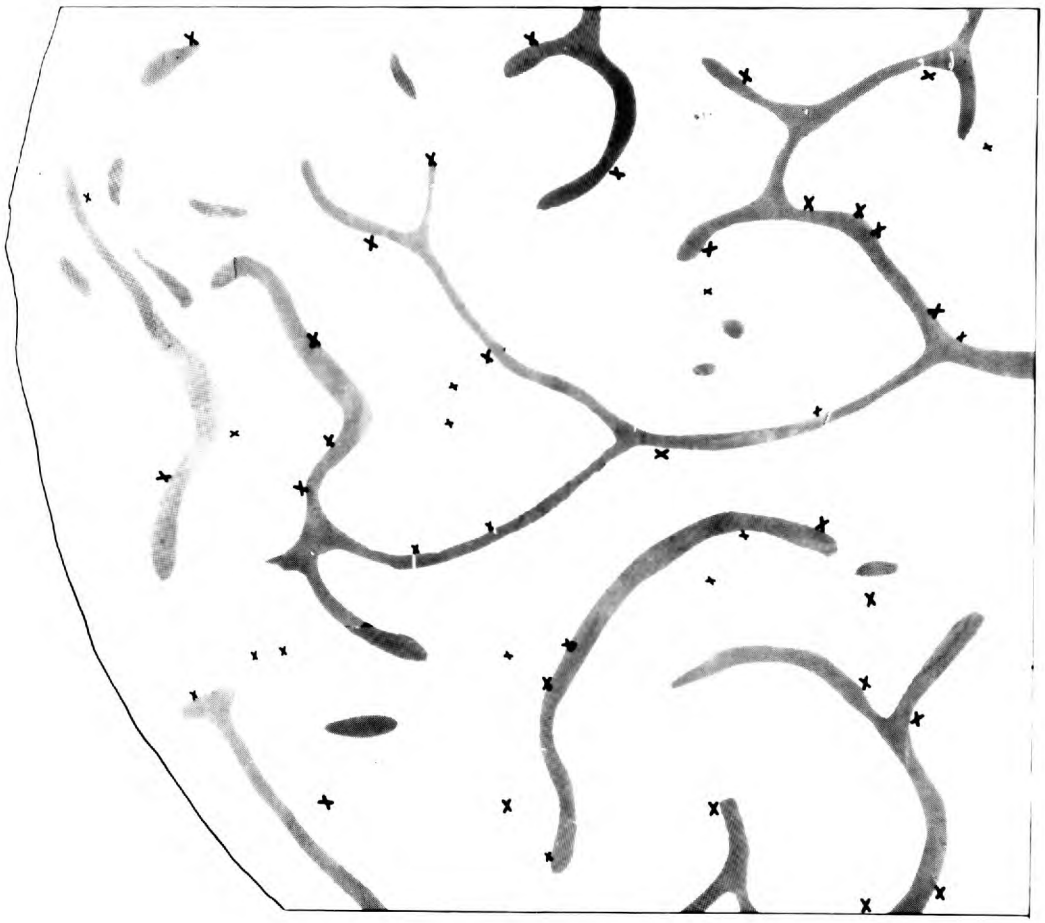


Fig. 6. - Diagram representing two fifths of the basal plate of the placenta with indication of site of placental septa and openings of the spiral arteries. Only septa of a height more than 0.5 cm. are indicated.



Fig. 7. - Opening of a spiral artery at the base of a placental septum. H.E. - x 6.4

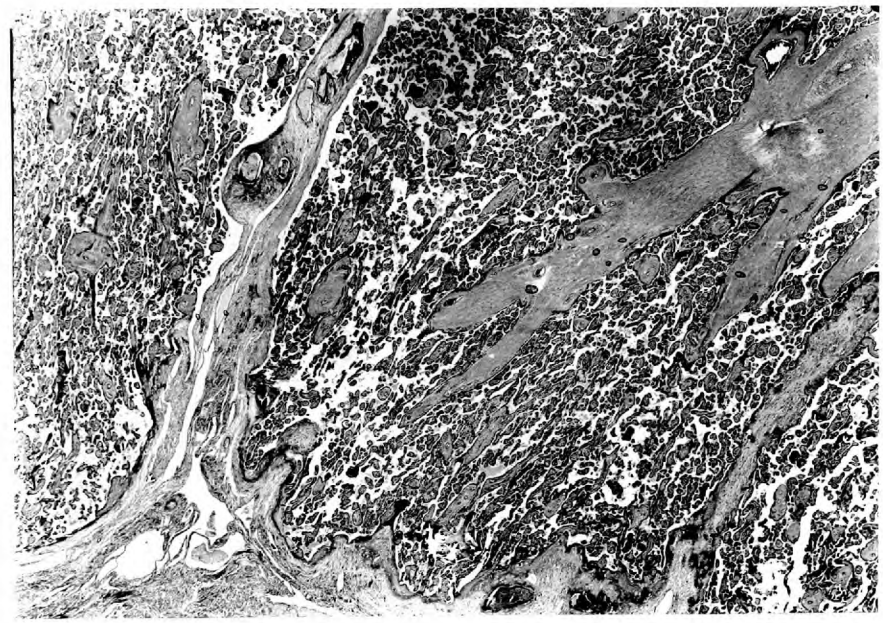


Fig. 8. - Spiral artery in a placental septum. H.E. - x 6.4



Fig. 9. - Spiral artery in the base and in the top of a placental septum. H.E. - x 8.5.

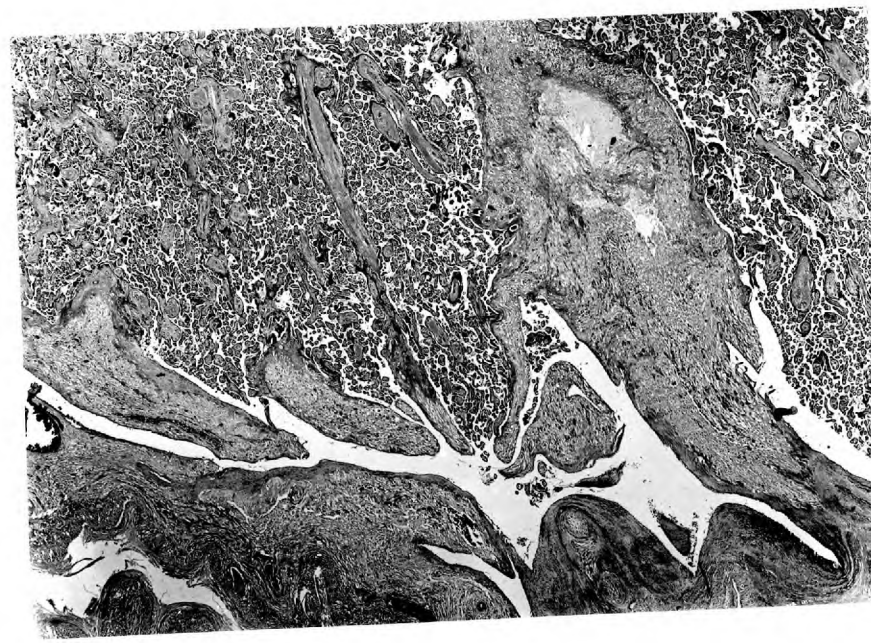


Fig. 10 - Multiple openings of a vein in the placental bed. H.E. - x 12.

B. The normal histological Features.

1. Vessels.

The spiral arteries of the placental bed are anatomically distinguished from the basal arterioles by the fact that the former communicate with the intervillous space, whereas the latter are restricted to the decidua and inner part of the myometrium.

A strict distinction between spiral arteries and basal arterioles can only be made on intact specimens with the placenta in situ, where the entire course of the vessel can be followed in step serial sections.

On large sections of hysterectomy specimens, however, it is usually possible to distinguish accurately spiral arteries from basal arterioles by the general appearance, the course and the size of the vessels.

Spiral arteries have a more or less perpendicular course to the plane of the myometrio-decidual junction, whereas basal arterioles run more or less parallel to the myometrio-decidual junction. The diameter of the basal arterioles is usually less than 100 microns, whereas in spiral arteries it varies between 100 and more than 1,000 microns.

a) Physiological Changes in the spiral Arteries.

(1) Histological Description.

At the end of a normal pregnancy the majority of the spiral arteries have characteristically lost several of the histological features of normal arteries and acquired new ones. The following description of these physiological changes is based on the appearance of the spiral artery at the myometrio-decidual junction at the end of a normal pregnancy.

The wall is characterised by a virtual absence of smooth muscle and elastica.

The outer layer of the wall consists of a fibrinoid layer of irregular thickness often undulating in which "large cells" are embedded (Fig. 11 - 13). These large cells are mononucleated, but sometimes bi- or multinucleated and many of them show definite signs of degeneration. The inner part of the wall consists mainly of fibrous tissue of variable tickness. This fibrous layer is probably derived from organised mural thrombi. Occasionally small vascular channels can be seen in these intimal cushions suggesting organisation of thrombus (Fig. 14).

The endothelial appearances vary. At the myometrial level the proliferative appearance of the endothelial layer may be due to the collapse of the vessels or oblique cutting. At the decidual level there is discontinuity of the endothelial lining and some of the cells, which are apparently replacing endothelium, morphologically resemble trophoblast (Fig. 15).

In spite of the thickness of the wall, the arterial lumen is sinusoidally dilated.

(2) Development during the second Half of Pregnancy.

In the present study 14 Caesarean hysterectomy specimens were used. Group A consisted of 11 specimens from between 36 and 40 weeks duration, and Group B of 3 specimens from pregnancies between 28 and 34 weeks duration.

In all specimens serial sections of a large part of the placental bed were prepared. Consequently, it was possible to make a survey of a great number of arteries and arterioles in each case.

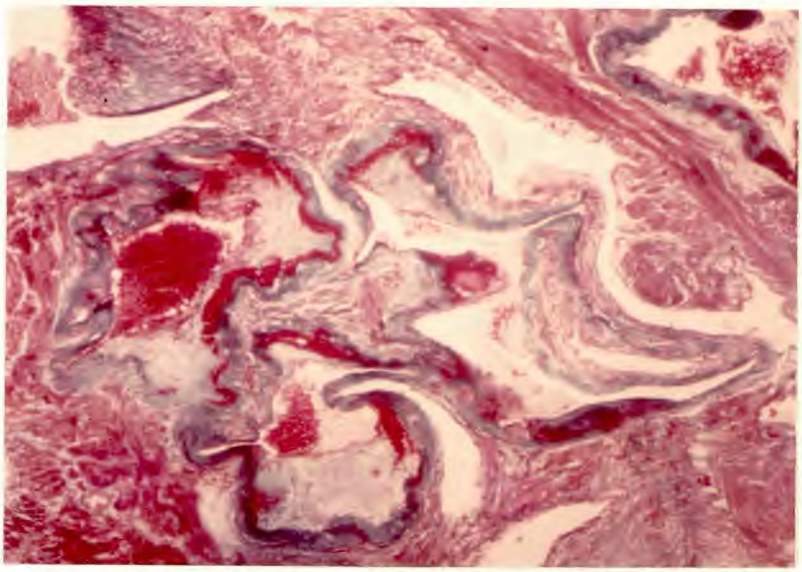


Fig. 11. - Normal pregnancy. Physiological changes in a spiral artery of the placental bed. Masson's trichrome - x 85.

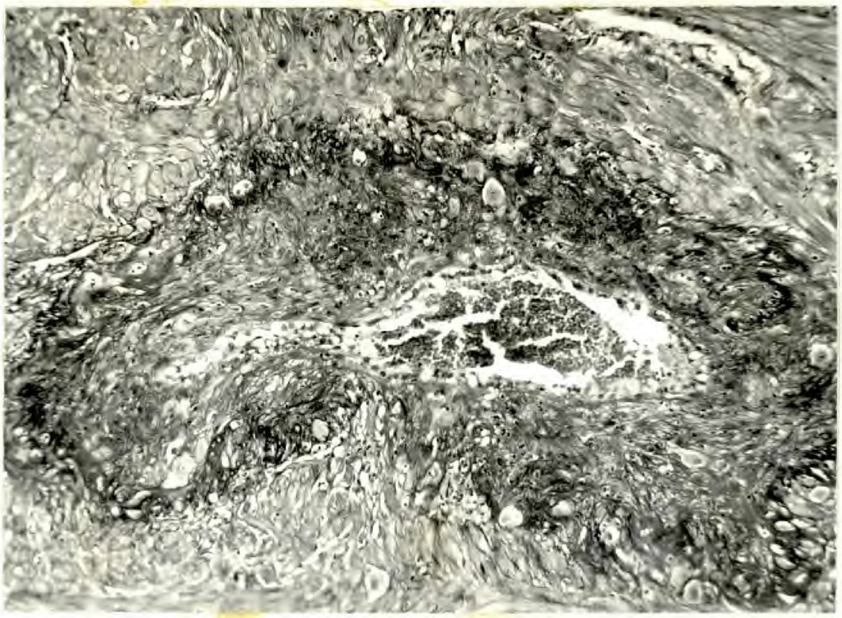


Fig. 12. - Absence of elastica in the wall of a spiral artery with physiological changes. Weigert's elastic stain - x 125.

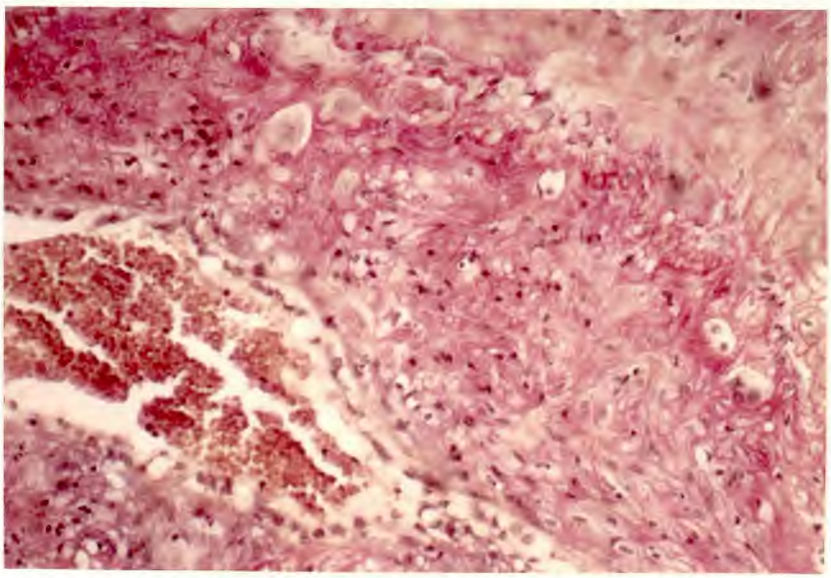


Fig. 13. - Presence of "large cells" in the wall of a spiral artery with physiological changes. Weigert's elastic stain. - x 225.

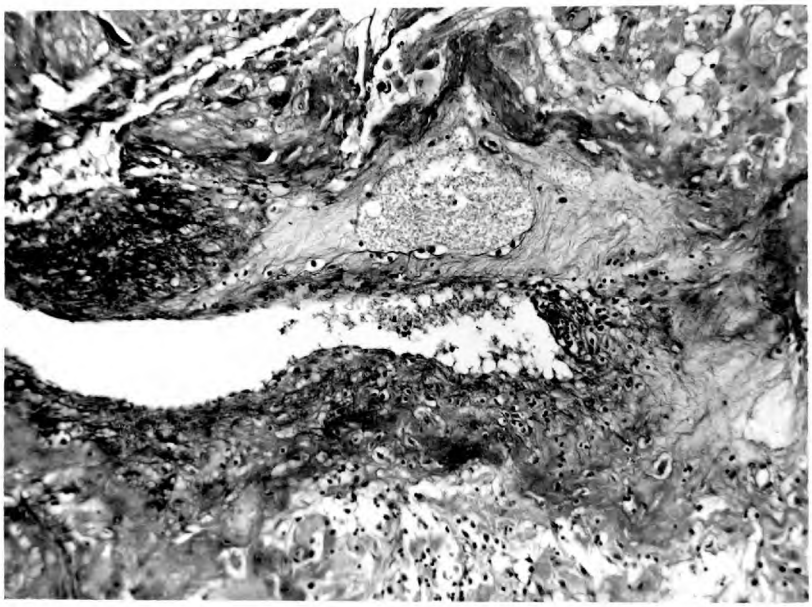


Fig. 14. - Normal pregnancy. Small intimal channels in the wall of a spiral artery with physiological change. Weigert's elastic stain. - x 125.

