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A STUDY OF HUMAN PLACENTAL GROWTH WITH OBSERVATIONS ON THE PLACENTA IN ERYTHROBLASTOSIS FOETALIS.

by

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THIS STUDY OF PLACENTAL GROWTH HAS BEEN AWARDED A WILLIAM BLAIR-BELL MEMORIAL LECTURESHIP BY THE ROYAL COLLEGE OF OBSTETRICIANS AND GYNAECOLOGISTS.

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PREFACE.

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PART ONE

THE ANATOMY OF THE PLACENTA.

INTRODUCTION

The human placenta is neither an easy structure to understand or to investigate. It is rather ironic that so little is known about this organ on which the continuity of mankind is utterly dependent. As late as 1950 it was stated by Hamilton and Boyd[37] that our knowledge of the intimate structure and growth of the placenta is still only a first approximation.

The external appearance of the placenta is familiar to all who practice obstetrics and has been described by many authors. The internal anatomy is however still a matter for discussion and there is a wide divergence of opinion. It may be asked why so little is known about the anatomy of the placenta when other organs of the body, and seemingly more complicated, have had their structure demonstrated. The explanation of this anomaly lies in the innate structure of the placenta. It is not easy to dissect the placenta. The foetal vessels present, as the dissection is continued, an ever increasing network of divisions and ultimately dissection must be abandoned or becomes so inaccurate that

it is of little value.

Dissection of the placenta was, until the introduction of the "injection corrosion" technique the only method of investigating the anatomy of the placenta. The accounts of placental anatomy given in the 18th and 19th century were all based on actual dissection of fresh placentae. John Hunter (1786) demonstrated the existence of a maternal blood circulation in the human placenta and this was confirmed long afterwards by Waldeyer (1890). Braxton Hicks [41] (1873) in an otherwise excellent article denied the existence of a maternal placental circulation and believed that the placenta was nourished by osmosis. Goodsir (1845)[31] published an account of the structure of the cotyledon based on dissection and this was confirmed in a further study by Farre (1856).[24] The description of the cotyledon, as given by Farre, resembled in his illustrations, that given much later by Bumm. The cotyledon resembled a "tree" or "bush" in its general outlines, the branches increasing in complexity as the periphery was reached. The most

peripheral areas being inserted into the decidua. Braxton Hicks (1873)[41] made several observations on the anatomy of the placenta. This article was remarkable for the accuracy of its anatomical dissections and illustrations. He used this demonstration as a vehicle for his belief that there was no maternal circulation within the placenta and nourishment was secured by osmosis. He claimed that the uterine maternal artery and vein supplying a cotyledon were continuous. He described, at the fringe of the cotyledon, long strands of tissue with a bulbous tip. These had also been described by Goodsir. It was his belief that they burrowed into the decidua. The significance of these long strands of tissue will be referred to later when the growth of the placenta is considered. He described also the way in which the foetal vessels at the decidua, burrow into the decidua and then re-emerge back into the placenta. This is the "chandelier" arrangement described by Spanner many years later, but no credit has been given to Braxton Hicks for his description.

Bumm in 1893[13] published an account of placental anatomy based on many years of patient dissection. He visualised the placenta being composed of tree-like fronds or villi extending from the foetal chorion to the maternal decidua. Some of these fronds were attached to the decidua but the majority floated free in the maternal blood. This was a simple arrangement and easy to understand. It is easy to understand how widely this concept was accepted and it remained an accepted fact until Spanner in 1935 proposed a completely new idea of placental anatomy. After Bumm the method of injecting the placental vessels with dyes or "fillers" such as gelatine or celloidin came to be used and various papers were published on the findings obtained by such methods. For example, in 1924, Kellog, Davis and Amolsch[20] published photographs of the placental vessels, obtained by filling these vessels, through the umbilical cord, with bismuth and taking x-ray photographs. Their results were a great advance in so far as they showed the mode of division of the placental

arteries and veins. Also the penetration of bismuth was sufficient to demonstrate the terminal arterioles and venules. This gave an appearance at the end of the placental vessels of a "basket-like" arrangement. These workers also used celloidin to fill the placental vessels, and when the material had hardened the placental tissue was corroded away with a suitable acid, leaving a cast of the placental vessels which could be handled and dissected. This injection-corrosion technique was a great advance. Not only could the mode of division of the placental vessels be seen, but the cast was in three dimensions and the relationship of the vessels to each other could be appreciated. It was appreciated that the umbilical arteries when they entered on the foetal surface of the placenta underwent a series of dichotomous divisions over the surface of the foetal chorion. At each of these divisions a proportion of the arteries would perforate the chorion and enter the substance of the placenta. These perforating branches would form the arterial blood supply of the villi.

It was appreciated too that these vessels formed the villi and ended in a maze of small branches which were located at the periphery of the maternal surface of the placenta. The foetal veins were observed to accompany the arteries more or less regularly. Kellog, Davis and Amolsch were unable to demonstrate any arterial anastomosis after the primary anastomosis of the umbilical arteries immediately before the insertion of the cord. They believed however that an arterio-venous anastomosis was present in the substance of each of the villi.

In 1935 Spanner[70] after ten years investigation, both of delivered placentae and placentae in situ, published an account of the foetal placental circulation. His views have been widely adopted and are still the basis of standard teaching in most countries. He studied not only corrosion casts but also injected placentae in situ. His results were excellent and no one has obtained better preparations with this technique. He described the placental vessels perforating the foetal

chorion and entering the villus. The villus then passed down to the maternal decidua where the most peripheral branches entered the decidua and after an interval re-emerged and passed up into the placenta. The "downwards and upwards" course of the vessels of the villi has been compared to the branches of an old-fashioned chandelier in their arrangement. Stieve,[72] rather derisively perhaps, called them "weeping willow trees" (Wie Trauerweiden). The extent of penetration into the smallest vessels, obtained by Spanner, was excellent and even terminal capillaries were entered. He described villi giving off long terminal capillaries which floated freely in the maternal blood. Spanner also described the presence of sphincters in the foetal veins of the villi which he considered were pressure regulating mechanisms. It is a tribute to the excellence of his work and opinions that even today many workers in this field still accept Spanner's conclusions more or less completely. At this point it is perhaps worth explaining that the term "villus" has been used

more or less synonymously for cotyledon or lobe.

Bacsich and Smout in 1938[1] published an account of the architecture of the larger foetal vessels in the placenta. Their account was concerned principally with the arteries of the placenta. The technique employed was that of injection and corrosion, using celluloid as the filler. They considered the pattern of the larger foetal vessels, the area of placenta supplied by each artery and the possibility of arterial anastomosis. With regard to the pattern of the arteries, placentae may be divided in two main types. Firstly a "dispersed" variety in which the two arteries divide dichotomously and diminish in calibre rapidly as the periphery of the placenta is reached. Secondly, a "magistral" variety in which the two arteries extend almost as far as the margin of the placenta before their calibre diminishes. Fraser (1923) described the dispersed variety of placenta. But to Schordania (1929) belongs the credit of distinguishing these two varieties of placenta and giving them the "dispersed" and "magistral"

classification. Schordania believed that the magistral variety of placenta produced a better developed foetus since the arteries were larger and could deliver a greater volume of blood. This observation has never been confirmed. Bacsich and Smout in their corrosion specimens were unable to find any evidence of sphincters in the veins of the cotyledonary trunks. These two authors found that the umbilical arteries were always of the same calibre and the only arterial anastomosis was the transverse connecting branch joining the two umbilical arteries at or near their insertion into the placenta. They considered that, because of no further arterial anastomosis in the placenta, this transverse branch was of great importance in maintaining an equality of arterial blood pressure in both halves of the placenta. In most cases the two arteries each supplied one half of the placenta, but occasionally one would supply only one-third, and also occasionally one artery would supply the periphery of the placenta and the other the central portion. The absence of

arterial anastomosis distal to the transverse branch at the insertion of the cord implied that all the foetal arteries were end arteries. Hyrtl[83] (1870) and Fraser[82] (1923) described frequent arterial anastomosis but this could not be confirmed in this work.

The transverse communicative branch is usually described in continental Europe as Hyrtl's anastomosis but the description is not used in this country. The author has been informed by Bacsich in a private communication that in the Hunterian Museum at Glasgow University there is a dissected placenta which shows that the transverse branch was known in Hunter's day and must antedate Hyrtl by many years. Like Spanner, Bacsich and Smout pointed out that all the main arterial branches of the placenta lie in a horizontal plane whilst in other parts of the body they are arranged in three dimensions. This difference is presumably related to the limited space available to the placenta within the uterus and the necessity therefore to lie horizontally.