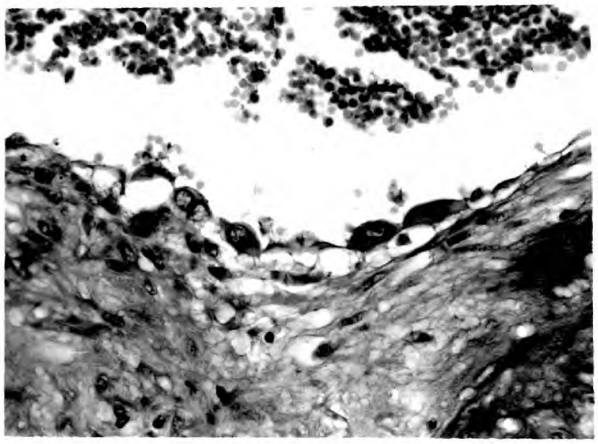


Fig. 15. - The cells lining the lumen of the spiral artery are suggestive of trophoblastic origin. Weigert's elastic stain. - x 220.

Table I details the distribution and nature of physiological changes in the spiral arteries at the various levels.

In all specimens the decidual part of the spiral arteries showed extensive physiological changes and no striking difference could be found between the groups.

However, a difference between groups was noted in the extent of the physiological changes in the myometrial part of the spiral artery.

In Group A the majority of the spiral arteries at this level were characterized by a thick wall, which consisted mainly of fibrous and fibrinoid tissue with large cells in the outer part, the lumen being widely dilated in sinusoidal fashion (Fig. 16).

In Group B there was an absence of a continuous intimal fibrous layer. The spiral arteries with physiological changes at the myometrio-decidual junction appeared as collapsed, large and rather thin walled vessels. The wall mainly consisted of a continuous fibrinoid layer with numerous large cells (Fig. 17). At some places a group of large cells was found in the lumen and some of these cells had apparently invaded the wall from the lumen (Fig. 13). These groups of cells morphologically resemble the plugs of cytotrophoblast seen in the lumen of the spiral arteries during the first half of pregnancy.

In one specimen of Group B the large cells and fibrinoid layer were absent as well and the vessels in the myometrium had preserved their arterial structure.

(3) Topographic Distribution.

The topographic distribution of the physiological changes in the spiral arteries has been studied in three specimens with the placenta 'in situ'.

TABLE I

PHYSIOLOGICAL CHANGES IN THE SPIRAL ARTERIES OF THE PLACENTAL BED

	Age	Parity	Pregnancy Duration (weeks)	Baby Weight (grams)	Physiological changes in the decidua	Physiological changes in the myometrium		
						Fibrinoid alteration	Large cells	Intimal fibrosis
Group A	26	1	40	4200	+	+	+	+
	38	3	38	3100	+	+	+	+
	30	3	40	3490	+	+	+	+
	35	4	38	3470	+	+	+	+
	36	7	39	4190	+	+	+	+
	41	5	38	2430	+	+	+	+
	24	3	39	3240	+	+	+	+
	27	2	38	2460	+	+	+	+
	30	6	36	2200 2290	+	+	+	+
	40	9	38	3600	+	+	+	+
	33	0	38	2580	+	+	+	+
Group B	26	0	29	1350	+	+	+	absent
	37	7	28	?	+	+	+	absent
	33	4	32	1250	+	absent	absent	absent

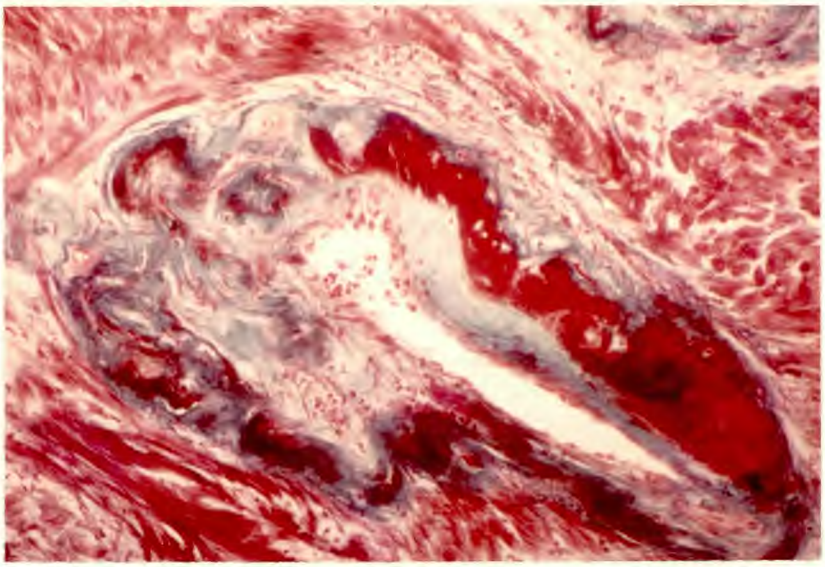


Fig. 16. - Physiological change in a spiral artery at term. Masson's trichrome - x 125.

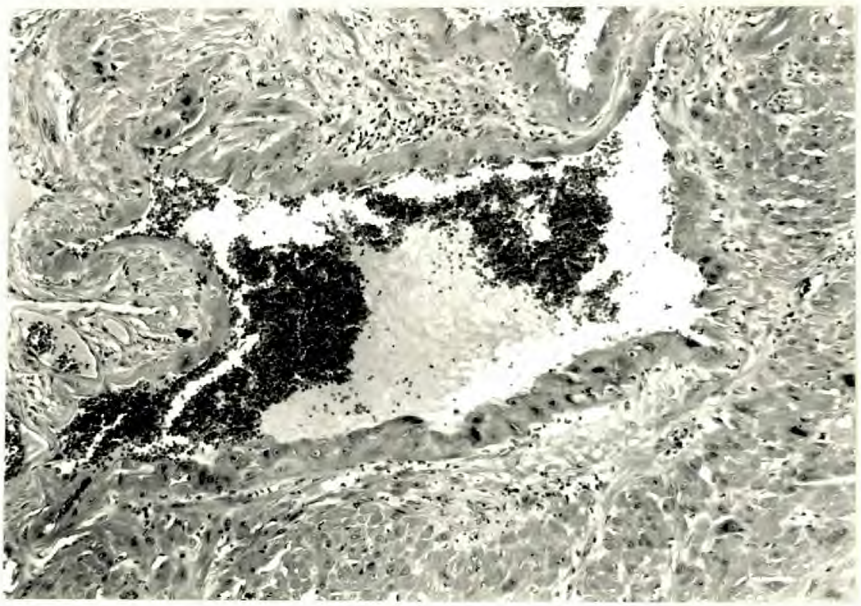


Fig. 17. - Physiological change in a spiral artery at 28 weeks gestation. H. E. - x 100.

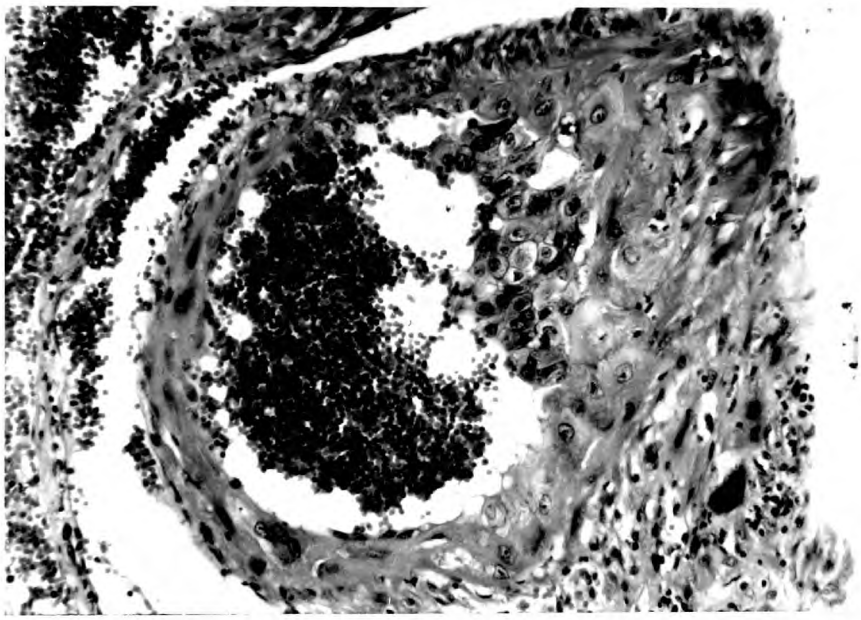


Fig. 18. - 28 Weeks gestation : intravascular plug of cells resembling cytotrophoblast. Note the histological similarity and direct continuity of the cells in the lumen and the "large cells" in the wall. H. E. - x 180.

(i) In the placental Area.

Some difference exists between the extent of physiological changes in the central and marginal areas of the placental bed. In the central, and paracentral, parts of the placental bed physiological changes of the spiral arteries are present not only in the decidua but also in the adjacent myometrium. In the most marginal part of the placental bed these changes are present in the decidual part of the spiral arteries but are almost absent in the myometrial segment.

(ii) In the non-placental Area.

The physiological changes as described have not been observed in the spiral arterioles in the decidua vera and adjacent myometrium.

b. Basal Arterioles.

The basal arterioles are of a size between 40 and 100 microns and the sinusoidal changes, as described in the spiral arteries communicating with the intervillous space, are not seen in them. It is, however, a feature common to all arteries and arterioles in the decidua basalis that the elastica is disrupted and has partly or completely disappeared from the arterial wall during the last trimester of pregnancy.

It is noteworthy that giant cells have not been seen in the wall of the basal arteroles, although they may be seen in the tissues around the basal arterioles (Fig. 19).

c. Veins.

The veins usually open at a sharp angle from the intervillous space and are flattened vessels running more or less parallel to the basal plate.

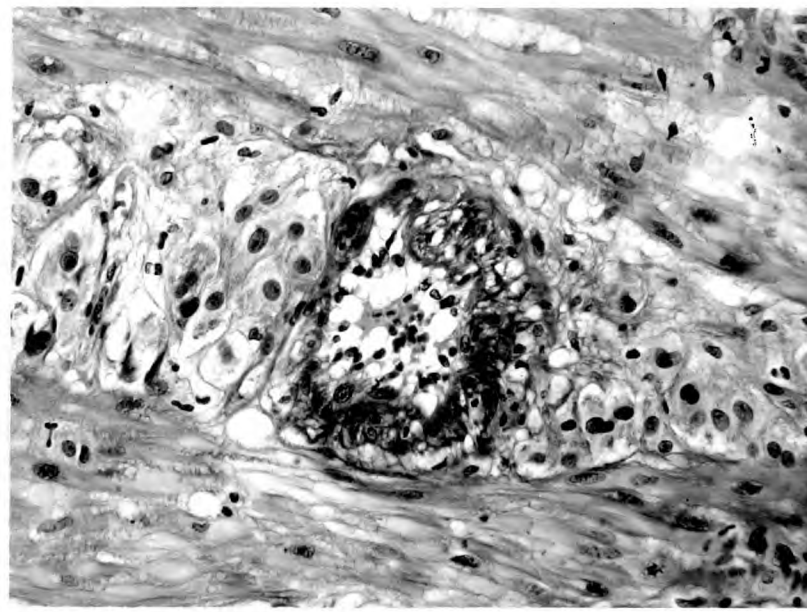


Fig. 19. - Normal basal arteriole in the placental bed. H. E. - x 220.

Phlebosclerosis is a common finding at the end of a normal pregnancy and consists of proliferative intimal cushions of variable thickness. Multinucleated giant cells are seen in close proximity to the walls of the veins and may line up in pallisade fashion against the wall, but the most striking feature, for which no explanation can as yet be offered, is the complete absence of any reaction to their presence. This is in marked contrast to what happens in the arteries.

2. The giant Cells.

At the end of a normal pregnancy giant cells are still present in great numbers scattered throughout the decidua and myometrium underlying the placental site. They are often absent in the marginal areas of the placental bed and are not found in the basal layers of the decidua vera. Some multinuclear giant cells occur in the very superficial layers of the decidual vera, between the amnion and the decidua itself.

The distribution of giant cells in the placental bed is random. Due to normal variation in density, it would be hazardous to consider the density of giant cells in a biopsy as representative for the whole placental bed.

Two types of giant cells are encountered in the placental bed : a) the mononuclear giant cells, which are morphologically distinct from the decidual cells but resemble cytotrophoblast. The cytoplasm of these giant cells is basophilic and the vesicular nucleus has dense and coarse aggregates of chromatin. These cells are normally present in the upper layer of the decidua and together with the fibrinoid layer of Nitabuch form the basal plate of the placenta. At the end of a normal pregnancy these cells are only occasionally seen in the deeper

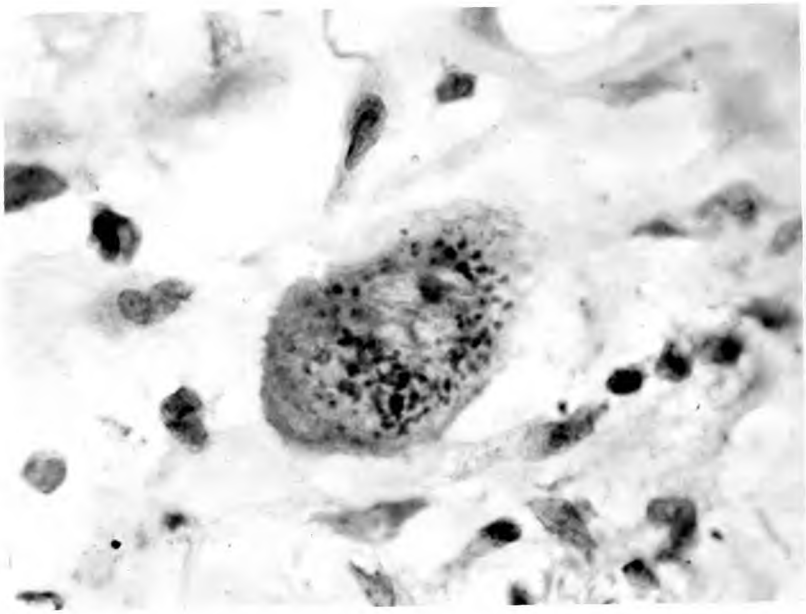


Fig. 20. Free iron in placental bed giant cell. Perl's reaction - x 420.

layers of the decidual stroma and in the adjacent myometrium.

b) The most prominent cells in the deeper layers of the decidua and the adjacent myometrium are the multinuclear giant cells. Some of these cells show phagocytic activity by ingesting red blood corpuscules and free iron can occasionally be demonstrated in their cytoplasm (Fig. 20).

II. VASCULAR PATHOLOGY.

A. Histological Description.

Hypertensive vascular lesions occur in both spiral arteries and basal arterioles of the placental bed.

1. Vessels retaining their arterial or arteriolar Structure.

This group of vessels includes the basal arterioles as well as those parts of the spiral arteries which have not undergone physiological changes. In these vessels the hypertensive vascular lesions are not obscured by physiological changes and, therefore, in them it is often easier to observe the hypertensive lesions.

In these vessels a distinction between two types of vascular lesions can be made. Firstly, lesions characterised by intimal, cellular and fibrotic hyperplasia and, secondly, lesions characterised by fibrinoid necrosis and lipophage infiltration, the so-called acute atherosis.

(i) Hyperplastic Lesions.

The characteristic features are intimal and medial hyperplasia and proliferative fibrosis of the arteries (spiral arteries without physiological changes) and intimal fibrosis of the

arterioles (basal arterioles) (Fig. 21, 22). These lesions are well known to occur in vessels in other organs exposed to essential or chronic hypertension.

(ii) Acute Atherosis.

The characteristic features of "acute atherosis" in arteries and arterioles of the placental bed consist of fibrinoid necrosis and lipophage infiltration (Fig. 23, 24).

In the arteries the fibrinoid necrosis can be minimal and the presence of foam cells is often the most prominent feature. When the elastica is preserved, foam cells can be found between duplicated layers of the internal elastica.

In the basal arterioles the fibrinoid necrosis is usually more prominent and the wall of the vessel stains intensely with the P. A. S. stain and red as for fibrin with the trichrome stain. In the presence of acute atherosis the lumen of these vessels also appears to be distended, but stenosis and even complete obliteration can occur as a result of an excessive increase of fibrinoid deposit and large numbers of lipophages.