Subsequently Stieve (1940-1948), a fellow German, disagreed in his published works with Spanner's findings. In particular he objected to the chandelier arrangement of villi and believed it to be quite untrue. Also, he objected to Spanner's contention that the terminal portions of the villus floated freely in maternal blood. This would constitute a "villous" type of placenta such as is found in the lower orders of mammals. This, he urged, is not borne out by histological examination. The terminal villi in histological section are seen to be mostly adherent and Stieve inferred that the terminal villi formed a labyrinth and would suggest that the human placenta is fundamentally "labyrinthine" in nature. He urged that all the villi should be regarded as adherent and without free terminal villi. The labyrinth of villi was described by him as a three dimensional lattice work or fringe (Gitterzotten) and analagous to a sponge, the maternal blood being present in the interstices of the fringe rather than free in the form of a lake. He also

believed that not only fusion of syncytium took place but also capillaries passed from one villus to another. Hamilton and Boyd (1951)[36] agreed with Stieve that fusion of syncytium between terminal villi certainly occurred, especially in the latter half of pregnancy. They doubted however whether all terminal villi should be regarded as fixed and also whether sharing of blood vessels took place except perhaps occasionally. Since Stieve's last paper in 1948 further investigations concerning the foetal placental circulation have been published. In 1951, Romney and Reid[64] carried out a series of injection-corrosion studies using a plastic, vinyl acetate, as a filler. This investigation was concerned mostly with the capillary bed of the placenta but an adequate account was given of the gross anatomy of the foetal placental circulation. The casts obtained were excellent. The capillaries were entered and could be shown, at least, in part. The general arrangement of the larger vessels was described and followed that given by Bacsich and Smout. They claimed to

have observed anastomosis between adjacent arteries on the foetal chorionic surface at the periphery of the placenta. In addition they noted that the placenta possessed a very extensive capillary bed which was most dense nearest to the decidua. They could not confirm Spanner's "chandelier" arrangement of vessels and could find no evidence of sphincters. They believed that the capillaries of the terminal villi, whilst extremely numerous were relatively short. The casts of the capillary vessels which were obtained led them to believe that the capillaries under the chorion differed from those at the decidua and concluded that they had perhaps a different function from each other. The next work on the placenta was published in 1954 by Wilkin.[78] He also used the injection-corrosion technique. He described the villus or cotyledon as being drum-shaped with vessels around the periphery and hollow in the centre. The base of the villus had a gap which he termed the crown (couronne). In addition he supported Spanner's chandelier arrangement of the villus vessels, and

believed that the gap marked the entrance of maternal vessels into the cotyledon.[14]

Crawford (1955, 1956) has proposed a new technique for the investigation of the anatomy of the placenta, and has made a number of observations on the basis of this technique. He has pointed out that the actual dissection of a placenta is preferable, to studies of placental casts made by the injection of corrosion technique. The injection-corrosion technique has certain innate objections. It is not easy to do and is most time-consuming, since the most perfect casts are obtained when injection of filler is carried out slowly over a period of several hours or days. Before injection can be made the placental vessels must be washed out with normal saline solution to get rid of foetal blood. This can produce vessel rupture and subsequent leakage. Thereafter the vessels must be washed out again with acetone to prevent premature hardening of the "filler" and ensure its farthest possible penetration. Acetone denatures vessel walls and makes them still more liable to rupture.

The "fillers" employed, for example latex, celloidin, celluloid, and vinyl acetate, all have a certain viscosity and a considerable pressure is necessary to force the filler along the vessel lumen. As a result of this and the preliminary washing out the filler usually leaks and distorts the casts. Artefact is an ever present possibility and since the actual foetal vessels are removed subsequently by corrosion with a suitable acid, there is no way of checking the accuracy of a cast or even of being sure that it is complete. It is not intended, by the above criticisms, to claim that the injection-corrosion technique has no merits. On the contrary it fills large foetal vessels very well and has given in careful hands, a clear understanding of the three dimensional relationship of these vessels to each other. With regard to the filling of smaller vessels and capillaries, the picture has been much less satisfactory. It is true that injections of indian ink or other colloidal dyes will fill these smaller vessels but dissection of the "fringe" of the cotyledon

is very difficult and demonstration of intact capillaries not really satisfying. The present writer considered that a possible solution to the difficulty of dissection in the placenta, might lie in a technique which made the placenta more amenable to dissection. After considerable experiment a method of digesting the placenta with the proteolytic ferment trypsin was evolved. This technique was published in 1955 (Crawford and Fraser 1955)[14]. In brief the technique consists in immersing a fresh placenta in a solution of one per cent sodium carbonate and adding enough commercial trypsin to make a one per cent solution. The placenta is incubated at 98.4°F. for a stated number of hours. The actual length of digestion permitted depends on the particular type of anatomy which it is desired to study. For the gross anatomy 36 hours is usually required as a minimum. If the digestion is allowed to proceed unchecked the entire placenta will be digested away. However, by curtailing digestion it is possible to remove maternal blood, fibrin and decidua without damaging the foetal

vessels. The removal of these substances which normally bind the cotyledons together allows the entire placenta to be dissected speedily and with precision. Trypsin accomplishes in a few hours a task that occupied Bumm many years of patient dissection. It is of advantage to fill the placental vessels after digestion with liquid gelatine suitably coloured red and blue to distinguish arteries and veins from each other. After injection the placenta is immersed in 10 per cent formol-saline to harden it and this makes dissection easier. For the demonstration of capillary vessels the foetal vessels are filled with a suitable colloidal dye solution before digestion is permitted. A period of 24 hours is sufficient. A longer period will remove the syncytium of the villi and damage the delicate capillary vessels. The capillaries are readily examined by mounting in melted gelatine mounting medium and applying pressure to the cover slip over the preparation. The effect of pressure on the preparation is to separate capillary vessels from each other in a fashion

that dissection could not attempt. It is therefore possible to see whole capillary vessels, and since the syncytium is also present the completeness of the capillary vessels can be assumed. This technique has permitted observations on the anatomy of the placenta which could not be achieved by existing techniques. These observations have been published elsewhere, Crawford (1956),[15,16,17] but will now be repeated in detail since they have a bearing on the growth of the placenta.

The anatomy will be described in three sections.

SECTION ONE: THE GROSS ANATOMY OF THE PLACENTA.

SECTION TWO: THE ANATOMY OF THE COTYLEDON.

SECTION THREE: THE ANATOMY OF THE VILLUS AND ITS CAPILLARY STRUCTURE.

SECTION ONE

THE GROSS ANATOMY OF THE PLACENTA.

This will be described under three headings, the umbilical cord; the foetal surface of the placenta; and the maternal surface of the placenta.

THE UMBILICAL CORD.

The chorionic covering of the cord is relatively resistant to the digestive power of trypsin. At the end of digestion the umbilical vessels are intact and can be catheterized readily with a suitable polythene catheter. Little pressure is required to fill the foetal vessels with the gelatine solution and it is rare for vessels to rupture during the process.

There are usually two arteries and one vein, but a single artery is occasionally found. If two arteries are present they communicate by a very short branch just before the insertion of the cord into the placenta. In many cases this communication is in the nature of an artery to artery anastomosis without any intervening branch. Immediately after this anastomosis the arteries divide into their primary divisions and pass forwards onto the foetal surface of the placenta. The umbilical arteries are of equal size and of smaller calibre than the umbilical vein. The arteries describe a helix or spiral around the vein and by their contractions are believed, by

many workers, to assist in the return of blood to the foetus. The significance of the transverse connective branch between them in ensuring an equality of blood pressure in all parts of the foetal vessels produced subsequently has already been alluded to.

THE FOETAL SURFACE OF THE PLACENTA.

The chorion over the foetal surface of the placenta is also resistant to trypsin and, unless excessive digestion has taken place, will be intact, providing a firm framework for the placental vessels. When the placenta is ready for examination it is seen to consist only of umbilical cord, chorion and the vessels with their related cotyledons. The main vessels run between two layers of chorion and are most firmly secured in place. It is necessary to employ sharp dissection to free a main trunk from the chorion.

Each umbilical artery divides as a rule before the chorion is reached but the form of its division depends on the type of placenta. The division of placentae into "dispersed" and "magistral" varieties has been referred to

already. The following description applies to the "dispersed" variety. The "magistral" variety will be considered later.

In the "dispersed" variety, each umbilical artery begins to divide before the placenta is reached and the divisions are usually of unequal size. The main trunk divides as a rule into several primary divisions. Two or three of these in each half of the placenta course forward over the chorionic surface. It will be shown later that there are more primary divisions but they cannot as yet be seen.

The fate of each of these primary divisions is subject to variation in individual placentae. It is quite usual for one division to end at once and enter a cotyledon, leaving the other primary divisions to continue their course. These vessels undergo further division into secondary branches. A proportion of these secondary divisions end in cotyledons and leave the remaining divisions to continue towards the periphery of the placenta. Division again takes place and a proportion of the tertiary divisions

will again end in cotyledons. The remainder are now approaching the periphery and a final division into cotyledonary arteries takes place at the limits of the chorion. In other words, at each division of the main vessel a number of the branches plunge immediately through the chorion to end in cotyledons while others continue their course in the chorion towards the periphery. This provides for a roughly concentric distribution of cotyledons.

In the "magistral" variety of placenta, each umbilical artery preserves its original calibre until almost the periphery of the placenta is reached. Each artery passes across the corresponding half of the placenta and gives off from time to time arterial branches. These are usually of smaller size and end as in the dispersed variety, by perforating the chorion and forming a cotyledon. The veins accompany the arterial branches more or less closely, and perforate the chorion with the artery.

From the level of the main artery down to the level of the last division lateral branches of

varying size, some extremely small, arise directly from the parent vessel and end after an interval in a cotyledon or sub-divide and the sub-divisions end in cotyledons. In general these vessels are much smaller than the main divisions of the umbilical arteries and the size of the corresponding cotyledons is in direct proportion to the vessel.