2. Spiral Arteries with physiological Changes.

The hypertensive lesions in the spiral arteries which have already undergone physiological changes consist of mural thrombi, intimal cellular proliferation, accumulation of fibrinoid, lipophage infiltration, and finally, perivascular plasma cell and lymphocytic infiltration. In effect, the lesions already described for the basal arterioles are superimposed upon the existing physiological changes in those arteries.



Fig. 21. - Essential Hypertension. Loose-cellular intimal proliferation in an artery in the inner third of the myometrium underlying the placenta. Weigert's elastic stain - x 125

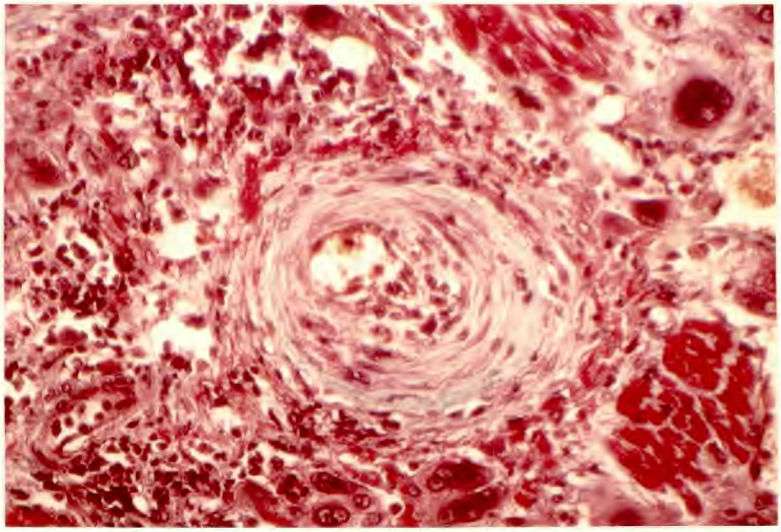


Fig. 22. - Essential Hypertension with Pre-eclampsia. Lamellar "onion-peel" hyperplasia in the proximal part of a spiral artery. Masson's trichrome - x 180.

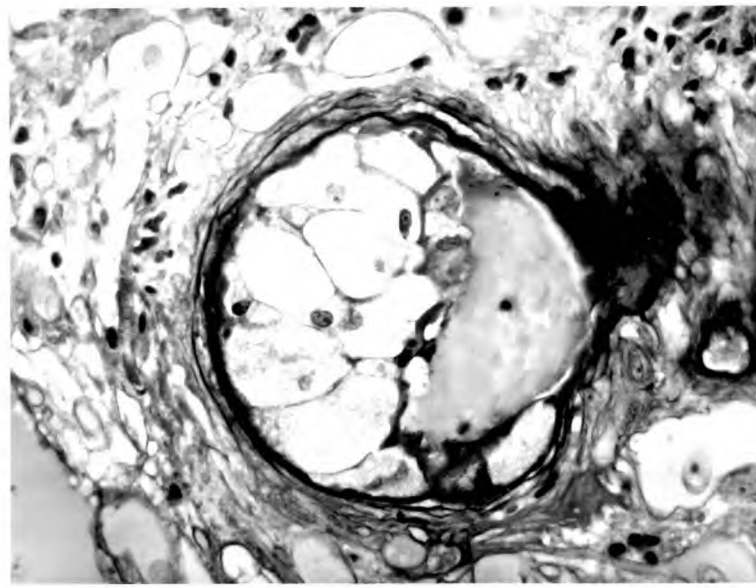


Fig. 23. - Essential Hypertension with pre-eclampsia.
Acute atherosis of a decidual arteriole. P. A. S. stain - x 235

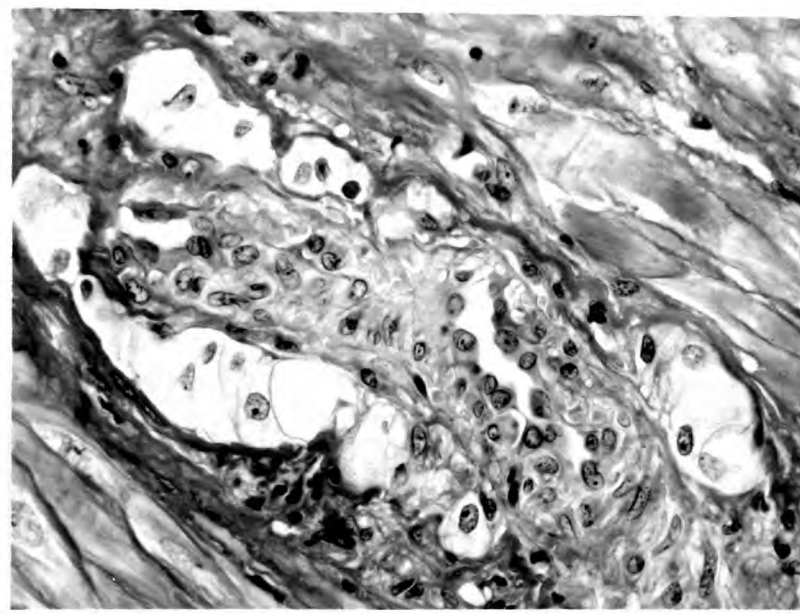


Fig. 24. - Essential hypertension with pre-eclampsia.
Acute atherosis in a myometrial arteriole. H. E. - x 235.

(i) Intimal cellular and fibrotic Hyperplasia.

The co-existence of intimal hyperplasia, perivascular plasma cells and lymphocytic reaction together with physiological changes gives the spiral artery a thick cellular appearance. The outer part of the wall consists of a layer of fibrinoid often undulating in outline with large cells and foci of plasma cells and lymphocytes. The main thickening of the wall is, however, produced by an intimal proliferation with much more sclerosis than is seen in normal pregnancies and which often apparently results in a reduction of the vascular lumen (Fig. 25, 26).

(ii) Acute Atherosis.

The consistent and striking feature of acute atherosis is an extension of the fibrinoid change normally seen but with lipophage infiltration (Fig. 27). The lipophages usually occur in groups and they may be found in any part of the wall. These cells are easily distinguished from the "large cells". The "large cells" occur as isolated cells, have a vesicular nucleus and often cytoplasmic elongations. Lipophages occur in groups, have a small pyknotic nucleus and their mutual compression often gives them a pseudo-epithelioid appearance.

In the early stage the presence of a group of lipophages in the wall may be the main feature of acute atherosis but in later stages the vascular lumen can be completely obstructed by an amorphous fibrinoid deposit and large groups of lipophages.

3. Veins.

Intimal proliferative cushion formation in the veins of the uterine wall has already been described as occuring in normal pregnancy and

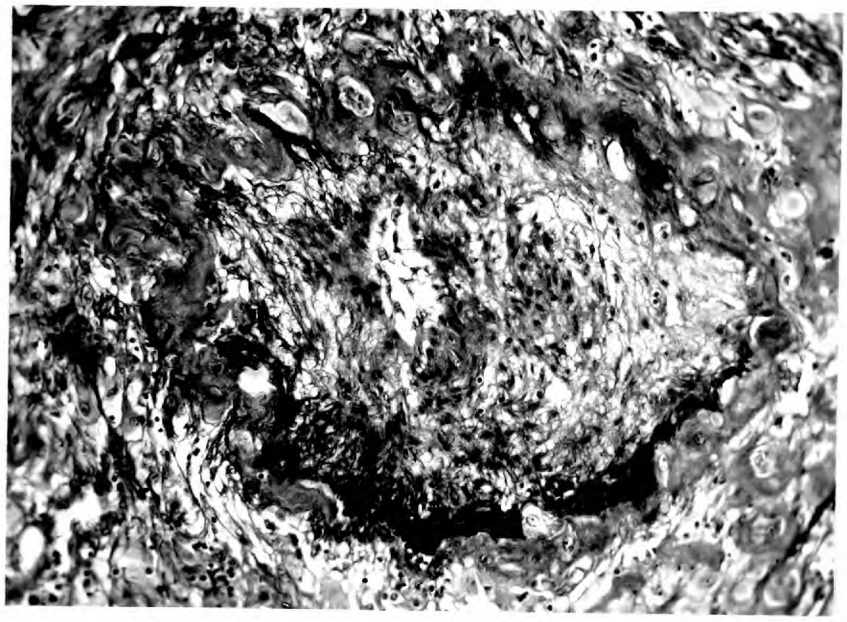


Fig. 25. - Essential hypertension. Hypertensive lesion of a spiral artery with physiological change. Weigert's elastic stain - x 125.

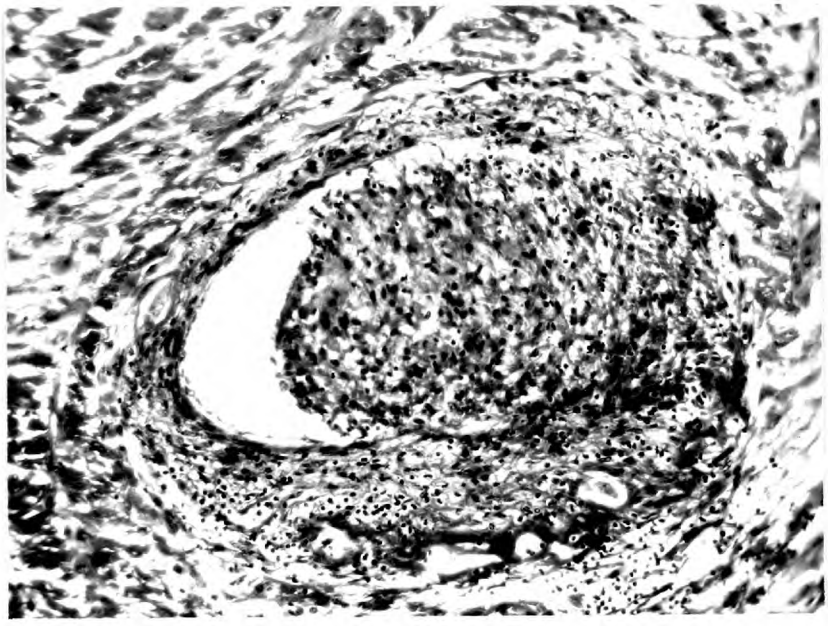


Fig. 26. - Essential Hypertension. Hypertensive lesion of a spiral artery with physiological change. H. E. - x 125.

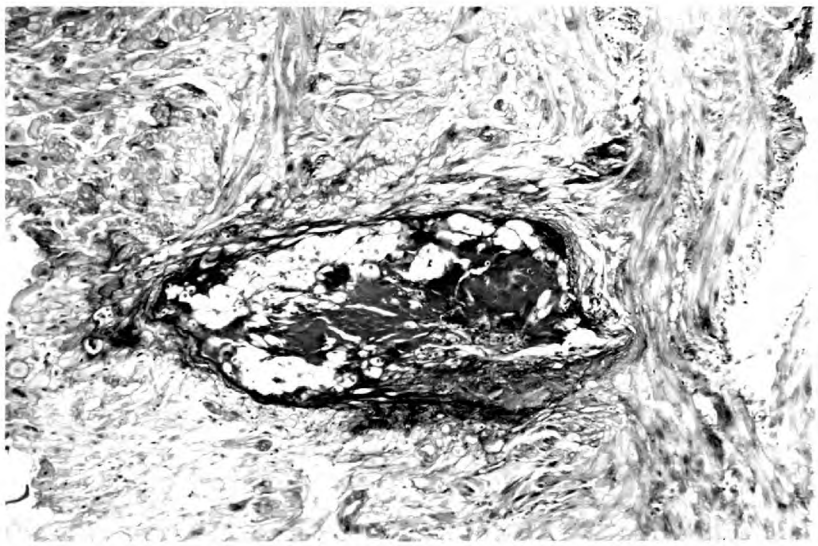


Fig. 27. Essential hypertension with pre-eclampsia. Acute atherosis of a spiral artery in the myometrium underlying the placenta. H. E. - x 85.



Fig. 28. - Hypertensive pregnancy. Intimal proliferation of a vein in the placental bed. Weigert's elastic stain - x 85.

may be increased in pregnancies complicated by essential hypertension (Fig. 28). Lipophage infiltration of the wall of veins has not been observed.

4. Topographic Distribution.

The topographic distribution of hypertensive vascular lesions was studied on the Caesarean hysterectomy specimens in hypertensive complications of pregnancy. Several arteries were followed by step serial sections in the placental and non-placental part of the uterine wall.

(i) In the Placental Area.

The distribution of hypertensive vascular lesions in this part of the uterine wall from without inwards is as follows :

In the outer and middle third of the myometrium the changes in the arteries, even in severe hypertensive complications, are in no way different from those seen in normal pregnancies. In effect only focal intimal fibrosis is occasionally present. The hypertensive vascular lesions already described appear in the inner third of the myometrium and extend from there towards the myometrio-decidual junction, decidual basalis and basal plate of the intervillous space.

(ii) In the non-placental Area.

From Table II it seems quite clear that acute atherosis occurs almost exclusively in the spiral arteries and basal arterioles of the placental bed.

In the non-placental part of the uterine wall acute atherosis was only found in the superficial decidual layers, but was absent in the myometrium and even at the myometrio-decidual junction.

TABLE II

TOPOGRAPHIC DISTRIBUTION OF ACUTE ATHEROSIS IN THE DECIDUA

Case Number	DECIDUA BASALIS		DECIDUA VERA	
	Number of vessels Examined	Affected	Number of vessels Examined	Affected
B63	23	15	18	2
B60	7	3	8	-
B33	8	3	5	-

B. Clinico-pathological Correlation.

1. Type of hypertensive Complication.

The histological appearance of the vascular lesions in the placental bed seems to be related primarily to the type and severity of hypertensive complication. The vessel appearances in association with each of the following hypertensive complications of pregnancy will now be considered.

a. Essential Hypertension.

In essential hypertension vascular lesions of the hyperplastic and fibrotic type occur in spiral arteries and basal arterioles of the placental bed. The degree of hyperplastic change may be difficult to evaluate and only a semiquantitative evaluation can be made by the observation of a large number of spiral arteries.

From Table III it appears that acute atherosis only rarely occurs in essential hypertension. When present it was found only in arteries already showing physiological changes.

b. Pre-eclampsia.

Whilst in pre-eclampsia some of the appearances described for essential hypertension may be seen, the consistent and striking feature is "acute atherosis" in spiral arteries and basal arterioles (Table III). Acute atherosis was never found in normotensive pregnancies.

c. Essential Hypertension with the Addition of Pre-eclampsia.

This condition is undoubtedly associated with the most extensive and severe vascular lesions in the placental bed.

Severe intimal and medial hyperplasia, intimal fibrosis, fibrinoid necrosis and lipophage infiltration are all encountered. There are also frequent and extensive mural thrombi in the dilated loops of the spiral arteries, and complete thrombotic occlusion may be found (Fig. 29).

2. Duration of Pre-eclampsia.

It would be worthwhile to know at what time after the onset of the symptoms of pre-eclampsia (rise in blood pressure, albuminuria) acute atherosis develops in the placental bed.

One hysterectomy specimen was obtained one week after the onset of pre-eclampsia with a rise in blood pressure and albuminuria. Although a large part of the placental bed was cut in step serial sections and 20 spiral arteries were examined, no acute atherosis was found in the arteries and arterioles of the placental bed.

TABLE III

INCIDENCE OF VASCULAR LESIONS IN THE PLACENTAL BED (HYSTERECTOMY SPECIMENS)

		SPIRAL ARTERIES			VEINS
	Case Number	Number of Vessels Examined	Number of Vessels with acute atherosis	Hyperplastic lesions	Phlebo-sclerosis
Normotensive	B57	6	0	+	+
	B63	13	0	-/+	+
	B68	16	0	-/+	+
	B64	23	0	-/+	+
	B72	20	0	-/+	+
	B43	10	0	-/+	+
	B69	15	0	-/+	+
Essential Hypertension					
Mild	B26	9	1	-/+	+
Severe	B70	15	1	+++	++
Pre-eclampsia (for 1 weeks) with Mild Essential Hypertension	B67	20	0	+/++	+++
Severe Pre-eclampsia	B60	7	3	+	+
Severe Essental Hypertension with Pre-eclampsia	B66	23	15	++	+
Nephrotic Syndrome (starting in early pregnancy)	B33	8	3	+	-

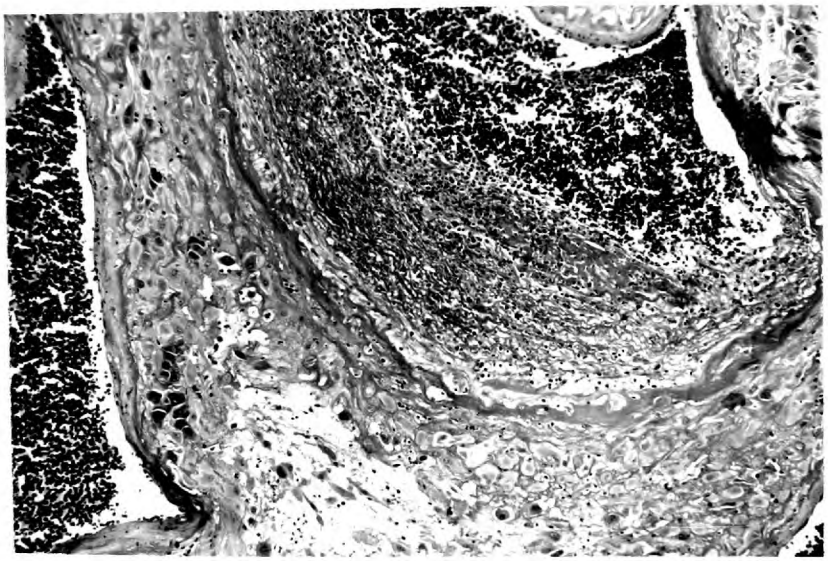


Fig. 29. - Essential hypertension with pre-eclampsia. Extensive mural thrombosis and some lipophage infiltration in the decidual part of a spiral artery. H. E. - x 85.

On the other hand acute atherosis has been found in placental bed biopsies from patients in whom the symptoms of pre-eclampsia were present for a duration of about 2 weeks.

III. LIPID STUDY.

The material for this study consisted of placental bed biopsies from 210 cases. In 121 cases the biopsy showed histological evidence of origin from the placental bed and only those cases are included in the present study. The clinical criteria for classifying the hypertensive consitions in this series are those proposed by DIXON and ROBERTSON (See Appendix IV)

A. Arteries and Arterioles.

It was essential in this study to distinguish between the spiral arteries with physiological changes and the vessels with a normal arterial or arteriolar structure.

1. Spiral Arteries.

As the average distribution of spiral arteries in a histological section is about one in every two square centimeter of the placental bed, it is clear that placental bed biopsies do not always contain segments of spiral arteries. Spiral arteries, which manifested physiological changes, were present in 31 out of 57 biopsies from the normotensive group and in 19 out of 64 biopsies from the hypertensive group.

a) In normotensive cases (31 cases) lipid could be demonstrated in some segments of the vessel, especially in association with fibrinoid deposition and in some of the "large cells" of the wall.

b) The predominant features of the spiral arteries with physiological changes in hypertensive cases (19 cases) are focal accumulation of lipophages in or around the wall and lipid infiltration of the proliferative intimal cushions. This was found in 16 out of the 19 cases in this group, which includes nine cases of borderline and mild essential hypertension (Fig. 30), nine cases of terminal hypertension and one case of pre-eclampsia

2. Basal Arterioles.

Table IV gives the incidence of lipid infiltration of the wall of these vessels in normotensive and hypertensive patients.

a) In the group of normotensive cases, two biopsies showed some lipid infiltration of the arterioles: one was from a patient in whom the blood pressure recorded as 95/65 mm. Hg in early pregnancy had gone up at term to 120/80 mm. Hg, and the other from a patient who had no ante natal care. Lipophages were not seen in any case.

b) In the group of essential hypertension three cases had some lipid infiltration of the arterioles. All three cases had albuminuria as well. In one of these cases there was an episode of unexplained albuminuria at 16 weeks and in the other two the albuminuria occurred at the time of antepartum haemorrhage. It was not, therefore, thought permissible to accept them as pre-eclamptic. Lipophages were not seen in any case.

c) In the group of episodic hypertension there was lipid infiltration of arterioles in only one of the five cases.

d) In the group of terminal hypertension lipid infiltration of the arterioles was present in 5 out of 22 cases. In one case lipophages were present in the wall as well (Fig. 32).

e) In pre-eclampsia the arterioles showed lipid and lipophage infiltration in 4 out of 5 cases (Fig. 33).

f) All 4 cases of essential hypertension with superimposed pre-eclampsia had lipid and lipophage infiltration of the wall of the arterioles (Fig. 34).

B. The basal decidual Stroma and adjacent Myometrium.

1. Normal Pregnancy.

Specimens from 14 normal pregnancies were studied. All were normotensive and were all delivered by Caesarean section between 38 weeks and term because of cephalo-pelvic disproportion.

In all these normal pregnancies no lipid was found in the basal decidual stroma and adjacent myometrium of the placental bed. Some lipid was sometimes present in the most superficial layer of the decidua. Some giant cells of the placental bed occasionally contained very small amounts of lipid. Glandular epithelium often contained lipid and the glandular space was sometimes rich in both lipid and lipophages (Fig. 36, 37).

It should, however, be emphasised that the decidual stroma and adjacent myometrium in the non-placental area of the uterine wall was almost always found to contain lipid both before and at term. It is, therefore, of paramount importance to confirm histologically the placental bed origin of the biopsy.

2. Abnormal Pregnancy.

Areas of diffuse lipid infiltration (D. L. I.) at the myometrio-decidual junction of the placental bed have been found in 32 out of the 121 cases. All these showed some obstetrical abnormality which was clinically associated with placental insufficiency.

TABLE IV

LIPID INFILTRATION OF BASAL ARTERIOLES OF THE PLACENTAL BED

	Number of cases	Positive
NORMOTENSIVE	57	2*
ESSENTIAL HYPERTENSION		
Borderline	9	1+
Mild	19	2+
EPISODIC HYPERTENSION	5	1
TERMINAL HYPERTENSION	22	5
PRE-ECLAMPSIA	5	4
ESSENTIAL HYPERTENSION with PRE-ECLAMPSIA	4	4

*) see
+) text

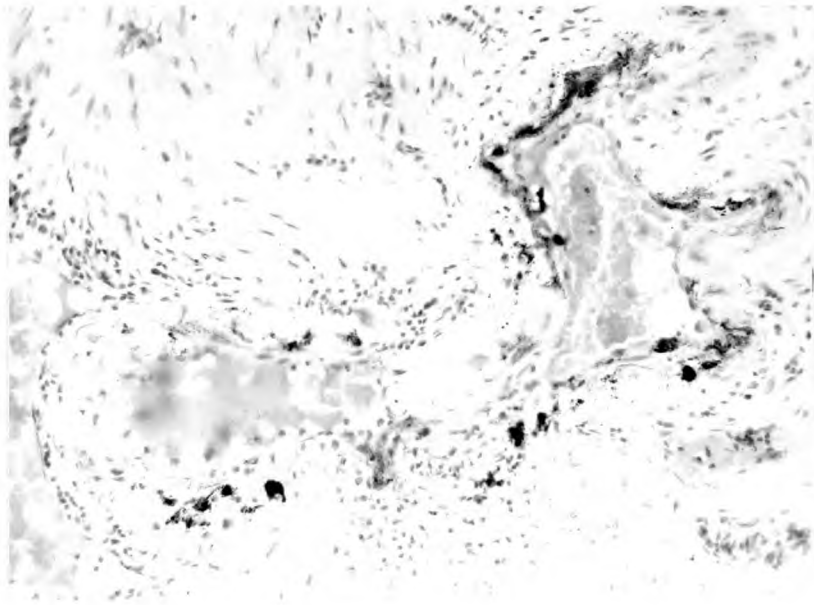


Fig. 30. - Mild essential hypertension. Lipid and some lipophages in the wall of a spiral artery. Oil Red O stain - x 85.

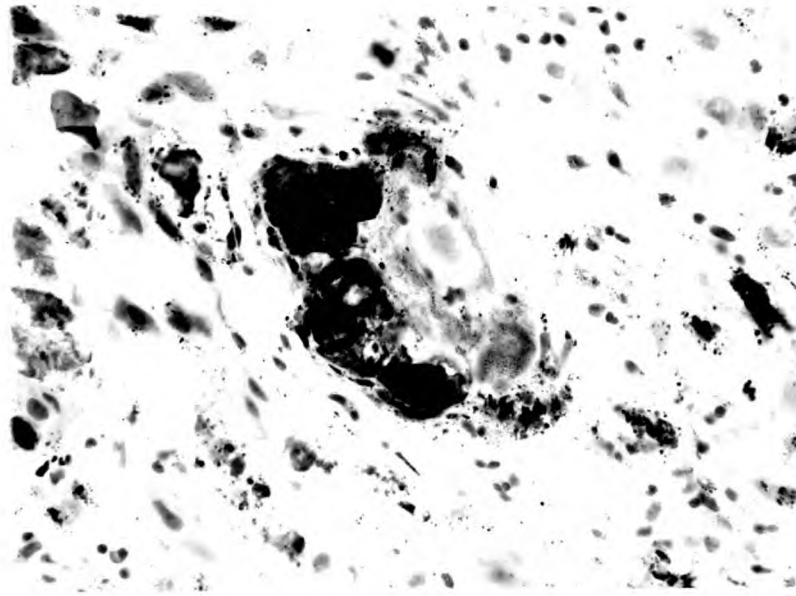


Fig. 32. - Terminal hypertension. Acute atherosis of a decidual arteriole. Oil Red O stain - x 220.

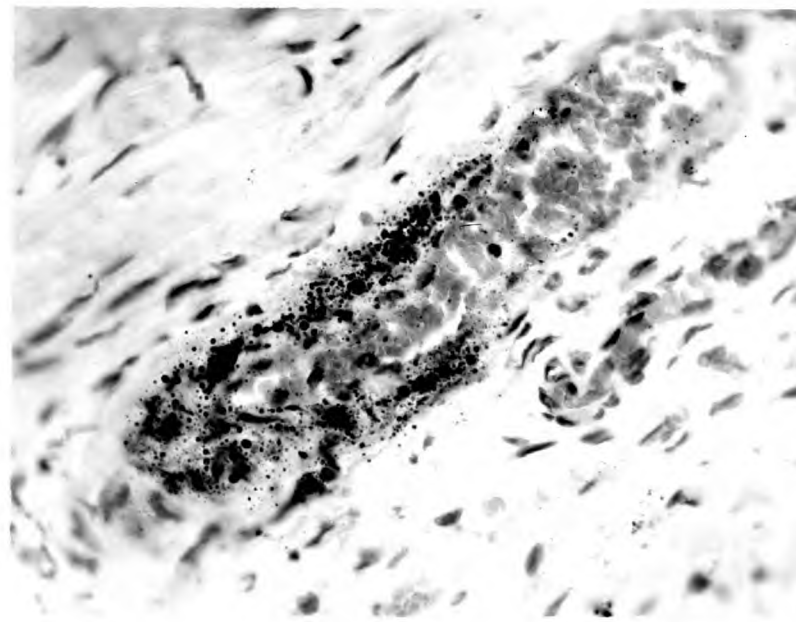


Fig. 33. - Pre-eclampsia. Lipid infiltration of the wall of a basal arteriole in the myometrium. Oil Red O stain - x 220.

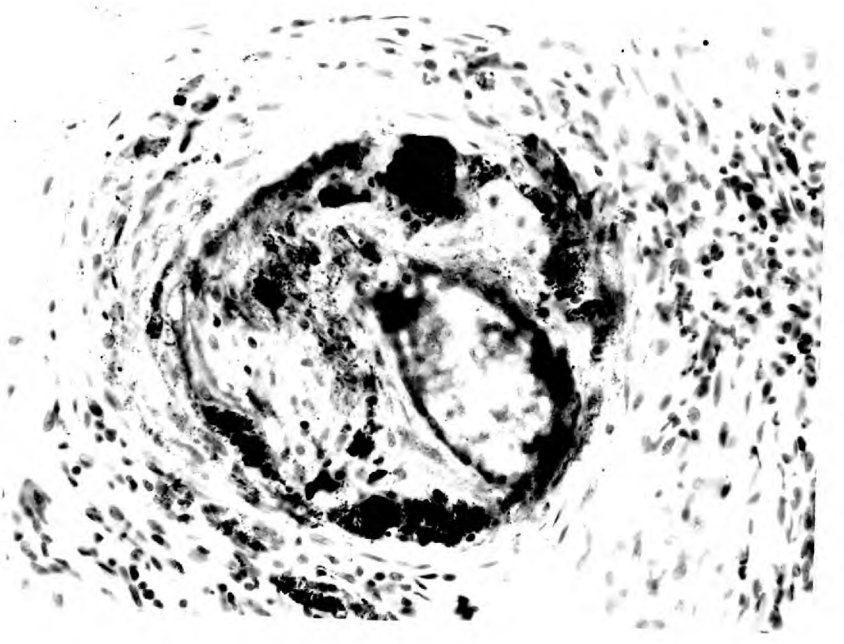


Fig. 34. - Essential hypertension with pre-eclampsia. Extensive lipid and lipophage infiltration of the arterial wall. Oil Red O stain - x 220.

In this condition of D. L. I. variable but notable amounts of lipid are found scattered patchily throughout the stroma of the whole thickness of decidua and extending into the superficial layer of myometrium. Lipid is seen both intra- and extra-cellular.

Table V gives the incidence of diffuse lipid infiltration (D. L. I.) of the placental bed in some complications of pregnancy.

TABLE V.

DIFFUSE LIPID INFILTRATION (D. L. I.) OF THE PLACENTAL BED.

	TOTAL.	POSITIVE.
CONTROLS	14	0
PROLONGED PREGNANCY	28	16
PRE-ECLAMPSIA) at or	8	5
TERMINAL HYPERTENSION) before	18	4
ESSENTIAL HYPERTENSION) term	25	3
SMALL FOR DATES BABIES	13	6
MATERNAL HEART DISEASE	3	3

The presence or absence of D. L. I. was not influenced by the association of a prolonged labour, a prolonged induction delivery interval nor by placenta praevia.

In five of the positive cases two of the above mentioned complications were present.

a) Prolonged Pregnancy.

In 23 cases the duration of pregnancy as calculated by Nägele's rule was 41 weeks or more. Areas of D. L. I. were present in 16 cases (Fig. 38, 39). In 5 cases there was clinical doubt about the duration of pregnancy as calculated by dates, and in three of these there was absence of D. L. I. of the placental bed.

Hypertension of one form or another was present in 4 of the negative cases but D. L. I. was found in the only prolonged pregnancy complicated by true pre-eclampsia.

In prolonged pregnancy no significant difference in the incidence of D. L. I. of the placental bed could be demonstrated between primigravidae (5 positive out of 9) and multigravidae (11 positive out of 19).

In specimens from postmature pregnancies virtually all the giant cells contain lipid droplets in their cytoplasm and, moreover, these cells are apparently reduced in numbers.

b) Maternal hypertensive Complications at or before Term.

In pre-eclamptic toxaemia 5 out of 8 cases were associated with D. L. I. of the placental bed.

In essential hypertension 3 out of 25 cases were positive and in terminal hypertension 4 out of 13.

In specimens examined from hypertensive patients there was an impression of an increase in number of mononuclear placental bed giant cells (Fig. 40). Many of the giant cells contained large amounts of lipid (Fig. 41).

c) Small for Dates Babies.

Table VI gives the clinical data and the histological lipid findings in the cases associated with small for dates babies. The criteria adopted for small for dates babies are given in Appendix V.

TABLE VI.

SMALL FOR DATES BABIES.

Birth Weight (Grams)	Duration of Pregnancy. (weeks)	Complications of Pregnancy.	D. L. I. of the Placental Bed.
1160	$37^{3}/7$	Fallot's tetralogy.	+
2360	$38^{2}/7$		-
2530	by dates: 46 clinically: 38		-
2380	$39^{2}/7$		-
2240	$41^{1}/7$		-
2100	$37^{1}/7$		-
2000	$37^{3}/7$	Pre-eclampsia	+
2100	appr. 38	Essential hypertention + pre-eclampsia	-
2000	appr. 38	Essential hypertension + pre-eclampsia	+
2040	$39^{3}/7$	Mild essential hypertension	+
1460	$33^{3}/7$	Terminal hypertension	+
2100	by dates: 46 clinically:40	Borderline essential hypertension	+
1880	$36^{1}/7$	Mild essential hypertension	-

The series is small, but it is probably significant that in the normotensive group only 1 out of 6 and in the hypertensive group 5 out of 7 cases had areas of D. L. I. of the placental bed.

d. Maternal Heart Disease.