Two aspects of the arterial circulation are of note. First, in all the placentae examined there was no evidence of collateral circulation, after the primary anastomosis, between the branches derived from the same parent artery or between the branches derived from either umbilical artery. Second, all of the arterial divisions, large or small, ended ultimately in cotyledons. A diligent search has been made for branches which might be concerned in the nutrition of the chorion but these, so far, have not been seen. It is possible that they do exist but were too small for the filler to enter. By the time that the terminal sub-divisions have taken place each half of the chorion is occupied by a network

of dividing and sub-dividing vessels and these as already mentioned do not communicate with each other or with the branches in the other half. This is illustrated in Figures 1 and 2. In some placentae, where one umbilical artery is larger than the other, it may occupy more than half of the chorion with its system of branches.

Usually, arterial branches lie superior to veins on the chorionic surface.

The umbilical vein is formed by the union of sub-divisions and divisions of veins much in the same way as the umbilical artery is distributed. The veins in the main accompany the corresponding arterial branches, and the size of the vein matches the artery. Many of the veins show lateral branches which accompany and begin with the small lateral arterial branches already described. These small veins may travel a considerable distance from the accompanying arterial branch before reaching the parent trunk and some of them describe a curved pathway to do so.

None of the veins which were examined showed

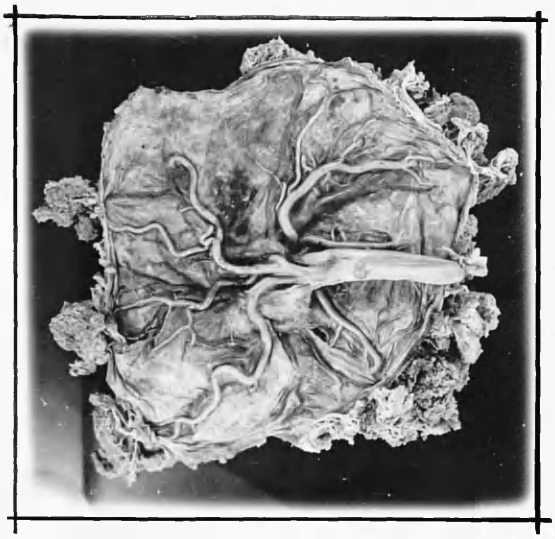

Figure No. 1. Reduced 12 times.

"Dispersed" placenta.

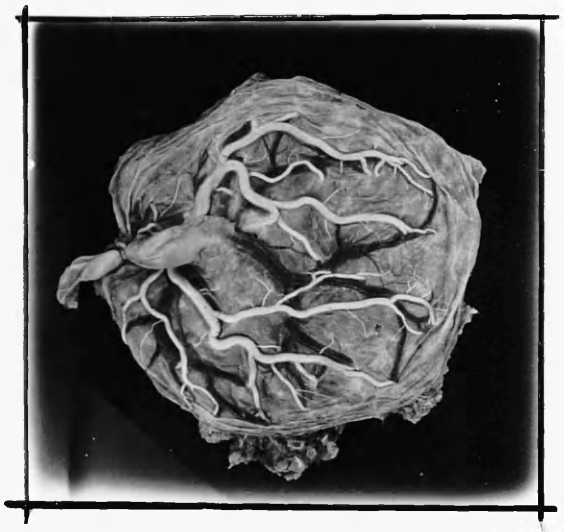

Figure No. 2. Reduced 12 times.

"Magistral" placenta.

evidence of sphincters. In some of the veins, however, there are constrictions at right angles to their course but these appear to be constrictions by the investing chorion rather than actual sphincters.

Figure 3 illustrates the general structure of the placenta. The chorion has been largely removed to facilitate demonstration. The relatively small amount of tissue present in a placenta is apparent.

THE MATERNAL SURFACE OF THE PLACENTA.

In the placental preparation the cotyledons are readily separated from each other and their structure easily examined. They vary greatly in size and complexity and, as previously stated, the calibre of the vessels supplying them is in direct proportion to the size of the individual cotyledon. It will also be seen that quite considerable areas of bare chorion separate the perforating vessels supplying the cotyledons.

The cotyledons are formed in two separate ways. It has already been mentioned that the total number of primary divisions of the umbilical

Figure No. 3. Life size.

artery is not immediately obvious from scrutiny of the foetal chorionic surface. Subsequent examination of the digested specimen reveals that there are deep branches springing from the under surface of the parent vessels and passing directly through the chorion to form cotyledons. Such deep vessels may arise at the stage of primary or secondary division of the main arteries. They are joined on the way as before by the related vein. Some of these branches may be quite large and themselves constitute primary or secondary divisions.

In the second way the cotyledons are formed by the arterial branches perforating the chorion as already described in company with their veins and entering a cotyledon together. The vessels supplying the largest cotyledons may be of considerable size and sometimes remain intact for 1-2 cm. before branching to form the cotyledon.

The artery and vein which enter the placenta to form the vascular stalk of the cotyledon, lie as a rule side by side. They may remain intact until the primary divisions of the cotyledon

begin, but sometimes this trunk will divide into two or more divisions of varying size and it is often difficult to be certain which is the main trunk. The artery and vein in these divisions divide more or less at the same time.

The artery and vein supplying a cotyledon have been described as running side by side but occasionally the vein in order to reach the cotyledon may describe a simple spiral over the artery which is running straight or the artery may describe a simple spiral over the vein. This spiral is essentially simple, consisting of one or two turns, and not comparable to the spiralling of endometrial vessels.

In all of the placentae examined there was no evidence of a collateral circulation; each cotyledon has its own separate blood supply.

DISCUSSION.

In this present study the anatomy of the foetal placental circulation differs in several ways from previous published work. The differences are mostly due, it is believed, to the inherent limitations of the injection-corrosion

technique which leaves only a cast of the arteries and veins and not the actual vessels. For example, Romney and Reid[64] described a dual arterial supply to a cotyledon at the margin of the placenta. In the digested and injected placenta it is quite clear that a collateral circulation does not occur. It is possible that the disadvantages of the corrosion technique may explain the findings of Romney and Reid. At the periphery of the placenta neighbouring arteries are quite near to each other and spilling of filler could create the artefact of a collateral circulation. Again, it has been shown in this study that all vessels end ultimately in cotyledons and such a finding is not possible when the placenta has been removed by corrosion because there is no way of checking that all vessels have been filled. The absence of foetal vessels which might be concerned in the nutrition of the placenta has been mentioned. This finding has been commented on by Zeek and Assali (1952)[80] who wonder if the placenta is nourished by the maternal circulation. Spanner described an

arrangement about the main vessels resembling vasa vasorum, and indeed in the present placental preparations small vessels can be seen arising from the main vessels. These could conceivably be mistaken for vasa vasorum, but examination of the digested specimen shows that all of them end in cotyledons, often extremely small. The present writer would not care to be dogmatic about this matter; vasa vasorum may well exist and as yet have not been seen.

Romney and Reid[64] and also Wilkin[78] have described spiralling of the vessels to the cotyledons, and a relationship to the coiled arterioles in the ovary and uterus has been suggested. This effect of spiralling has also been noted in the present study but it is a simple spiral of one or two turns involving either artery or vein and is clearly due to the artery or the vein passing the one over the other in order to enter a cotyledon side by side.

In contrast to Spanner, no valve-like structures have been seen in the main venous trunks. The absence of these valves has been

commented on previously by Romney and Reid. Constrictions due to the investing chorion have been seen running transversely across the main venous trunks and this could presumably produce the impression of a valve-like structure. Further dissection and histological study will be necessary to confirm this point.

SECTION TWO.

THE ANATOMY OF THE COTYLEDON.

THE ORIGIN OF THE COTYLEDON.

A cotyledon can be described as that portion of the foetal placental circulation which will bear at the termination of its smallest vessels, the capillary vessels. The cotyledon is composed of a system of dividing and sub-dividing arteries and veins, the divisions becoming more numerous as the periphery is reached. It can be formed in a number of ways. Most commonly it is derived from the arteries and veins which have been seen to perforate the foetal surface of the chorion. The cotyledons derived from such vessels may be of different sizes, the larger ones originating from the larger vessels. Again, the cotyledons may be derived from the deep surface of the vessels on the foetal chorion and enter the placenta directly and are not seen from the foetal surface.

Cotyledons are in three sizes, large, medium, and small, and the average placenta contains about two hundred. The large are the least numerous and on the average number ten.

The medium cotyledons are perhaps fifty in number, and the small cotyledons make up the remainder. The numbers of cotyledons vary greatly in individual placentae and 200 is only an average figure.

THE STRUCTURE OF THE COTYLEDON.

A large cotyledon at term will be described in detail. It differs in no way from the smaller cotyledons except that being larger, there are more branches.

The large cotyledon extends to the maternal decidua and takes part in the fixation of the placenta. This also applies to the medium cotyledon. The primary vascular trunk containing artery and vein, which will form the cotyledon, run side by side as a rule and are firmly invested by chorion. It varies in length from 1 to 2 centimetres before dividing. These details are illustrated by Figure 4.