The present series includes three cases of maternal heart disease : congenital familial cardiomyopathy, Fallot's tetralogy, and mitral incompetence. All three patients were normotensive and were delivered between 37 and 39 weeks by elective Caesarean section for cephalopelvic disproportion and clinical placental insufficiency. The birth weight of the babies in the three cases was respectively 2840, 1160 and 2900 g.

In all three cases there was extensive D. L. I. of both decidua and myometrium of the placental bed (Fig. 42, 43 a and b), but the common factor in these cases is obscure.

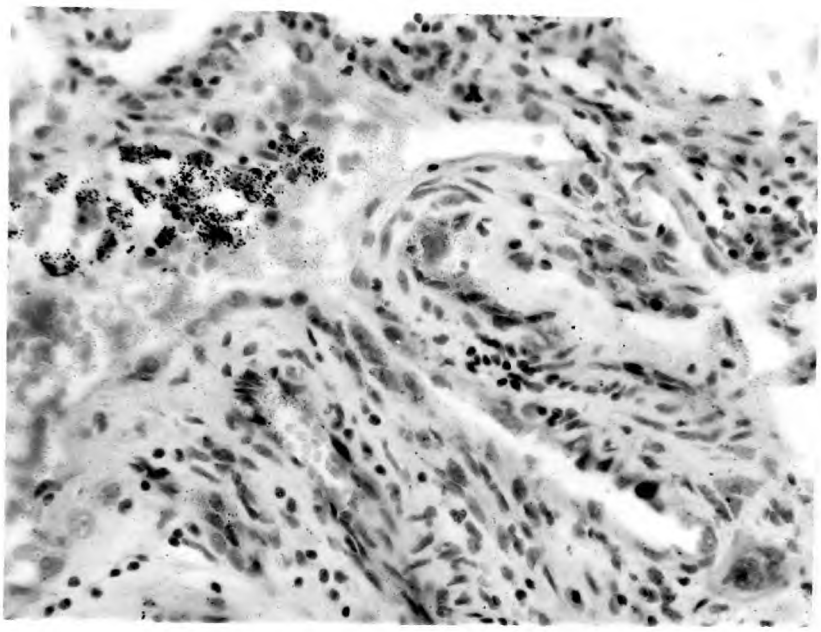


Fig. 36. - Normal pregnancy. Absence of lipid in stroma and giant cells of the placental bed. Lipophages are present in decidual gland. Oil Red O stain - x 220.

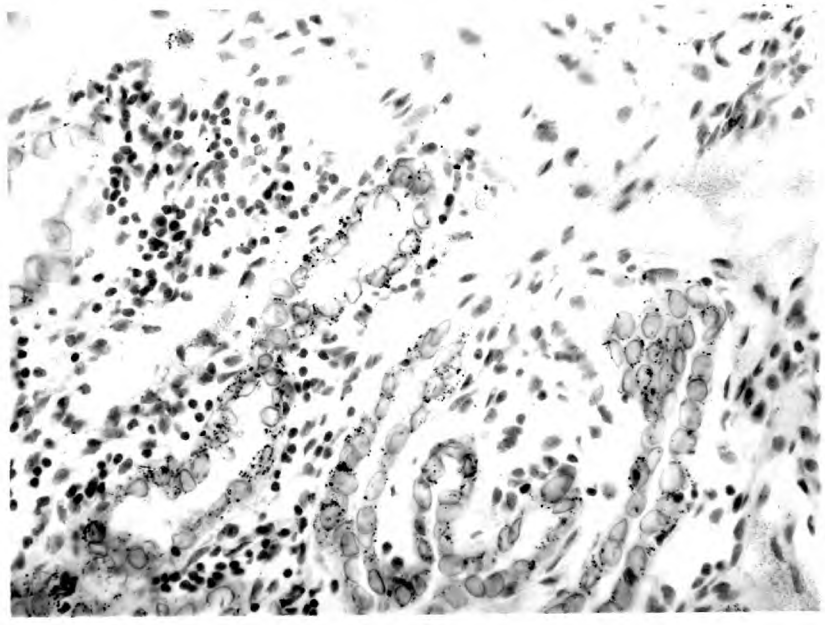


Fig. 37. - Normal pregnancy. Absence of lipid in placental bed tissue except in glandular epithelium. Oil Red O stain - x 220.



Fig. 38 - Prolonged pregnancy. Diffuse lipid infiltration of the decidua in the placental bed. Oil Red O - x 220

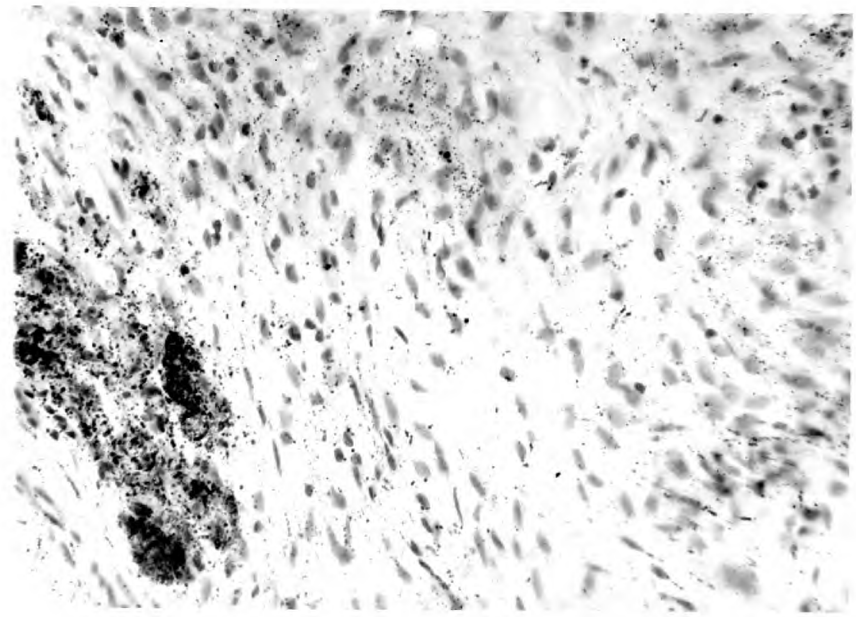


Fig. 39. - Prolonged pregnancy. Diffuse lipid infiltration of the myometrio-decidual junction in the placental bed. Oil Red O - x 125.

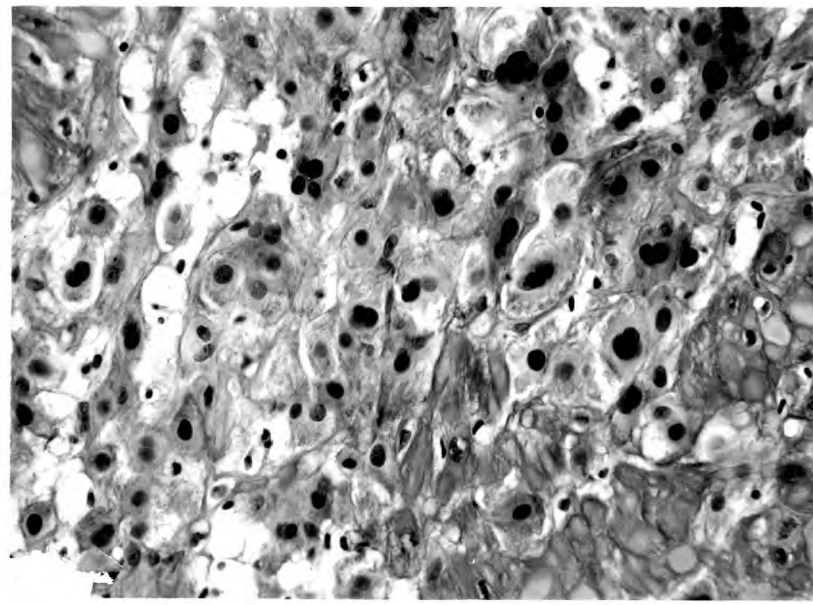


Fig. 40. - Pre-eclampsia. Group of mono- end multi-nucleated giant cells in myometrium. H. E. - x 225.

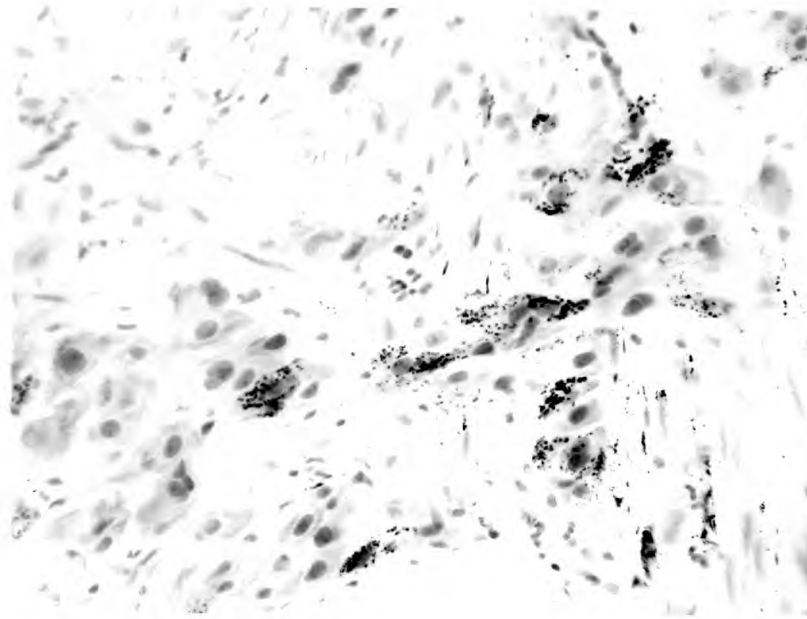


Fig. 41. - Terminal Hypertension. Group of giant cells in myometrium : several of the giant cells contain lipid. Oil Red O stain - x 225.

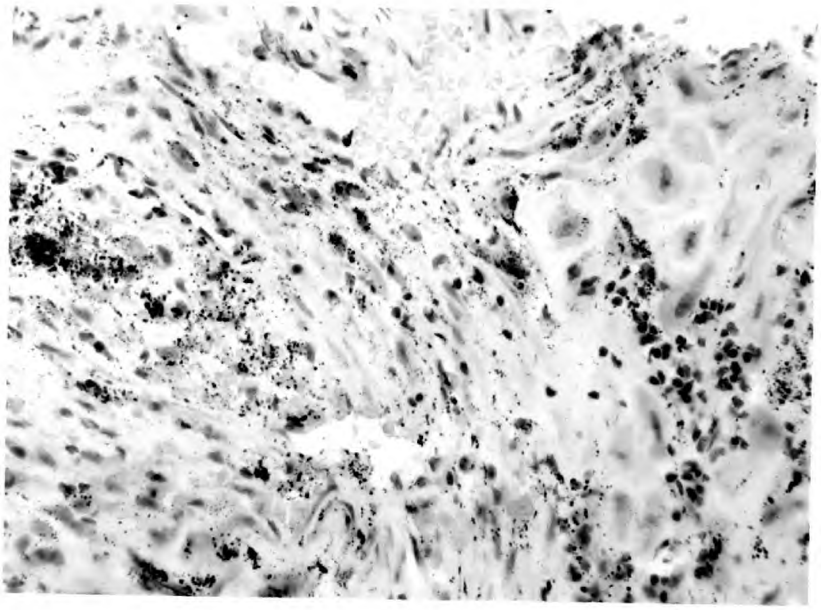


Fig. 43 a. - Fallot's tetralogy. D. L. I. at the myometrio-decidual junction. Oil Red O stain - x 220.

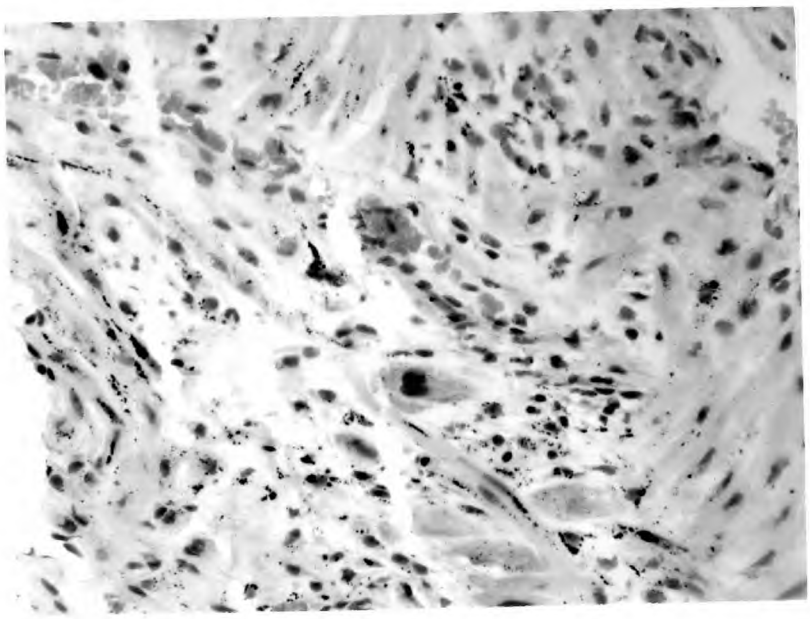


Fig. 43 b. - Fallot's tetralogy. D. L. I. of the myometrium. Note the presence of a giant cell. Oil Red O stain - x 220.

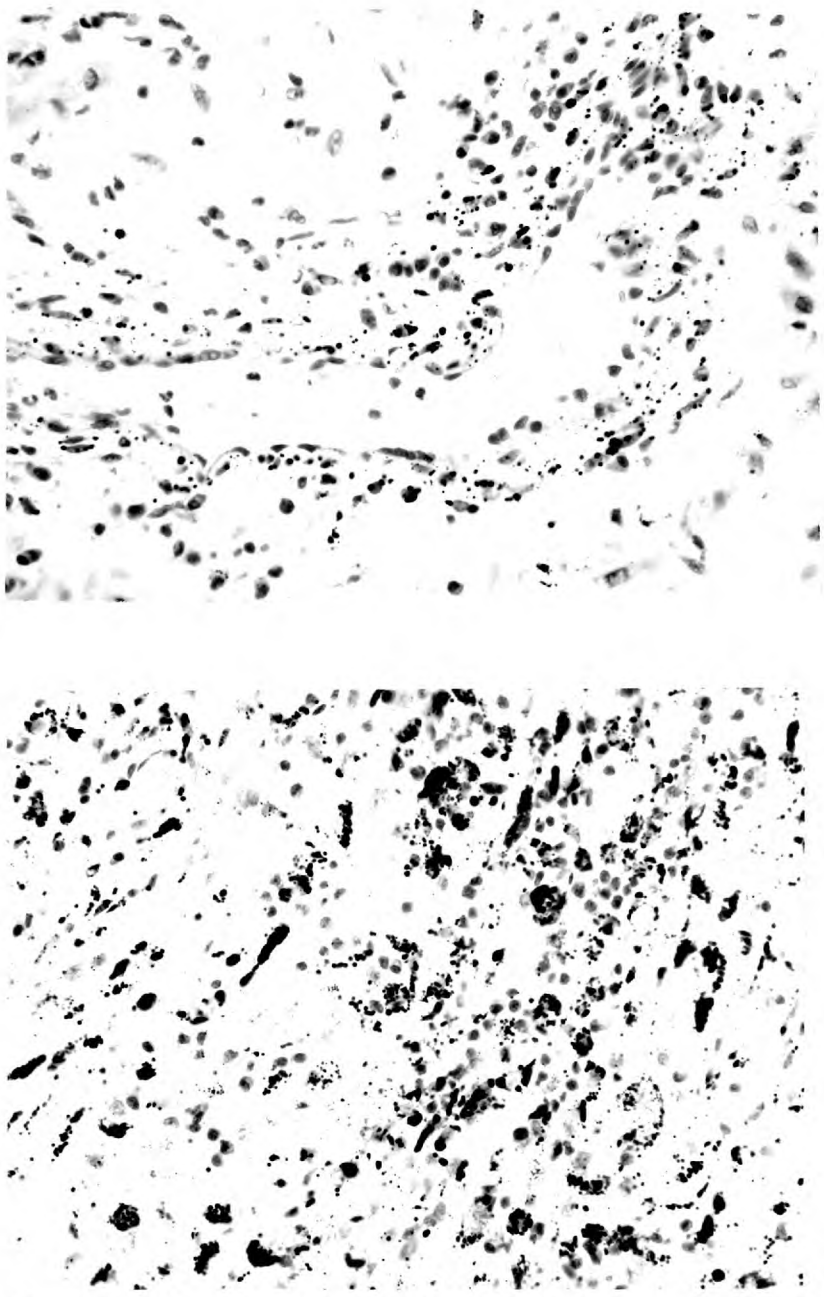


Fig. 42. - Congenital familial cardiomyopathy. Meconium stained amniotic fluid. Two areas of D. L. I. in the placental bed. Oil Red O stain - x 225.

DISCUSSION.

A. Anatomical Data on the spiral Arteries.

During the course of the present study it has been necessary to attempt to solve three specific anatomical problems :

1) First : what is the number of spiral arteries supplying the intervillous space at term?

2) Second : what is the precise location of the arterial openings in relation to the basal plate and the septa?

3) Third : do these arteries open into the intervillous space by single or multiple orifices?

Although any reconstruction technique has disadvantages the technique based on histological sections has definite advantages over other methods using injection or dissection.

For proper fixation and embedding the uterus with the placenta 'in situ' had to be cut into several blocks, each approximately 1 cm. thick. The loss of a certain amount of tissue at the cutting surface of the blocks is unavoidable, as during the procedures of fixation, embedding, cutting and mounting each block or section undergoes some degree of distortion.

On the other hand, the histological technique has the great advantage of permitting direct microscopical identification of every structure. This proved to be essential to identify villi anchoring into the placental bed from placental septa. Microscopical examination is also essential for the exact localization of the arterial and venous channels

The techniques by which specimens of human uteri with the placenta in situ are collected require comment. Such specimens from term pregnancies are only available at the time of either necroscopy or Caesarean hysterectomy. In specimens obtained by Caesarean

hysterectomy prompt fixation is possible and it thus offers definite histological advantages. On the other hand, allowance has to be made for the degree of retraction which inevitably occurs on opening the amniotic cavity in life. The apparent irregular lining of the basal plate is probably a result of retraction, but septa of any size are structures which cannot be created by partial retraction of an in situ placenta without entirely disrupting the decidua.

From the examination of the step serial sections of two fifths of an in situ placenta it was found that 48 arteries entered the intervillous space. This leads to an average of one spiral artery for every two square centimeters of basal plate. Virtually all opened into the intervillous space by a single orifice. The distribution of the openings appears to be quite random, but occasionally two or three arteries seem to be grouped together. SPANNER (1936) and BOYD (1956) report a considerably larger number of arterial openings. The discrepancy in the total number of arteries reported may in part be due to the fact that in the immature placenta one artery possibly communicates with the intervillous space through more than one orifice and in part to the fact that partial counts may induce error in calculations.

The low figures given by the present investigation is, however, still much higher than the total numbers of arteries seen to be open at any one time in the human by the use of cineradiographic techniques.

It would, however, be unwise to place too much reliance on the number of spiral arteries as revealed by these techniques as it is known in both the Rhesus monkey and the human that not all arteries appear to be functionally open at any given moment and that two consecutive cineradiographic sessions may show a completely different

distribution of arterial spurts (MARTIN et al., 1964).

In spite of many reports there is as yet no agreement as to the exact situation of the arterial openings in the human. In the present anatomical study serial sections showed that most arteries opened into the intervillous space somewhere above the general level of the decidual plate, whether in the lower part of a septum or in a protrusion of basal plate. One does, however, find that, occasionally, arteries of smaller size open at the level of the decidual plate with no relationship to either a septum or basal plate protrusion. It is, however, significant that every sizable septum has at least one spiral artery opening at its base. To some extent, therefore, the present findings confirm those of BUMM (1890, 1893), excepting that few arteries opened as far up the septa as BUMM suggested and that no evidence was found to suggest that the arterial openings are directed inwards towards the side of a foetal cotyledon. It was also not possible to confirm BUMM's finding of a multitude of openings for each artery.

The construction of the maternal side of the placenta also gave the opportunity to confirm the fact that the septa vary a good deal in height and length, that they are frequently perforated and quite haphazardly distributed and suggests that these structures must allow a free intercommunication between every part of the intervillous space. A septum appeared in many instances to separate a group of arterial openings from a group of venous drainage openings. This leads again to the speculation that the septa play a more important part in the direction of the blood flow through the intervillous space than had previously been attributed to them.

The existence of coinciding functional and anatomical compartments of both foetal and maternal components of the placenta appears to have been accepted almost without discussion by the majority of workers who have accepted the concept of random opening of arteries and veins throughout the entire basal plate. The finding of great irregularity of the distribution and size of the septa seems to make it legitimate to doubt whether each foetal cotyledon, i.e. each major stem villus, lies within a surrounding ring or maternal septa complete with arterial supply and venous drainage and separated from its neighbours by the surrounding ring of septa. It would seem that the large number of diagrams in the literature showing a neat anatomical compartmentation of the functional units do not represent the true morphology of the placenta.

B. Methods of histological Investigation.

The present morphological study is based on two methods of investigating the placental bed : the technique of the placental bed biopsies taken by the vaginal route or at the time of Caesarean section, and the examination of uteri removed by Caesarean hysterectomy with the placenta still attached to the uterine wall in some of them.

The validity of vascular studies based exclusively on biopsies from the placental bed, foetal membranes or basal plate of the delivered placenta depends on several factors.

Before accepting any results from a study based on placental bed biopsies it is important to be sure that the biopsies have been taken from the placental bed. In 1961 DIXON and ROBERTSON reported an improvement of their technique by first incising the

middle of the placenta as it begins to separate at Caesarean section and taking the first biopsy through the incision. After delivery of the placenta the initial biopsy site is located and further biopsies are taken from the surrounding area.

It has been pointed out in the present study that there are three histological criteria applicable for recognizing the placental bed origin of a biopsy: the presence of giant cells in the decidua or myometrium, the physiological changes in the arteries and, lastly, the presence of villi attached to the decidua. When these criteria, especially the presence of giant cells, are used, it is surprising how often a biopsy taken after delivery of the placenta proves to be from the non-placental area or, possibly from the very edge of the placental bed and therefore not representative for the placental bed.

A second essential qualification of every study of the pathology of small arteries is that pathological changes in these vessel often are focal or even segmental and that therefore an extensive examination of the vessels is necessary for an accurate evaluation.

If both precautions - histological verification of the exact origin of the biopsy and step serial sectioning of the biopsy - are not taken (DUPARC, 1960, PINKERTON,1963 and JONAS and REWELL, 1963) it is clear that the presence of vascular lesions will be underestimated or even overlooked.

Even with these precautions biopsies from the placental bed, foetal membranes and basal plate of the placenta have often proved to be to some extent inadequate for a systematic study of the spiral arteries and have often caused errors in evaluation and interpretation of vessel changes.

Studies based on placental bed biopsies by DIXON and ROBERTSON (1958, 1961), PINKERTON (1963), JONAS and REWELL (1963), on uterine curettage by DUPARC (1960), and on rolls of foetal membranes by ZEEK and ASSALI (1950) could not reveal the true arterial nature of the large, sinusoidal vessels with a fibrinoid wall. Studies by McKELVEY (1939), BURSTEIN and collaborators (1957), SHANKLIN (1958) and MARAIS (1962 b, c, d,) are partially invalidated by the fact that in the basal plate the structure of the spiral artery is confusing and that some of the structures described by them as arterial are possibly venous or even artifacts resulting from the destructive effect of separation and expulsion of the placenta. In the present study this difficulty of recognition of an artery from a vein in the decidua and superficial myometrium has been overcome by the knowledge gained from the study of the step serial sections of intact uteri where the vessels in this region could be traced deeper into the myometrium so revealing their true structure.

C. The physiological Changes of the spiral Arteries.

HAMILTON and BOYD (1960) have described in detail the normal changes which occur in the spiral arteries of the decidua basalis during early pregnancy.

In the present study the serial sectioning of uteri removed by Caesarean hysterectomy has made possible a systematic approach to the histological study of the spiral arteries during the third trimester of pregnancy.

The vessel changes, described by HAMILTON and BOYD, apparently extend deeper towards the myometrio-decidual

junction and into the myometrium after the 14th week of pregnancy. By the end of pregnancy there is a virtual absence of smooth muscle and elastica in the majority of the spiral arteries at the myometrio-decidual junction, and the wall mainly consists of fibrinoid and fibrous tissue of variable thickness. The outer fibrinoid layer probably represents the degenerated elastic and muscular coats of the artery. The large cells are likely to be of trophoblastic origin and to be related to the plugs of cytotrophoblast which are described as invading the arterial lumen during the first half of pregnancy. At 28 weeks of pregnancy some clusters of large cells resembling those of the cytotrophoblastic plugs can be found lying in the arterial lumen and apparently invading the wall of the artery. These clusters are no longer seen at term, but some cells morphologically resembling the cytotrophoblast apparently replace the endothelium. The development of the intimal fibrous layer in the spiral artery with physiological changes seems to be the result of the organisation of small mural thrombi in the dilated vessel.

These vessel changes must be regarded as a physiological response of the spiral arteries to the pregnancy. In order to avoid any possible confusion with the established terminology of vascular pathology, it seemed preferable to refer to this vessel change as a physiological one.

A direct role of the invading trophoblast in the production of the physiological vessel changes has not yet been fully proved, but is very likely in view of the findings of HAMILTON and BOYD (1960) in early pregnancy and the present findings in late pregnancy.

It is possible that multiple small thrombotic phenomena and subsequent organization in the arteries lead to a progressive narrowing of these vessels as suggested by FRIEDLÄNDER (1870) and MARAIS (1962c). Although in some of these vessels an apparent stenosis occurs as a result of excessive thickening of the wall by fibrinoid or fibrous tissue, the great majority of the spiral arteries at the end of pregnancy have a widely dilated vascular lumen. The wall of these vessels often appears to be partially collapsed as a result of removal and fixation of the tissue, but their festooned appearance strongly suggests that 'in vivo' these vessels are widely dilated. It is possible that a relative stenosis of these vessels can develop after term, but this has not yet been proved.

D. Hypertensive vascular Lesions.

The present findings confirm and extend the observations made by previous authors (DIXON and ROBERTSON, 1958, 1961, DUPARC, 1960, MARAIS, 1963) that in pregnancies complicated by pre-eclamptic toxaemia the reduction in the choriodecidual blood flow (BROWNE and VEALL 1953) is associated with organic vascular lesions in the arteries of the placental bed. New data on the hypertensive vascular lesions in the uterus have resulted from the study of hysterectomy specimens and from the lipid studies of the placental bed biopsies.

From the study of hysterectomy specimens by serial histological sections it is possible to make a clear distinction between the hypertensive vascular lesions and the physiological changes in the spiral vessels in late pregnancy (Table VII).

TABLE VII

VASCULAR CHANGES PRESENT IN THE PLACENTAL BED AT THE END OF PREGNANCY.

	PHYSIOLOGICAL CHANGE	HYPERTENSIVE VASCULAR LESIONS.
Vessels affected :	Spiral arteries communicating with the intervillous space.	Spiral arteries and basal arterioles.
Histological features :	Virtual absence of elastica and smooth muscle; Presence of fibrinoid layer with large cells and intimal fibrosis; Endothelial changes and small mural thrombi; Sinusoidal lumen.	Hyperplastic lesions; Acute atherosis; Extensive intravascular thrombosis; Stenosis and occlusion of arterial lumen.
Clinical implications :	Present in every pregnancy.	Pregnancies with hypertensive complications.
Aetiology related to:	Invading trophoblast.	Maternal hypertensive complication

In the superficial layers of the decidua the hypertensive lesions are indeed always mixed with physiological changes in the vessels making interpretation extremely difficult and hazardous. It is, therefore, not surprising that some authors who have based their observations exclusively on the study of the basal plate of the placenta, have attributed to the physiological changes a pathological significance (SCHWARTZ and McNALLEY, 1923, McKELVEY, 1939, MARAIS, 1962, 1963).

MARAIS (1962) who considered that the vascular changes occurring in the spiral artery after 28 weeks are caused by their unusual structure (acute spiralling, successive lengths of narrow and wide lumen, shelves projecting into the lumen) thought that hypertensive vascular lesions in these arteries are an acceleration of the physiological changes. This view is not entirely consistent with the present findings. Our view is that the physiological changes are most likely to be related to the presence of trophoblast and to result primarily in an enormous dilatation of the spiral artery. These changes are a physiological response of the spiral arteries to the pregnancy.

Hypertensive vascular lesions are probably the direct result of the chronic or acute hypertensive condition.

Hyperplastic vascular lesions and acute atherosis occur in both spiral arteries and basal arterioles and, unlike the physiological changes, result in vascular stenosis and occlusion. One can certainly agree with the observations of MARAIS that in normal pregnancies small mural thrombi occur in the spiral arteries with physiological changes.

Hypertensive vascular lesions are easier to observe in the placental bed biopsies than in the basal plate of the delivered placenta because the basal arterioles and the proximal part of some spiral arteries are unaffected by physiological changes. It was mainly on these muscular, basal arterioles that DIXON and ROBERTSON (1958, 1961) based their observations on degenerative and occlusive vascular lesions in hypertension and noted that no lesions comparable to those in hypertensive cases occurred in normal pregnancy.

With the use of large sections of hysterectomy specimens it has been possible to demonstrate that in the uterus hypertensive vascular lesions are found almost exclusively in the placental bed. Severe arteriolar lesions in the non-placental area occur to some extent in the superficial layer of the decidua, but have only very rarely been observed at the myometrio-decidual junction in this area. DUPARC (1960), PINKERTON (1963) and JONAS and REWELL (1963) did not take the precaution of verifying histologically the origin of their material from the placental bed which is probably one of the main reasons why they did not observe arterio- and arteriolonecrotic lesions and have underestimated the incidence of such lesions.

A third observation from the hysterectomy specimens is that the most severe hypertensive occlusive lesions are often sited at the myometrio-decidual junction and that the terminal part of the spiral artery may show only mural thromboses.

The significance of the topographic distribution of hypertensive vascular lesions in the uterine wall particularly their preferential site in the placental area is not clear.

A detailed study of the origin of foam cells in acute atherosis has been beyond the scope of the present investigations. MARAIS (1962 d) regards them as intimal cells. This has not been confirmed by the lipid study of the acute atherosis lesions in the arterioles of the placental bed. MARAIS apparently confuses the degenerate "large cells" in the wall of arteries showing physiological changes with the lipophages of acute atherosis. The physiological "large cells" occur singly, have a vesicular nucleus with aggregates of chromatin and the cytoplasm often has an elongated shape. Lipophages in acute atherosis almost always occur in groups, have a small pyknotic nucleus and their mutual compression often gives them a pseudo-epithelioid appearance.

E. Clinico-pathological Correlation.

It has been possible to correlate very exactly the histological findings in both series of the placental bed biopsies and hysterectomy specimens with the clinical histories of the patients from whom they were obtained.

The present study confirms that hyperplastic and necrotic lesions are characteristic of pregnancies complicated by hypertension.

All gradations of these lesions, however, have been seen and obviously there are some cases which are on the borderline between normality and disease. With the use of lipid stains it was possible to demonstrate definite vascular lesions much earlier in their evolution than had been possible with either haematoxylin and eosin or Masson trichrome stains.

The extent and nature of the vascular lesions found depends to some extent on the duration, clinical severity and type of hypertensive complication suffered by the pregnant women.

Although in hypertensive pregnancies a close relationship exists between the number of diseased arteries in the placental bed and the clinical severity of the hypertensive complication, it should be noted that occasionally in clinically mild conditions the vascular lesions were more severe than one would have expected, e.g. acute atherosis in the presence of terminal hypertension. On the other hand, even severe hypertensive complications do not necessarily affect every artery in the placental bed. It is obvious that a biopsy from the placental bed is not always representative of the entire placental bed.

a. Type of hypertensive Complications (according to the classification of DIXON and ROBERTSON, 1958).

In essential hypertension the predominant vascular lesions are hyperplastic and proliferative lesions, namely arteriosclerosis in the spiral arteries and basal arterioles of the placental bed. Acute atherosis was only occasionally found on the hysterectomy specimens in cases complicated by essential hypertension.