Figure 4. This photograph shows a placenta still attached to the uterus. The chorion has been reflected upwards. The primary vascular trunks which form the cotyledons are seen perforating the chorion. The bare areas

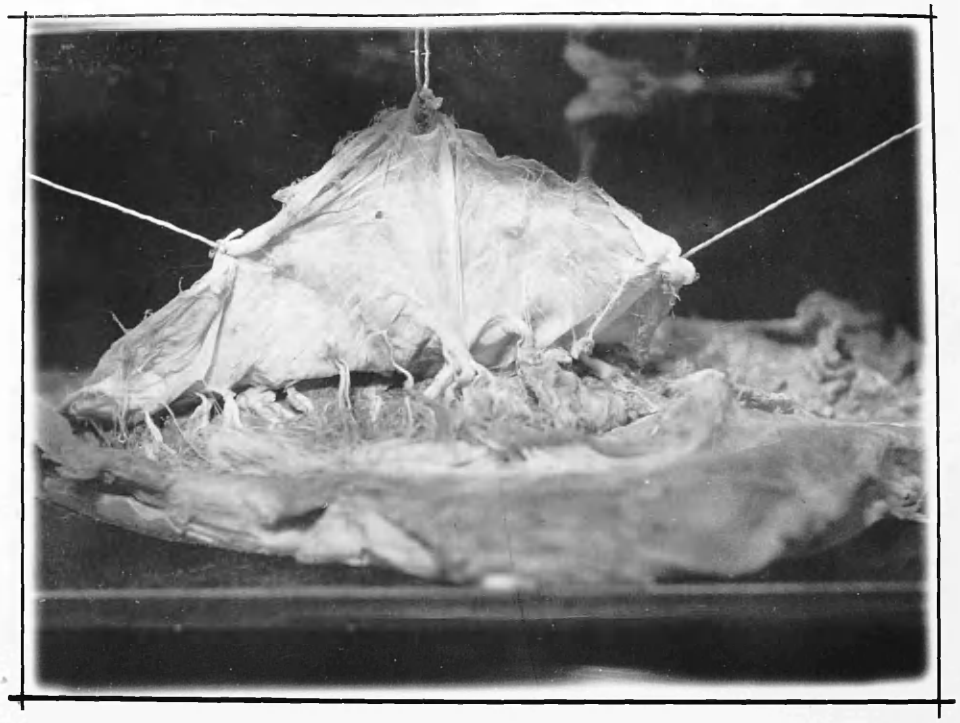

Figure No. 4. Life size.

between the origin of the vascular trunks are most apparent. The cotyledons are seen to be in very close apposition to each other, but between their superior surfaces and the chorion considerable free space is present. This free space is created by the separation of the superior surfaces from the chorion during digestion and is largely an artefact.

The type of primary division falls into two groups. In one group the vascular trunk divides into two or perhaps three secondary branches of equal size and occurs most commonly in the dispersed variety of placenta. In the other group the first division produces a large number of equal secondary divisions, perhaps six or more and this occurs more often in the magistral variety. However, in many placentae the mode of divisions is much less clear and is a mixture of these two groups. The subsequent divisions of the secondary trunks appear to be the same in each group and no clear distinction can be made. The secondary trunks all contain artery and vein and both vessels in the primary

trunks divide at the same time. These secondary vascular trunks divide again and continue their division until the fringe of the cotyledon is reached. The mode of division is dichotomous in nature. At all levels in the primary, secondary or subsequent divisions extra divisions are produced and these tend to obscure the pattern of repeated division. At the fringe, the vessels have the calibre of arteriole and venule and these bear as lateral projections the capillary vessels. Figures 5, 6 and 7 illustrate these points.

Figure 5. This shows a large cotyledon, which has been sufficiently dissected to demonstrate its basic structure. The division of the primary vascular trunks into secondary divisions and the subsequent division of these branches, is also shown.

It will be apparent that the bulk of the small branches are borne peripherally leaving the larger branches comparatively bare.

Figure 6. The cotyledon in this photograph has been dissected more completely. The primary and subsequent divisions of the vascular trunks

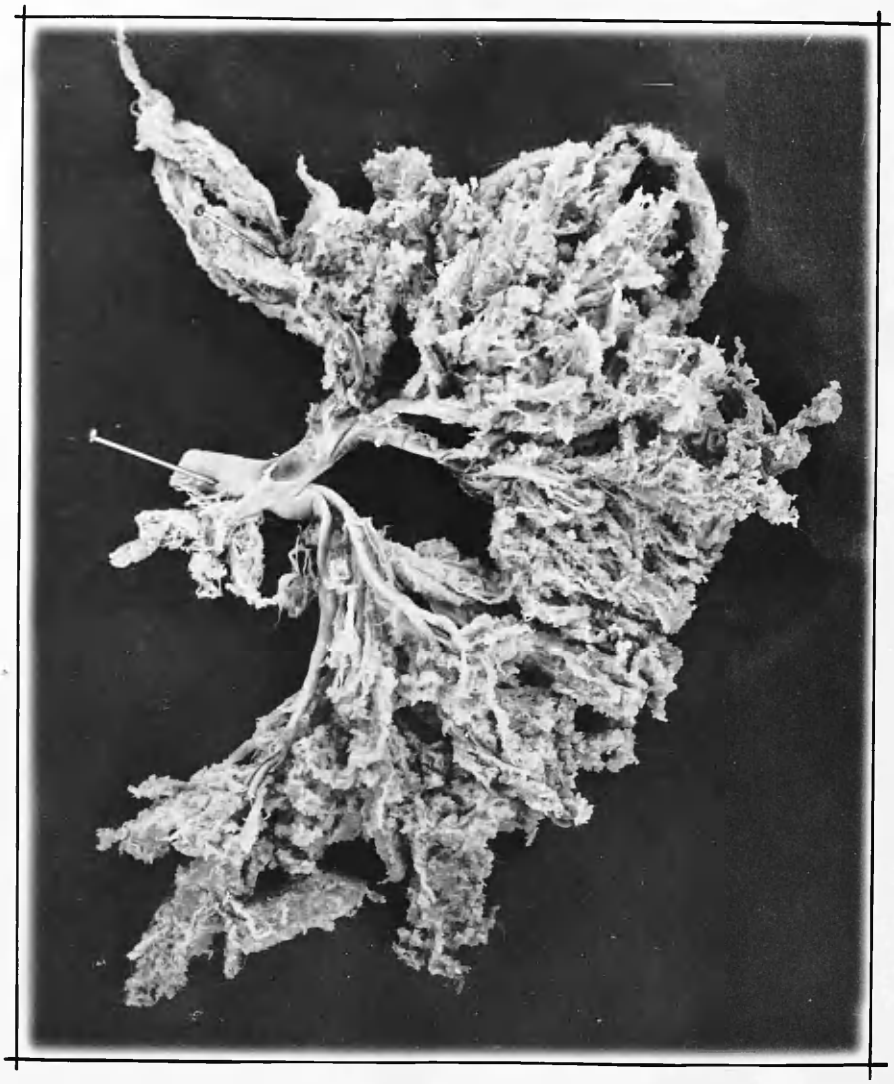

Figure No. 5. X 2.

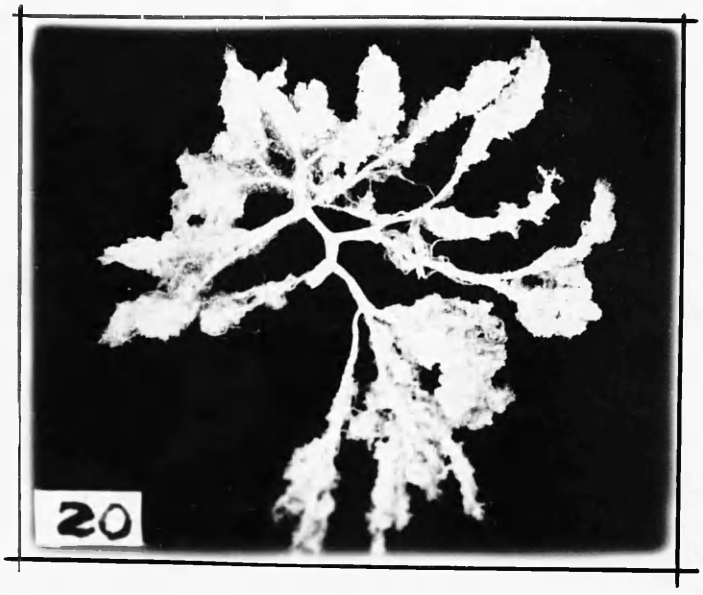

Figure No. 6. X 2.

are clearly seen. This type of regular dichotomous division is found most commonly in the "dispersed" type of placenta.

Figure 7. This is also a dissected cotyledon but the division of the primary vascular trunk has produced a great many secondary divisions. This type of division is found more commonly in the "magistral" variety of placenta.