The lipid study of the placental bed biopsies from essential hypertension has confirmed the occasional presence of lipid in the basal arterioles ,but revealed a persistent presence of lipid and even of some lipophages in the spiral arteries which also show physiological changes

It is impossible to define an exact level of maternal blood pressure above which hypertensive vascular lesions always occur in the placental bed, as there is no sharp dividing line between

the normal degree of fibrosis, a feature of the physiological changes at the end of pregnancy, and the earliest hyperplastic lesions in the spiral arteries. Nevertheless, this study of spiral arteries and basal arterioles has shown that definite hypertensive vascular lesions invariably occur with a maternal blood pressure above 140/90 mm. Hg and often, although not invariably, with a blood pressure ranging between 120/80 and 140/90 mm. Hg. They have never been seen in patients whose blood pressure was never recorded above 120/80 mm. Hg.

Pre-eclampsia is characteristically associated with acute atherosis. The lipid study of the placental bed biopsies has confirmed this. The lesions may be extremely severe and extensive even when the amount of albuminuria is small or intermittent.

In the group of terminal hypertension lipid infiltration of the vessel wall was present in about one quarter of the cases, but fully developed acute atherosis was rare. It should, however, be noted that in the majority of cases the highest blood pressure recorded was 140/90 mm. Hg. It seems, therefore, that the effect of terminal hypertension on the placental bed vessels is similar to, but milder than pre-eclampsia, and this is, of course, in keeping with the foetal prognosis in the two conditions.

Pre-eclampsia superadded to pre-existing hypertension is associated with the most severe and extensive lesions of sclerosis, necrosis and intravascular thrombosis in the placental bed.

From these findings it appears that acute atherosis is associated with a sudden development or worsening of hypertension in pregnancy. It is, therefore, always present in pre-eclampsia and common in terminal hypertension, but rare in other hypertensive complications such as renal disease and uncomplicated essential hypertension.

The hyperplastic lesions in the placental bed in essential hypertension are similar to those found in other organs exposed to hypertension. It seems, therefore, that these lesions are characteristic of chronic hypertension during pregnancy but it is noteworthy that their appearance is much more rapid than in other organs.

The haemodynamic implications of the present findings are of considerable interest. Acute atherosis appears to cause rapid and severe reduction of the vascular lumen. When symptoms of pre-eclampsia had been present for 2 weeks of more, it was common to find groups of lipophages and large amounts of a fibrinoid-like substance causing stenosis and even complete obstruction of vessels in the placental bed.

Hyperplastic vascular lesions, as might be expected, have a much slower progression. In one hysterectomy specimen from a patient with severe essential hypertension during pregnancy every spiral artery showed marked hyperplastic lesions, but the majority showed only a relatively mild degree of stenosis. It seems reasonable to assume that time for adaptation to the altered haemodynamics is necessary for the maintenance of a reasonably adequate maternal blood supply

to the placenta in hypertension. Certainly in essential hypertension with superimposed pre-eclampsia, the hyperplastic vascular lesions and acute atherosis rapidly result in gross vascular damage and stenosis.

b. Duration of hypertensive Complications.

From the present findings it appears that in pre-eclampsia acute atherosis is not well developed before a week or more has elapsed from the onset of symptoms. On the other hand, acute atherosis can develop, in the absence of albuminuria, in association with a rise in blood pressure during the second half of pregnancy. This is illustrated by the vascular lesions in the placental bed occurring in a patient, in whom the blood pressure recorded as 95/60 mm. Hg in early pregnancy had gone up at 38 weeks to 145/85 mm. Hg and remained at that level for two weeks before delivery (Fig. 32).

It therefore seems that the time required for acute atherosis to develop depends on both the severity and acuteness of the hypertension and on the time of appearance and severity of albuminuria.

It also seems possible that acute atherosis takes longer to develop in early than in late pregnancy. This is suggested by a case in which severe hypertension and massive albuminuria was present for several weeks and a hysterectomy was performed at 14 weeks of pregnancy. Although more than half the placental bed was examined with step serial sections only a few early lesions of acute atherosis could be found (Fig 44, 45),

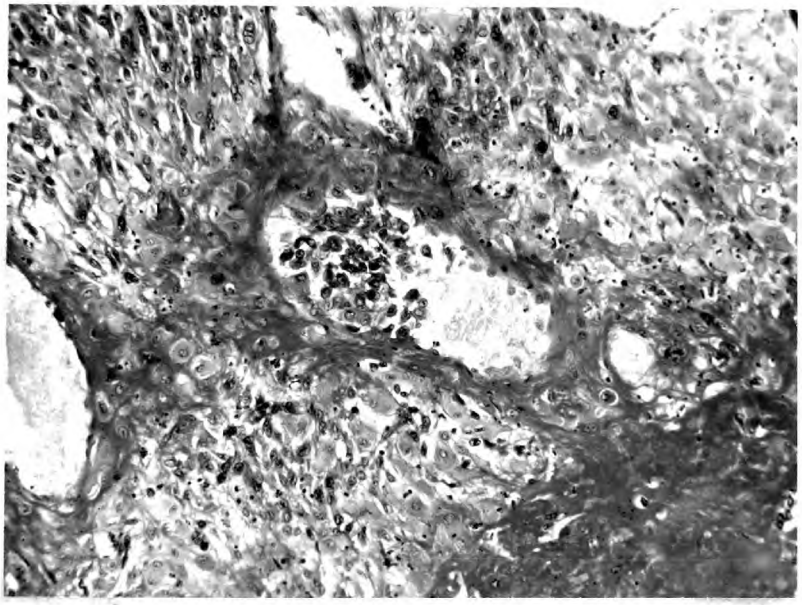


Fig. 44. - Severe hypertension and albuminuria at 14 weeks gestation. Normal changes of spiral artery in first half of pregnancy. Note the cells in the lumen which serial sectioning shows to be in continuity with the basal cytotrophoblast. H. E. - x 220.

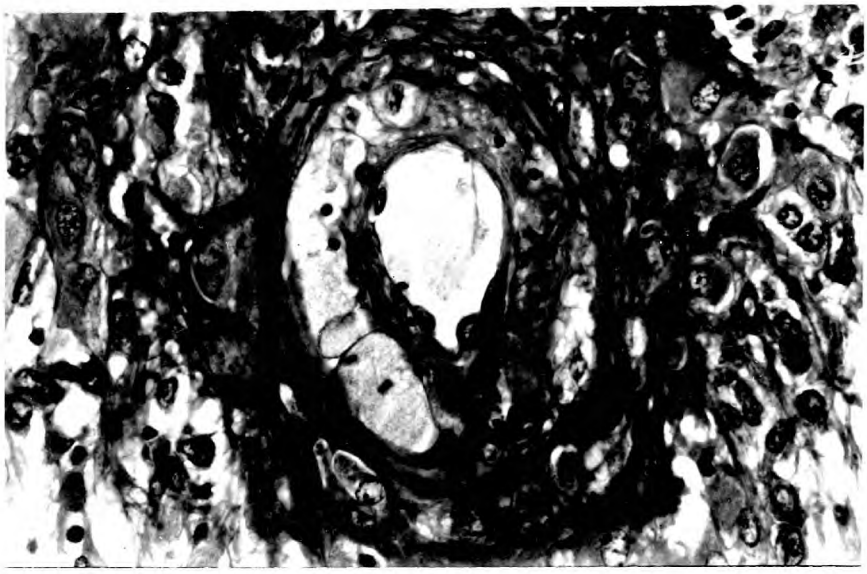


Fig. 45. - Same case as Fig. 44. Acute atherosis of a spiral artery in the placental bed. H. E. - x 370.

c. Racial Factor.

The suggestion of JONAS and REWELL that pre-eclamptic toxaemia affects the spiral arteries in the Negroes more rapidly than in Europeans is certainly false as the vast majority of the present material was obtained from Europeans. The reasons for their negative findings in Europeans have been discussed earlier in this work.

F. Lipid Changes in the placental Bed.

The use of lipid stains has proved to be one of the most useful histological tools for investigating the placental bed in normal and abnormal conditions. The findings of the present work are summarized in Table VIII.

1) Normal Pregnancies.

The absence of lipid in the decidual stroma and myometrium of the placental bed in normal pregnancy is striking. Lipid may be found in small quantities in the decidual glands. Giant cells in both decidua and myometrium occasionally contain a few lipid droplets at the end of pregnancy.

On the other hand, the stroma, glands and myometrium in the non-placental area nearly always contain lipid before the end of pregnancy. The significance of this finding is not clear.

2) Hypertensive Pregnancies.

Reference has already been made to the striking lipid infiltration of the wall of placental bed arteries and arterioles in the presence of hypertension.

TABLE VIII

PATTERN OF VASCULAR CHANGES AND DISTRIBUTION OF LIPIDS IN THE PLACENTAL BED IN DIFFERENT CONDITIONS.

	Spiral Arteries	Spiral arteries and Basal arterioles.		D. L. I. of placental bed	Lipid infiltration of	
	Physiological Changes	Hyperplastic Lesions	Acute Atherosis		Spiral arteries	Basal arterioles
Normal Pregnancy at term.	+ +	-	-	-	-/+	-
Essential Hypertension.	+ +	+ +	-	-/+	+	-/+
Pre-eclampsia.	+ +	+	+ +	+ +	+ +	+ +
Postmaturity.	+ + with possible excess of intimal fibrosis	-	-	+ +	-/+	-

It is, therefore, remarkable that D. L. I. of the decidual stroma and myometrium underlying the placenta does not commonly occur in essential hypertension as the apparently increased incidence of D. L. I. of the placental bed in cases of pre-eclampsia would seem to indicate that is is a degenerative change secondary to vascular impairment. One may speculate that in essential hypertension the physiology of the uterus has time to adapt to the alterations in haemodynamics and so prevent the occurrence of D. L. I..

The irregular distribution of giant cells in the placental bed at the end of pregnancy makes it hazardous to evaluate on a biopsy any increase or decrease in the number of such cells. Nevertheless, in the myometrio-decidual junction and myometrium an apparent increase in the total number of giant cells was often found in hypertensive conditions. In hypertension, the cytoplasm of many of these cells is heavily charged with lipid, while others contain no lipid at all.

From studies on the delivered placenta it is known that a proliferative reaction in the cytotrophoblast, consisting of a proliferation at the Langhans cell level and a differentiation into large cytotrophoblast cells, is a finding common to the majority of cases of so called "placental insufficiency" (WIGGLESWORTH, 1962, FOX, 1964, WILKIN, 1965), and it may be that the appearance of large numbers of mononuclear giant cells at the myometrio-decidual junction is a similar reaction on the maternal side of the placenta.

3. In Postmaturity.

Lipid changes occurred frequently in the decidual stroma

and myometrium underlying the placenta, once pregnancy had passed 41 weeks. This association was highly significant when tested against the incidence of D. L. I. in normal pregnancies between 38 weeks and term. At first, the lipid is patchily distributed but finally it becomes spread over the entire biopsy.

At the same time giant cells appear to be infrequent and their cytoplasm almost always contain small amounts of lipid. It would seem highly probable that many of these cells have degenerated completely and that their previous existence is recorded by a collection of lipid at their site.

Although lipid droplets were occasionally present in the wall of the very small arterioles and capillaries in areas with stromal lipid, they were never found in the wall of small arteries. This histochemical finding confirms the histological study of DIXON and ROBERTSON (1961), who were unable to demonstrate vascular abnormalities in placental bed biopsies.

The finding of D. L. I. of the placental bed from postmature pregnancies is certainly not specific for these pregnancies as it has been demonstrated in other conditions, especially in the presence of maternal heart disease and some cases of "small for dates babies".

The most impressive finding has been that when foetal hypoxia had been clinically suspected, there appeared to be a definite increase in D. L. I. in the placental bed.

One can only speculate about the significance and mechanism of production of the lipid infiltration of the placental bed in these instances. Taken in conjunction with the findings of DIXON and collaborators (1963) of a gradually decreasing choriodecidual blood flow when pregnancy

approaches and passes term, it would seem likely that the lipid infiltration of the stroma is the result of a diminished maternal blood flow, which is leading to degeneration of the maternal side of the placenta. The present study, however, still leaves unanswered the question of the cause of the diminution in flow in these cases.

The present findings on the histology of the placental bed strongly support the view that in many abnormal conditions of pregnancy the so called "placental insufficiency" is secondary to changes in the placental bed and that accordingly these conditions should be distinguished from others where the placental changes are found to be the primary factor causing placental insufficiency.

G. Relationship between vascular Lesions in the placental Bed and placental Infarction,

Several authors (YOUNG, 1914, BARTHOLOMEW and KRACKE, 1932, STEIGRAD, 1952, LITTLE, 1960, WILKIN, 1960, 1961, 1965) have shown that there is a statistically significant association between hypertensive complications of pregnancy and placental infarction. The question arises whether or not the vascular lesions in the placental bed are responsible for the presence of placental infarction.

WILKIN (1965) defines "true" placental infarction as a well defined area of the placenta, which is characterized by the collapse of the intervillous space and degeneration of the foetal elements (trophoblast, stroma, vessels).

It is clear that a histological study of the relationship between arterial lesions in the placental bed and placental infarction must be

based on intact specimens. Such a study has only been carried out by SEITZ, who demonstrated as long ago as 1903 that in the area underlying a placental infarct vascular occlusions occurred in the myometrium. This is substantiated by the present findings that in pre-eclamptic toxaemia vascular lesions develop at the myometrial site of the placental bed and lead to occlusion and thrombosis of the spiral artery (Fig. 46). SEITZ, however, did not carry out step serial sections to study in detail the relationship between vascular lesions in the spiral arteries and placental infarction.

With modern obstetric practice, it is, however, extremely difficult to collect intact specimens during the second half of pregnancy. By introducing a special technique for Caesarean hysterectomy, 3 specimens have been collected with the placenta at least partially in situ. There was no infarction of the placenta present in these cases, but some anatomical and histological findings of the present study are probably related to the appearance of infarcts in the placenta.

At the end of pregnancy the spiral arteries in the central and paracentral part of the placenta show extensive physiological changes. The great majority of these vessels are large and sinusoidally dilated and they provide a broad communication between the large arteries in the outer part of the myometrium and the intervillous space. Septa of variable height and length allow free intercommunication of every part of the intervillous space. In spite of these facts infarction occurs in the centre of the placenta (Fig. 47).

In the most marginal part of the placental bed the physiological changes in the spiral arteries are limited to the superficial decidua.

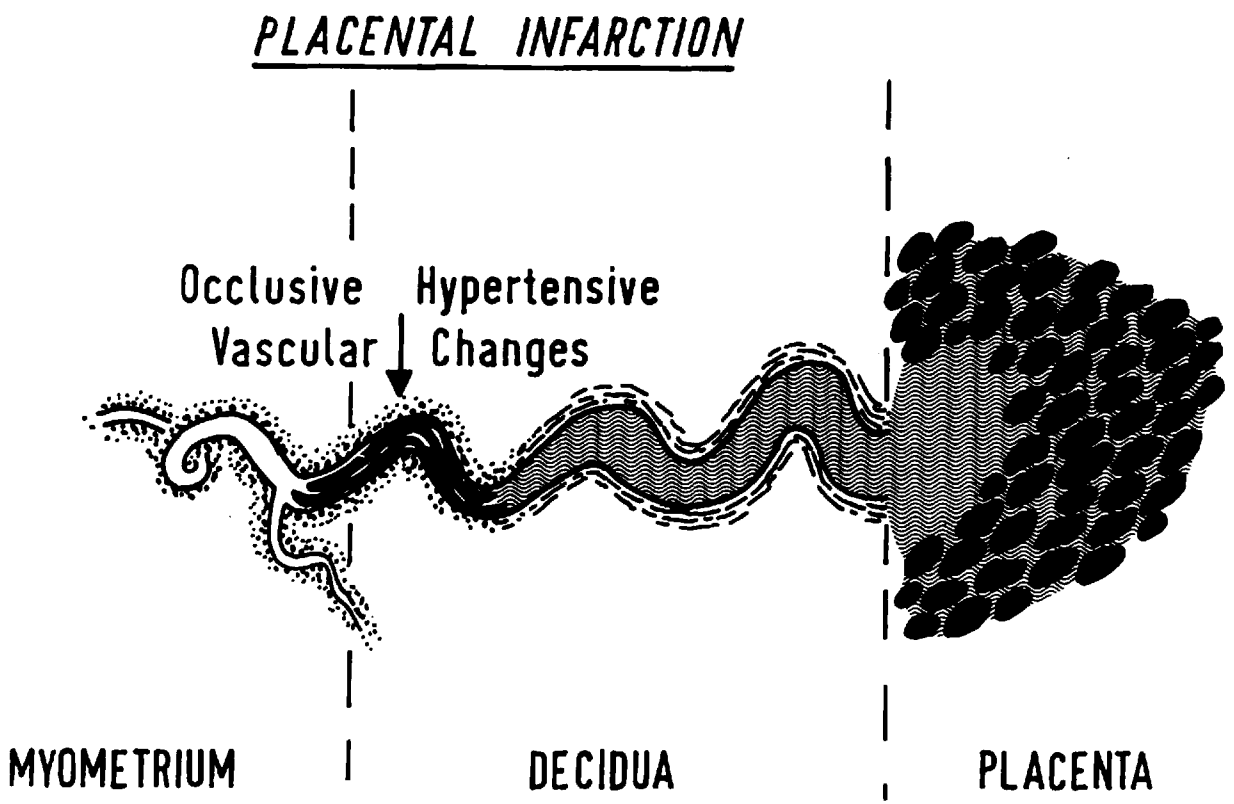


Fig. 46. - Diagrammatic representation of the relationship between obstructive lesions in the spiral artery and placental infarction.