Anatomical dissection is unsatisfactory at the "fringe" level and the anatomy is best studied in microscopic preparations. The secondary divisions have the effect of partitioning the cotyledon into a series of sub-cotyledons and this effect is intensified by the subsequent divisions. The whole cotyledon rapidly increases in bulk, in consequence of these divisions, as the periphery is reached. Although the sub-cotyledons are separate structures it is apparent, on dissecting a cotyledon, that in life they are very intimately related to each other. At their common surfaces there is considerable intermingling of vessels and this also applies to

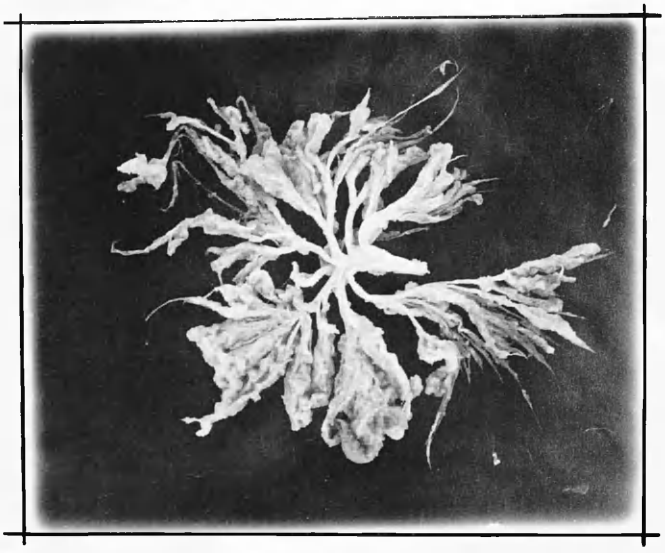

Figure No. 7. Life size.

the vessels within each sub-cotyledon. This intermingling of vascular trunks indicates that there is a continuity of placental tissue throughout the whole cotyledon. Also, since neighbouring cotyledons send interdigitations into each others substance, and in addition show intermingling of small vessels at their related free surfaces, there is quite evident continuity of placental tissue throughout the entire length and depth of the placenta.

The large cotyledon is cone shaped, with its apex at the chorion and its base against the decidua. On coronal section it has a thick outer rim of "fringe" and a centre of the larger vascular trunks which are comparatively free from small vessels. This effect is more clearly evident when a cotyledon is dissected. On the outside, on all surfaces, only fringe is seen, and the larger vascular trunks only appear when the smaller branches of the fringe can be separated from each other and the interior exposed. In terms of the circulation of maternal blood this arrangement implies that there will be

considerable opposition to the flow of maternal blood at the "fringe". The opposition will however, be very much less as the interior of the cotyledon is reached, and be minimal in its centre. The branches of each cotyledon nearest to the maternal surface of the chorion are often adherent to it and this implies that the maternal blood will be within the cotyledon at all times, except perhaps immediately under the chorion. The idea of a "lake" of maternal blood, as visualised by Spanner,[70] within the placenta is not borne out by the structure and relationship of the cotyledons.

The medium sized cotyledons show the same anatomical arrangement as the larger ones, and are distinguished only by their smaller size. In some placentae it is difficult to make this distinction as they are all of similar size.

The small cotyledons never reach the decidua and are, of necessity, found under the maternal chorion and frequently show adhesions to it. They are the most numerous but are frequently no bigger than one centimetre in length and of

negligible weight. This constrasts with a large cotyledon which may be 5 centimetres long and weigh 5 grammes. The structure is simpler, since after fewer divisions the fringe is produced. However they have basically the same structure, and the smaller vessels intermingle with each other and the "fringe" of larger neighbouring cotyledons. The continuity of placental tissue appears therefore to be complete.

THE FIXATION OF THE COTYLEDON.

This aspect of placental anatomy is best studied by examining placentae still attached to the uterus. However, many mature placentae are delivered with the decidual coating over the lobes remarkably complete and very suitable for study. When a cotyledon is separated from the decidual coating over its base, it is apparent that some areas of the base are more adherent than elsewhere. These adherent areas vary in number and position over the base, and if the placenta has been injected with a coloured dye these areas fill badly and stand out in contrast to the surrounding well coloured areas of the

cotyledon.

In these areas the most peripheral vascular trunks run into the decidua and end blindly. Above them are vascular trunks pursuing the same course but not entering the decidua and curving back into the placenta again. The downwards and upwards course of these vessels is, of course, the "chandelier" arrangement of Spanner but those that do enter the decidua end blindly. The probable explanation for this is found on histological examination. The "end" peripheral vascular trunks possess foetal vessels which are undergoing an obliterative periarteritis and endarteritis. This explains why they fill badly with filler or dye. It would seem rational to assume that as the vascular degenerative changes proceed with increasive placental maturity the terminal or "upwards" part of the vascular trunk atrophies and disappears. As a further proof of atrophy it is observed that these vascular trunks produce very few small vessels, and therefore few capillaries. Their metabolic activity appears to have been

subordinated to the mechanical one of fixation. At the periphery of the placenta the same fixing trunks are seen around its whole extent. They are elongated cotyledons and after entering the decidua may run in it for 1 cm. or more before ending. The vascular trunks of such cotyledons are usually solid and show no vessels within them.

THE "BARE" AREAS OF CHORION.

On dissecting a digested placenta it becomes apparent that considerable bare areas of maternal chorion intervene between the origins of the vascular trunks of the cotyledons. These areas are not artefacts and are found in all placentae. This finding might indicate that there is considerable free space in the placenta and a "lake" of maternal blood quite possible. It is more rational to assume that they are completely filled by the cotyledons when distended with maternal blood. These bare areas do indicate however the large volume of maternal blood which is present in the placenta at any unit of time.

THE LOBES OF THE PLACENTA.

The lobes of the placenta constitute one of its most conspicuous features. They have been described and commented upon by many writers. They number on the average twenty to forty but the precise number is never certain because they are separated by grooves or fissures of varying depths and completeness. In consequence many lobes blend into their neighbours and make a precise count difficult or impossible.

The dissection of a placenta reveals that the lobes are aggregations of cotyledons all intimately related to each other. The numbers of cotyledons and their size determines the bulk of the lobe. The grooves between them indicate in a general sort of fashion the boundary between adjacent groups of cotyledons. Figures 8 - 15 illustrate the structures described above.

Figure 8. In the preparations shown in the photograph the placenta is still attached to the uterus. In the upper preparations the placenta has been left undisturbed. In the lower preparation the placenta has been gently separated except in these areas where fixation is more

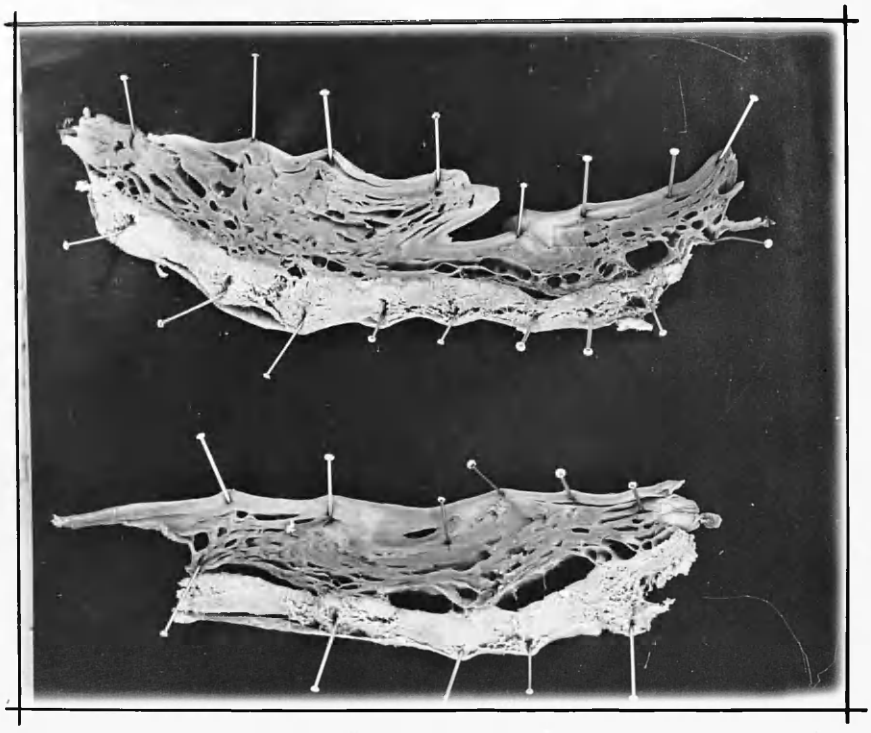

Figure No. 8. Life size.

intimate. The tremendous development of the maternal vessels beneath the placenta is most apparent.

Figure 9. This photograph shows sections of uterine wall removed from the vicinity of the placental site. It is apparent that the maternal vessels increase as the placental site is reached, and are greatest under the placenta.

Figure 10. A fixing area of cotyledon has been gently removed from the uterus along with its related decidua. The peripheral vascular trunks of the cotyledon are seen to be inserted into the decidua where they end without any suggestion of emerging from the decidua and re-entering the placenta.

Figure 11. A single fixing trunk has been dissected free and is shown in this photograph. The dark areas at the ends of the divisions are portions of decidua into which the terminations of the vessels were inserted. The absence of small branches from these vessels is quite evident.

Figure 12. The terminations of the fixing

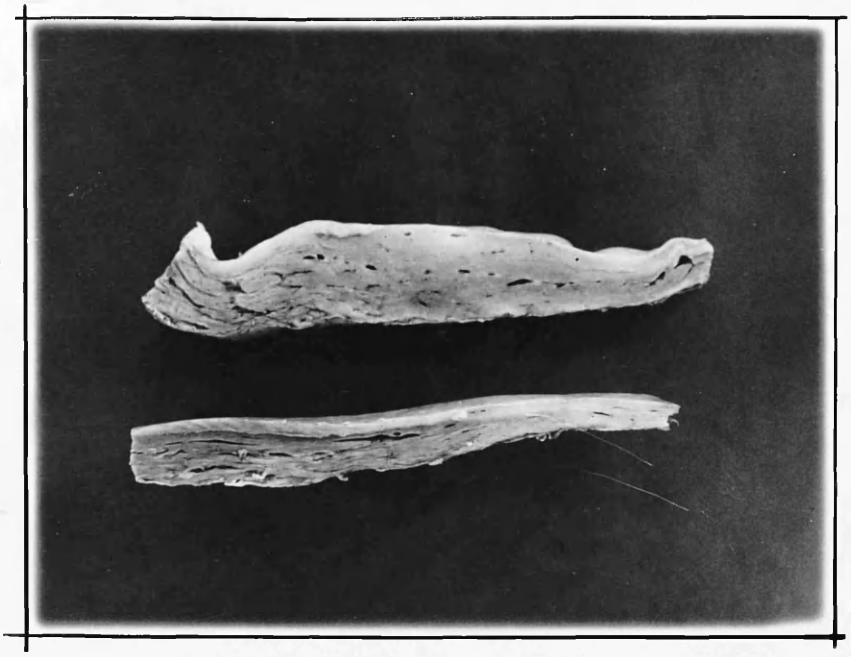

Figure No. 9. Life size.

In each strip of uterine tissue the placental site is on the left.

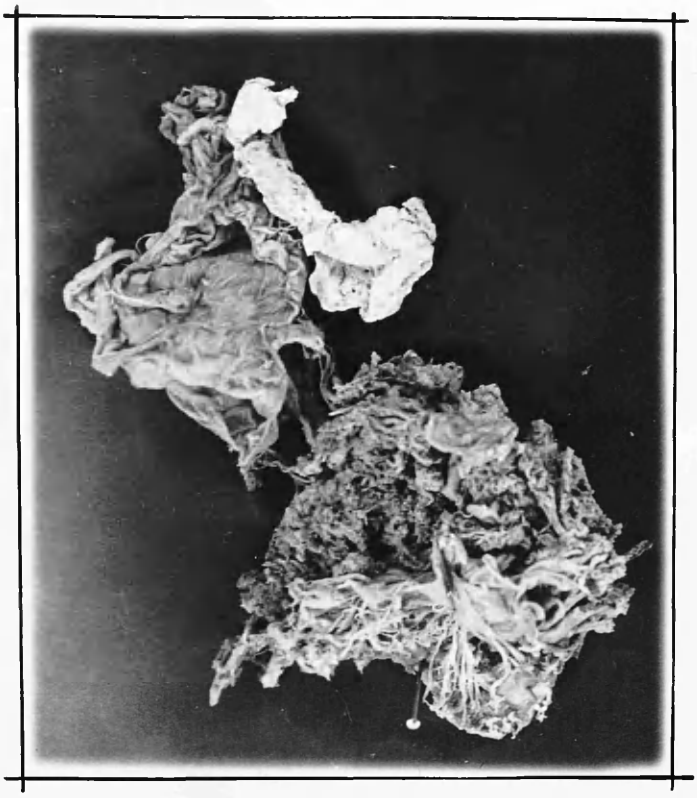

Figure No. 10. Life size.

Figure No. 11. X 80.

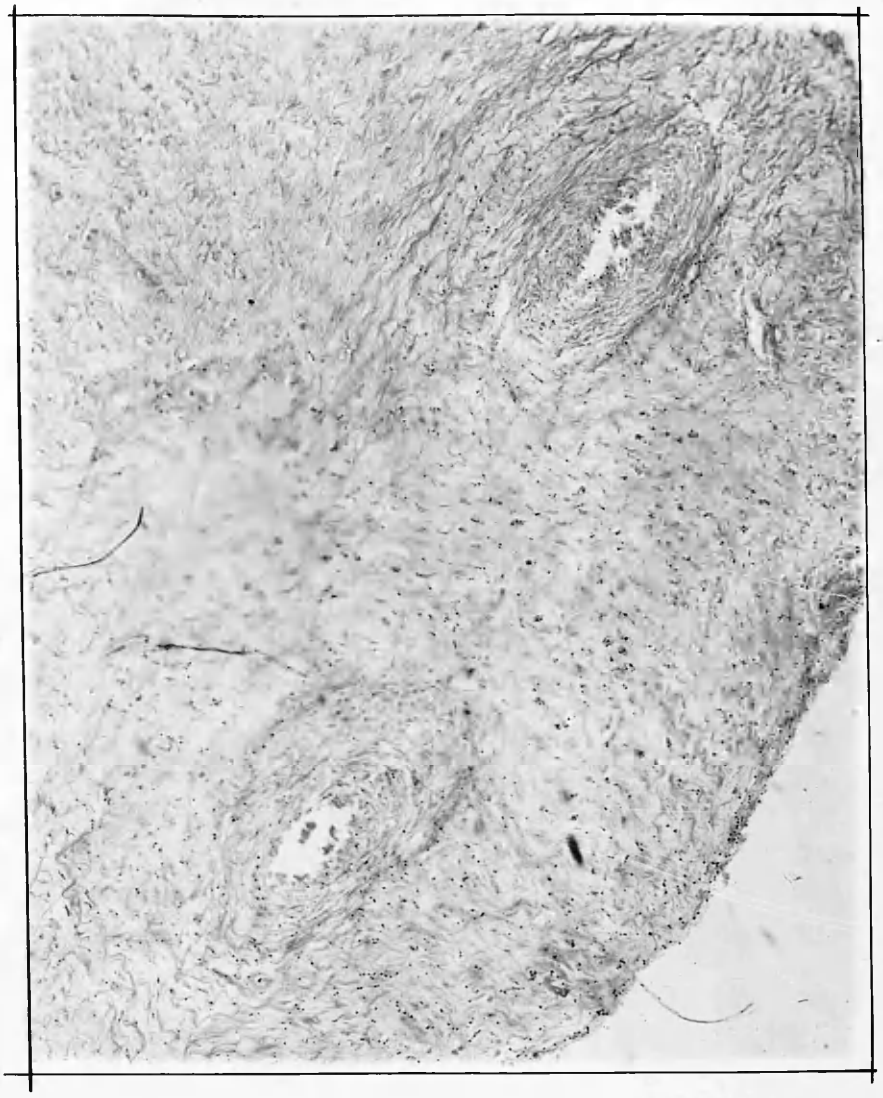

Figure No. 12. X 400.

trunks when examined histologically show an obliterative endarteritis of the vessels in the trunks. Some vessels are closed completely or, as in the photograph, obliteration of the lumen is not yet complete. These vessels fill badly with "filler" and in corrosion specimens are not preserved. This may in part account for much of the controversy regarding the presence or absence of Spanner's "chandelier" arrangement of the villi.

Figure 13. This photograph demonstrates the 'fixing' trunks at the periphery of the placenta. The chorion has been reflected upwards to expose their origin from the chorion and their insertion into the maternal decidua.

Figure 14. A single fixing trunk has been removed from the periphery and is shown after dissection. The divisions are long and elongated and show comparatively few side branches. The dark areas at the ends of the divisions are the portion of decidua into which they were inserted in situ.

Figure 15. These peripheral fixing trunks are,

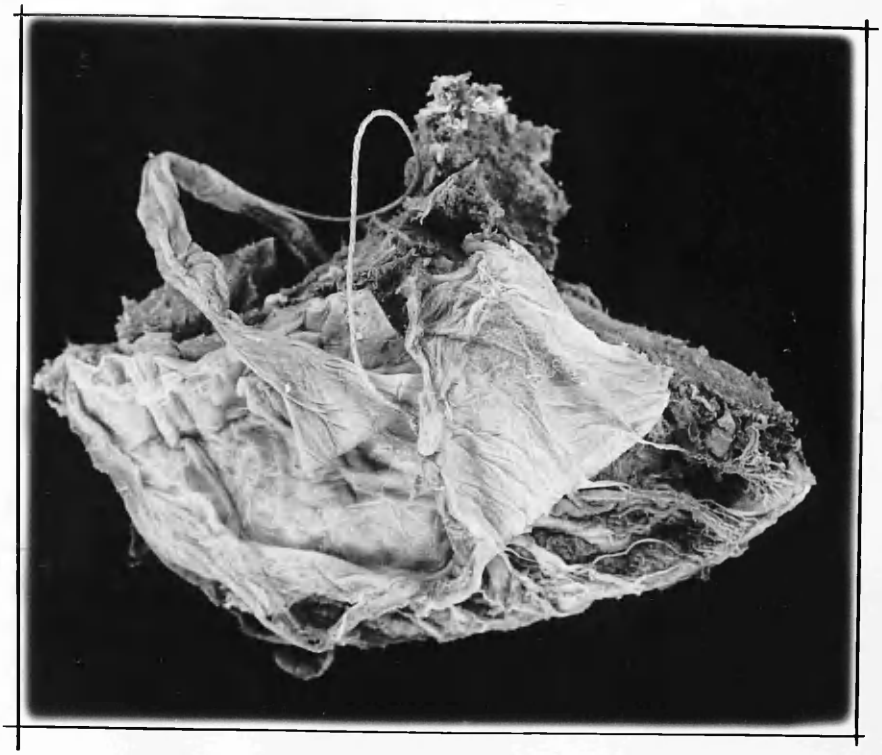

Figure No. 13. Life size.