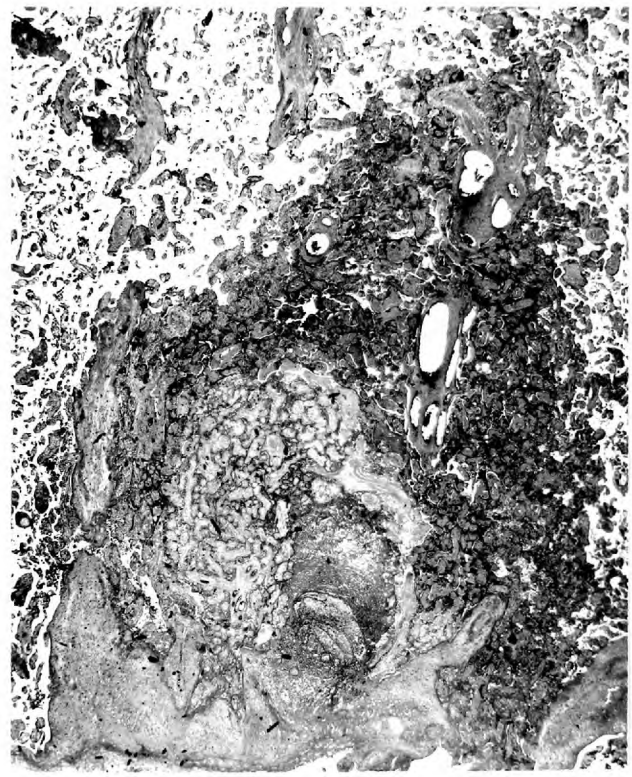


Fig. 47. - Infarction in a central area of a placenta. Serial sectioning shows the thrombosis to be at the opening of a maternal vessel. H.E. - x 14.

The spiral artery at the myometrio-decidual junction in this area frequently has the size of an arteriole of the non-placental area. The collateral circulation is more limited in the marginal than in the central part of the placenta, and a septum in this area may well result in the isolation of an area from the rest of the placenta.

Both these factors, the size of the spiral arteries and the presence of septa in the margin of the placenta, may account for a higher incidence of the placental infarcts in this area as shown by WILKIN (1965).

The presence of infarcts in the central or paracentral part of the placenta occurs probably only in cases where there is extensive and severe vascular pathology in the placental bed with considerable reduction of the intervillous blood flow. In the present study one hysterectomy specimen with placenta in situ showed hyperplastic lesions in all spiral arteries and stenosis in some of these vessels. The placenta, however, did not show any sign of infarction. It seems, therefore, likely that even severe vascular pathology can be present in the placental bed without causing infarction of the placenta. On the other hand, it is probable, as WIGGLESWORTH (1964) has suggested, that a relatively small area of placental infarction may indicate a widespread reduction in utero-placental blood flow, especially if the infarct is centrally situated in the area where the collateral supply would be expected to be best developed.

SUMMARY AND CONCLUSIONS.

1. The maternal blood supply to the intervillous space of the human placenta at term is provided by an average of one spiral artery for every two square centimeters of basal plate. The majority of spiral arteries open at the base of a septum or in a protrusion of the basal plate. It is significant that every sizable septum has one or more spiral arteries opening at its base. Virtually every artery opens with a single orifice and the distribution of these appears to be quite random.

2. Veins drain all over the basal plate and have often multiple openings.

3. The septa are of an irregular size, apparently haphazardly distributed and allow free intercommunication between every part of the intervillous space.

4. The histological criteria for identifying the placental bed origin of a biopsy of the uterine wall are :

a. the presence of giant cells in the decidua and myometrium;

b. the presence of physiological changes in the arteries;

c. the adherence of villi to the decidua.

The presence of any one of these criteria is sufficient to identify a biopsy as originating from the placental bed.

5. In normal pregnancy extensive changes occur in the arterial vessels of the placental bed. In order to avoid any possible confusion with the established terminology of vascular pathology, this change in the spiral arteries has been called "physiological".

6. Physiological changes occur in the spiral arteries communicating with the intervillous space and are characterized by the disappearance of the normal muscular and elastic structure of arteries and their replacement by fibrinoid containing "large cells". The vascular lumen is sinusoidally dilated.

7. Physiological changes in the spiral arteries, including invasive cells in the arterial lumen occur in early pregnancy in the superficial decidual layer and apparently extend during the second half of pregnancy deeper into the decidua and underlying myometrium.

8. At 28 weeks gestation some "large cells" in the wall can be traced directly from plugs of cells in the arterial lumen which are probably of trophoblastic origin.

9. After 28 weeks the arterial wall becomes progressively fibrotic and thickened. The invasive cells have almost completely disappeared from the arterial lumen by the end of pregnancy.

10. In the marginal area of the placental bed the physiological changes are absent in the myometrial part of the spiral arteries. In the non-placental part of the uterine wall the above mentioned physiological vessel changes are absent in both decidua and myometrium.

11. Basal arterioles, which do not communicate with the intervillous space, preserve their muscular structure, but have often partially or completely lost their elastic membranes.

12. Proliferative intimal cushions are a common finding in veins at the end of pregnancy.

13. In pregnancies complicated by hypertensive syndromes the preferential site for vascular lesions are the arteries and arterioles of the placental bed and the most severe, occlusive vascular lesions are found at the level of the myometrio-decidual junction.

14. Vascular lesions in the non-placental area are milder and only present in the superficial layer of the decidua vera. They do not seem to be present at the myometrio-decidual junction outside the placental area.

15. The vascular lesions characteristic of essential hypertension are arterio- and arteriolosclerosis. Pre-eclampsia is characterized by arterio- and arteriolonecrosis as manifest by fibrinoid necrosis and infiltration of the wall with lipid and lipophages. The number of arteries affected appears to be closely related to the clinical severity of hypertensive complication.

16. Histological studies of lipid in the placental bed have shown an absence of lipid in the basal decidual stroma and adjoining myometrium in normal pregnancies before and at term.

17. Pre-eclampsia is characterised by an infiltration of lipid and lipophages in the wall of both spiral arteries and basal arterioles. In essential hypertension there is often an abnormal lipid infiltration of the spiral arteries. In pregnancies complicated by hypertension there is also an apparent increase in mononuclear giant cells at the myometrio-decidual junction of the placental bed and some of these are heavily infiltrated with lipid.

18. . In postmaturity the decidual stroma and myometrium of the placental bed is frequently the site of a diffuse lipid infiltration. This lipid infiltration is apparently associated with degeneration

and disappearance of the giant cells. The presence of lipid in the placental bed is thought to be a degenerative change as a result of impairment in maternal blood supply.

19. A diffuse lipid infiltration of the placental bed is also found in other complications of pregnancy, which are known to be associated with placental insufficiency, especially pre-eclampsia, maternal heart disease and small for dates babies.

20. A hypothesis is advanced explaining the role of the spiral arteries in the pathogenesis of placental infarction. Primary occlusion of the spiral artery at the myometrio-decidual junction is likely to cause infarction of both decidua and placenta. Occlusion of a single spiral artery is thought to lead to placental necrosis only if there is a general reduction in the choriodecidual blood flow as a result of a widespread vascular pathology in the placental bed.

APPENDICES.

APPENDIX I.

TECHNIQUE FOR FROZEN SECTIONS AND OIL RED O STAINING.

Biopsies were fixed in 10% neutral formalin-saline for no longer than 4 weeks. Each biopsy was thoroughly washed in running tap water before freezing.

The placental bed biopsy being normally irregular in shape, a flat surface was trimmed on one side to fix the biopsy properly to the holder. This surface was orientated so that both decidua and myometrium were cut in each section.

Biopsies were frozen to the holder by immersion in liquid nitrogen (-170°C). This was done in two steps, by first immersing only the holder in the liquid until the base of the biopsy is frozen on the holder, then followed by complete immersion of the specimen for about 10 seconds.

Sections were cut at a temperature of - 20°C. on the "Pearse" refrigerated microtome (cryostat) as produced by SLEE (South London Electrical Equipment Co. Ltd.).

At least six sections at different levels were collected from each biopsy and stained with Oil Red O in isopropyl alcohol.

The method for Oil Red O staining is as follows :

1. Oil Red O in isopropyl alcohol * 10 min.

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*Stock Solution : Oil Red O 5 g.
isopropyl alcohol 98% 100 ml.

Working solution: Stock solution 6 parts
Distilled water 4 parts

Filter through Whatmann no. 42.

2. Differentiate in 60% isopropyl alcohol.
3. wash in distilled water
4. Mayer's haematoxylin
5. wash in running tap water
6. mount in Aquamount (G. T. Gurr)

Results : Neutral lipids : red

Nuclei : dark-blue.

APPENDIX II.

HISTOLOGICAL TECHNIQUE FOR LARGE SECTIONS OF THE UTERUS.

The following techniques were employed for processing and cutting the uteri with placenta ' in situ' and postpartum uteri.

FIXATION.

The uterus was cut into parallel blocks each measuring 0.7 to 1.0 cm in thickness. Blocks were fixed in 10% neutral formalin-saline for at least 4 weeks.

DEHYDRATION, CLEARING and EMBEDDING.

The following schedule of processing was adopted for embedding large blocks of the whole uterus :

1. wash in running tap water : 4 - 6 h.
2. alcohol 70% : 12 - 24 h.
3. alcohol 94% - 2 changes : 12 - 24 h. each
4. absolute alcohol - 2 changes : 12 - 24 h. each
5. methyl benzoate until the blocks sink to the bottom; if they do not sink after 24 hours a second change is made.
6. benzene - 2 changes : 12 - 24 h.
7. melted paraffin at 56° - 58° C under a constant vacuum of 450 mm. Hg - 2 changes: 8 - 12 h.
8. embed and cool quickly. The moulding forms consisted of two L-shaped metal pieces and a metal base plate. Some vegetable oil was applied to the inner surface of the moulding forms to prevent the paraffin from sticking too firmly to the metal.

CUTTING.

A commercial M. S. E. sledge microtome adapted with the MOORE-stage for cutting large blocks was used.

One of the main difficulties encountered was the varying thickness of sections.

1. improper fixation of the block on the MOORE-stage. It is often the centre of the block which is not properly fixed on the stage. Therefore, special care has to be taken to trim a smooth surface, and to heat both the block and the stage with a Bunsen-flame before fixing the block on the stage;
2. a dull knife;
3. too slanted or too vertical a knife tilt;
4. too loose or too well fixed feeding mechanism of the microtome. Large sections were routinely cut at 8 microns.

ATTACHING SECTIONS TO SLIDES.

The glass slides on which sections were attached measured 115 x 75 x 0.8 mm.. The slides were cleaned in 1% HCL in 70% alcohol for one hour and then washed in running tap water for several hours. With clean slides it was not necessary to use albumin fixative.

Sections were floated out on a water bath at 50° - 52° C. and thereafter stored in an incubator at 36° C for a minimum period of 48 hours before staining.

STAINING.

The staining techniques for large sections are exactly the same as for routine sections, except that the staining jars are of a larger size. After staining, the slides were stored in an incubator at 36°C for 1 month and, preferably, even longer.

APPENDIX III

CLASSIFICATION OF HYPERTENSIVE COMPLICATIONS OF PREGNANCY ACCORDING TO THE AMERICAN COMMITTEE ON MATERNAL WELFARE. (EASTMAN, 1950).

PRE-ECLAMPSIA.

The development, after the twenty-fourth week of pregnancy, of one or more of the following criteria :

- a systolic blood pressure of 140 mm. Hg or more, or a rise of 30 mm. or more above the usual level; a diastolic pressure of 90 mm. or more, or a rise of 15 mm. or more above the usual level ;
- proteinuria of significant degree;
- persistent oedema of the hands or face.

Pre-eclampsia is classified as "severe" if any of the following signs or symptoms is present. If none is present the pre-eclampsia is classified as "mild".

1. Blood pressure of 160 or more systolic, or 110 or more diastolic;
2. Proteinuria of 5 g or more in 24 hours;
3. Cliguria (400 ml or less per 24 hours);
4. Cerebral or visual disturbances;
5. Pulmonary oedema or cyanosis.

ECLAMPSIA is characterized by the same signs of pre-eclampsia with convulsions and coma superimposed.

ESSENTIAL HYPERTENSION.

The blood pressure levels necessary for classifying a patient in this group are 140 mm. Hg systolic or 90 mm. Hg diastolic. Those levels must be demonstrable before the twenty-fourth week of gestation.

This disease does not include cases of chronic hypertension secondary to inflammatory disease of the kidney or urinary obstruction.

ESSENTIAL HYPERTENSION WITH SUPERIMPOSED PRE-ECLAMPSIA.

The criteria are as follows : first, evidence that the patient is suffering from essential hypertension, as stated above, and second, evidence of the superimposition of an acute process, as demonstrated by an elevation of systolic pressure of 30 mm. Hg or more, an elevation in diastolic pressure of 15 mm. or more, or the development of a significant degree of proteinuria, separately or together.

Acute nephritis, chronic glomerulonephritis, nephrosis, and other renal conditions that stem from inflammatory or metabolic etiology are not included.

APPENDIX IV.

CLASSIFICATION OF HYPERTENSIVE COMPLICATIONS OF PREGNANCY ACCORDING TO DIXON AND ROBERTSON (1958).

1. NORMOTENSION - Blood pressure never recorded above 120/80 mm. Hg. No oedema nor albuminuria which could not be ascribed to some definite local cause.

2. ESSENTIAL HYPERTENSION - Blood pressure exceeding 120/80 mm. Hg in the non-pregnant state or the first half of pregnancy. Consistent or frequent recordings in excess of 140/90 and 160/100 mm. Hg placed the patient in the moderate and severe categories respectively. The remainder were classified as mild essential hypertensives.

3. PRE-ECLAMPSIA- Blood pressure rising above 120/80 mm. Hg for the first time after the 20th week of pregnancy with the development of albuminuria for which no local cause could be found. The presence or absence of oedema did not influence selection.

4. TERMINAL HYPERTENSION - As for 3 but without albuminuria. Once again no account was taken of oedema.

5. EPISODIC HYPERTENSION - This group represents a number of patients who had been hypertensive at one or a few occasions, but who spontaneously or after hospital treatment, had been normotensive for the last weeks preceding the delivery.

APPENDIX V.

STANDARD DEVIATION LIMITS OF BIRTH WEIGHT BY WEEKS OF GESTATION-POPULATION. (According to M. DAWKINS).

	MEAN	<- 2 SD	- 2	-1 SD
36 weeks (days : 252 - 258)	2.85 kg	< 1.6 kg	1.6	2.1 kg
37 weeks (days : 259 - 265)	3.01	< 2.0	2.0	2.4
38 weeks (days : 266 - 272)	3.15	< 2.2	2.2	2.6
39 weeks (days : 273 - 279)	3.33	< 2.4	2.4	2.7
40 weeks (days : 280 - 286)	3.41	< 2.5	2.5	2.9
41 weeks (days : 287 - 293)	3.48	< 2.5	2.5	2.9
42 weeks (days : 294 - 300)	3.52	< 2.5	2.5	2.9
43 weeks (days : 301 - 307)	3.48	< 2.5	2.5	2.9
43 weeks (days : 307)	the same limits taken as for 43 weeks.			

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