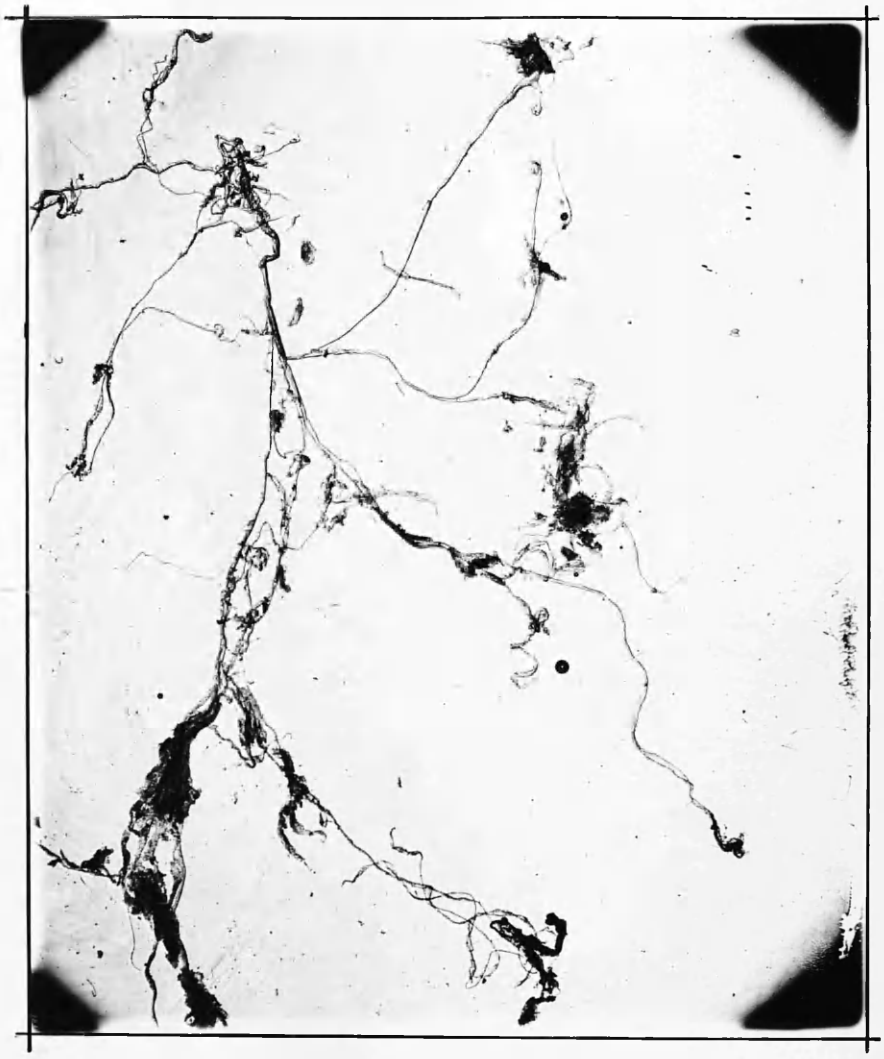

Figure No. 14. X 80.

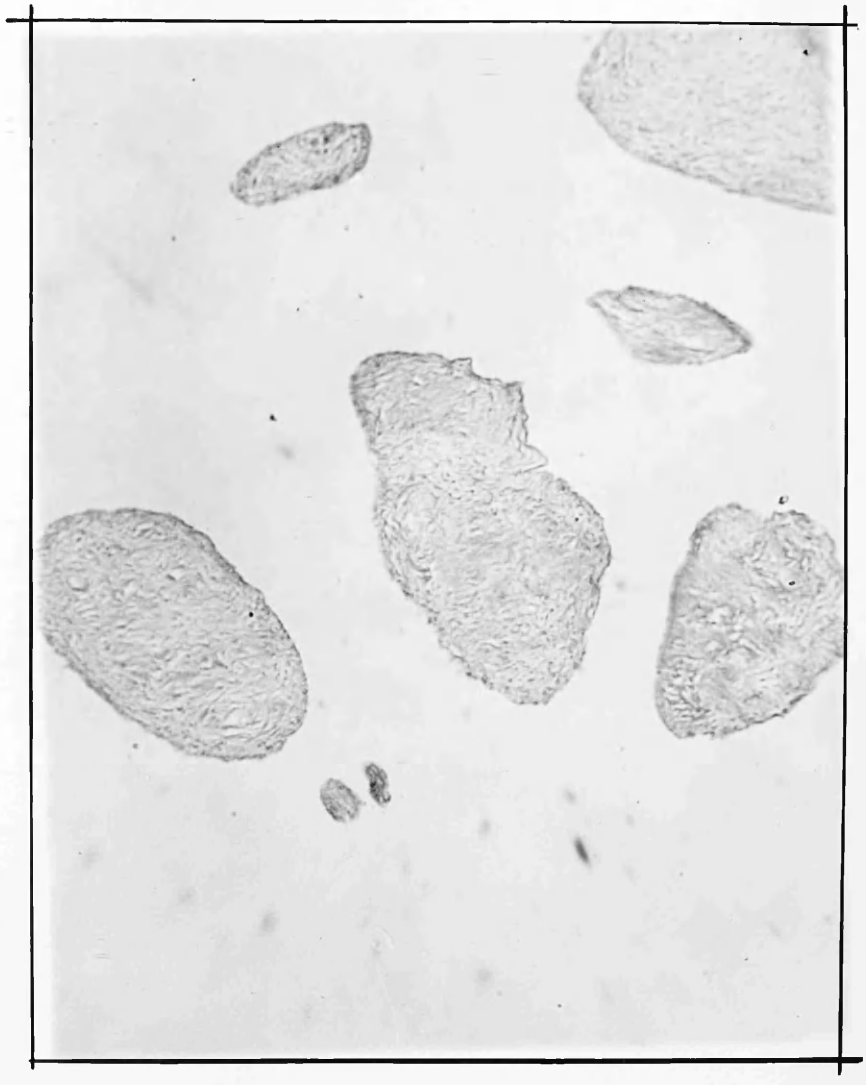

Figure No. 15. X 400.

when examined histologically, seen to be quite solid. Vessels are rarely seen within them. These trunks, since 'filler' would not enter them, do not survive corrosion.

SECTION THREE.

THE ANATOMY OF THE VILLUS AND ITS CAPILLARY STRUCTURE.

THE ANATOMY OF THE VILLUS AND ITS CAPILLARY STRUCTURE.

The anatomy of this region of the placenta is without doubt the most interesting and the most difficult to study. The technical difficulties in the way of a complete demonstration of placental capillaries have been alluded to already. It has also been pointed out that digestion of this area with trypsin makes dissection very much easier and, in consequence, has led to the complete demonstration of the capillary vessel. The capillary vessels and their covering syncytium represent the areas of the placenta where vital metabolic activities are occurring which ensure the survival and growth of the foetus. It is no truism to declare that a more complete anatomical understanding of this region will undoubtedly lead to a better understanding of the physiology and pathology of the placenta.

The "fringe" area of the cotyledon or the "Gitterzotten" of Stieve is made up of the terminal divisions of the cotyledonary vascular trunks

which at this level have the calibre of arterioles and venules. These vessels bear the capillaries as lateral projections in their course and end themselves in capillary vessels. These capillary vessels are enclosed by syncytium which forms a complete covering and more proximally blends with the chorion enclosing the larger vessels.

The "fringe" area is formed at the peripheral region of the cotyledon and, as already explained, covers the entire cotyledon. This covering is much more complete and dense at the base and sides of the cotyledon than it is at its apex. It forms a very characteristic and striking feature of the digested cotyledon after dissection. When floated out in water some idea can be obtained of the tremendous extent of the capillary bed in each cotyledon. The fringe is not so apparent where the fixing trunks are sited and this is related to the comparative absence of capillary vessels at these areas. The presence of "fringe" really indicates the areas concerned with metabolic

activities rather than the fixation of the placenta.

The first demonstration of a complete capillary vessel appears to have been made by Finn Bøe in 1953.[10] Browne (1950)[81] has shown a complete capillary with its covering syncytium, but the illustration did not make it clear whether this represented an actual villus or a drawing of one. The preparations of capillary vessels which were made by Finn Bøe were obtained by injecting the foetal vessels with indian ink and teasing the fringe material apart to separate capillaries from each other. They resembled very closely the results which were first obtained by the author in a subsequent year (1955). These preparations were of great interest but were hardly good enough to enable a precise study of the capillary vessels to be made. Finn Bøe was of the opinion that four vessels probably were concerned in the formation of the capillary structure within the villus and was of the opinion that a vascular anastomosis existed.[64] Romney and Reid (1951) were of the

opinion that capillary vessels were extremely numerous but rather short structures. This opinion was based on the fact that the origins of the capillary vessels were only 1 mm. apart. It should be made clear that these authors showed only incomplete preparations of capillary vessels. Spanner, much earlier (1935) had been of the opinion that capillary vessels were very long structures. Romney and Reid believed that the disposition of the capillary bed was greatest nearest to the decidua and least under the chorion. Wilkin (1954) shared this opinion and pointed out that it was situated around the periphery of the cotyledon rather than within its centre. Figures 16 and 17 illustrate the structure of the "fringe".

Figure 16. This photograph shows the "fringe" or capillary region of the cotyledon. The larger vessels have filled with dye but this has not extended into the capillary vessels. The use of a dye is necessary to reveal the structure of these delicate and numerous vessels.

Figure 17. This photograph shows in much higher magnification the terminal branches of the

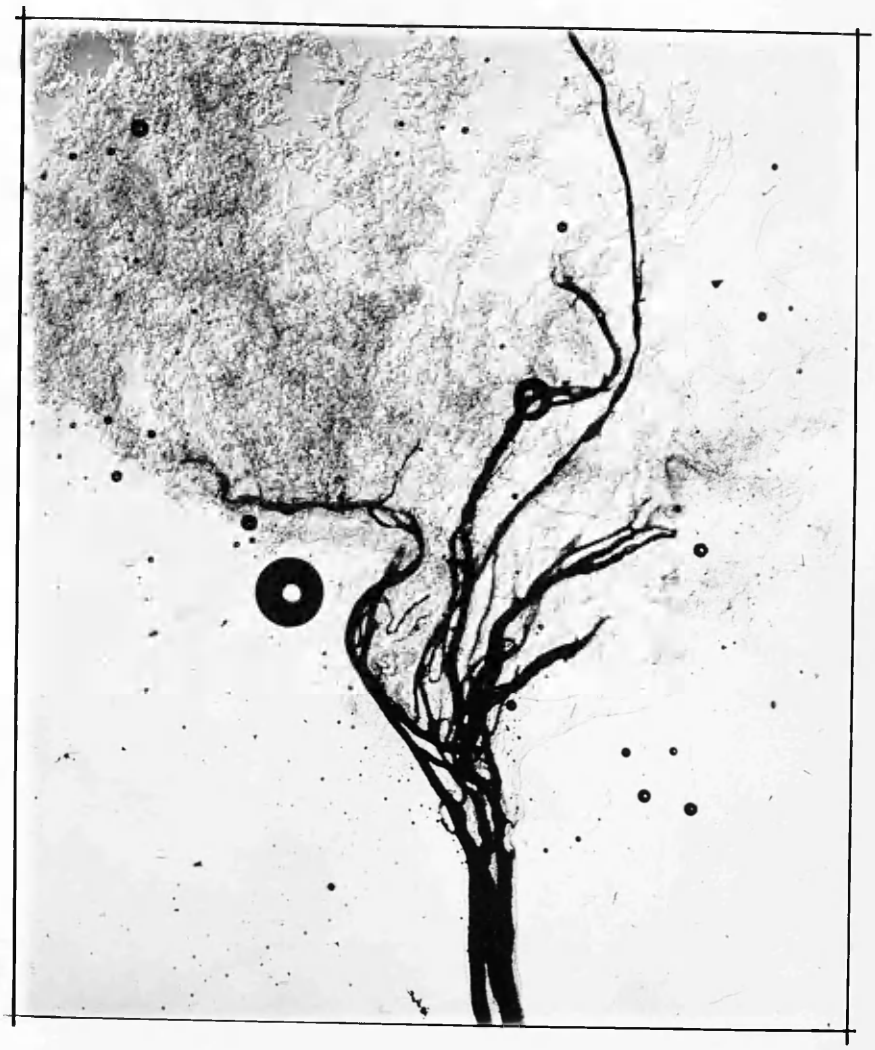

Figure No. 16. X 80.

Figure No. 17. X 80.

cotyledon. The capillaries appear as balls of tissue and are formed by an aggregation of many capillaries. This aggregation is produced as an artefact by the method of preparation, and is of no value in studying capillaries but shows very well the terminal divisions of the cotyledon.

THE ANATOMY OF THE CAPILLARY VESSEL.

Introduction:

The use of trypsin in the elucidation of the anatomy of the "fringe" area has simplified the task. Preparations are readily made of capillary vessels and have permitted the total number and structure of the vessels within the villus to be seen. It has been found by experiment that capillary vessels are much more completely filled if the vein alone is filled with dye. If artery and vein are filled simultaneously the penetration of dye is incomplete and this is presumably due to the inability of fluid within the capillary vessels to escape in front of the dye, and so allow full penetration.

THE CAPILLARY VESSEL.

The size, number and complexity of the capillary vessels vary greatly. As a rule the first capillaries given off by the parent arteriole and venule are small and simple structures. In the earliest preparations made they consisted of single capillary vessel passing from the arteriole to the venule and showing, in its course, very few convolutions. The syncytium covered the entire vessel and where convolutions occurred they were reproduced by corresponding elevations of the syncytium. In later preparations, by modifying the technique, it was found that in addition to the peripheral capillary vessel there was a central system of vessels, freely anastomosing with each other and with the peripheral vessel. The calibre of these central vessels appeared to be less. In the formation of this vascular structure four separate vessels were concerned. They could be seen entering the base of the villus, side by side, and subsequently forming the anastomosis already described. These vessels were, of course,

not all in one plane.

More distally the capillary vessels became longer and more complicated. They showed more and more convolutions and the final capillaries were large and extremely complicated structures. The convolutions were not all in one plane and were, as before, reproduced by projections of the covering syncytium. The system of anastomosing vessels within the villus was again present, but frequently very complex and not easy to follow. The most complicated capillary vessels were found in the most peripheral regions of the fringe. Many of them showed a remarkable resemblance to a renal glomerulus. Vincent Hall (1956)[35] in studies of the human renal glomerulus has described the structure of the capillary vessel within it. It consists of a peripheral vessel with a central system of anastomosing vessels within it which also communicate with the peripheral vessel. This description resembles very closely the vascular structure of the placental capillary. It seems reasonably certain that an anastomosing system

of such vessels must indicate, at the least, the presence of a vascular shunt. In view of the ability of the renal cortex to divert blood by a shunt mechanism, it is not unreasonable to assume that this can occur also in the placenta.

Figure 18. This photograph shows the type of capillary preparation obtained when the parent artery and vein are injected simultaneously. A very long convoluted capillary vessel is present, with its convolutions reproduced by the covering syncytium and forming lobulated projections. The nuclei of the syncytium are most apparent.

Figure 19. This more complicated capillary vessel is generally seen in the most peripheral regions of the fringe. Many vessels are present within the villus and with its covering syncytium is not unlike a renal glomerulus.

Figure 20. This preparation was obtained by injecting only the parent vein with dye. The villus is a comparatively simple structure but a system of anastomosing vessels is clearly

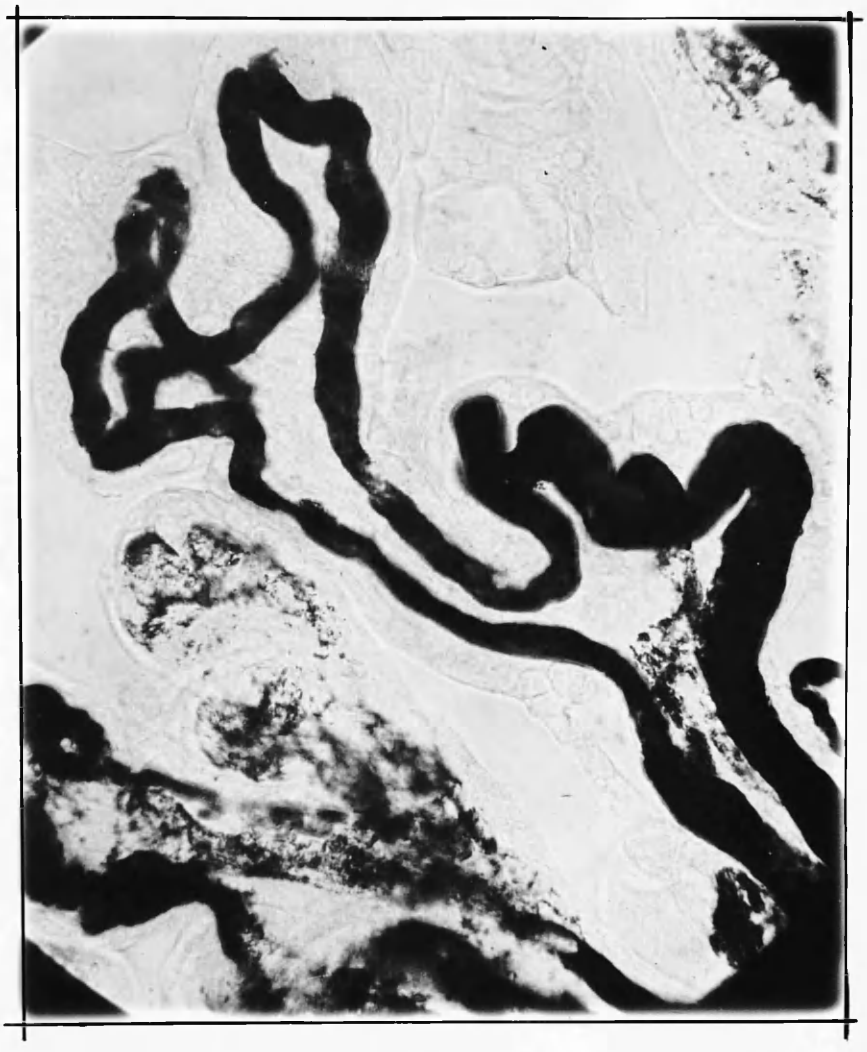

Figure No. 18. X 700.

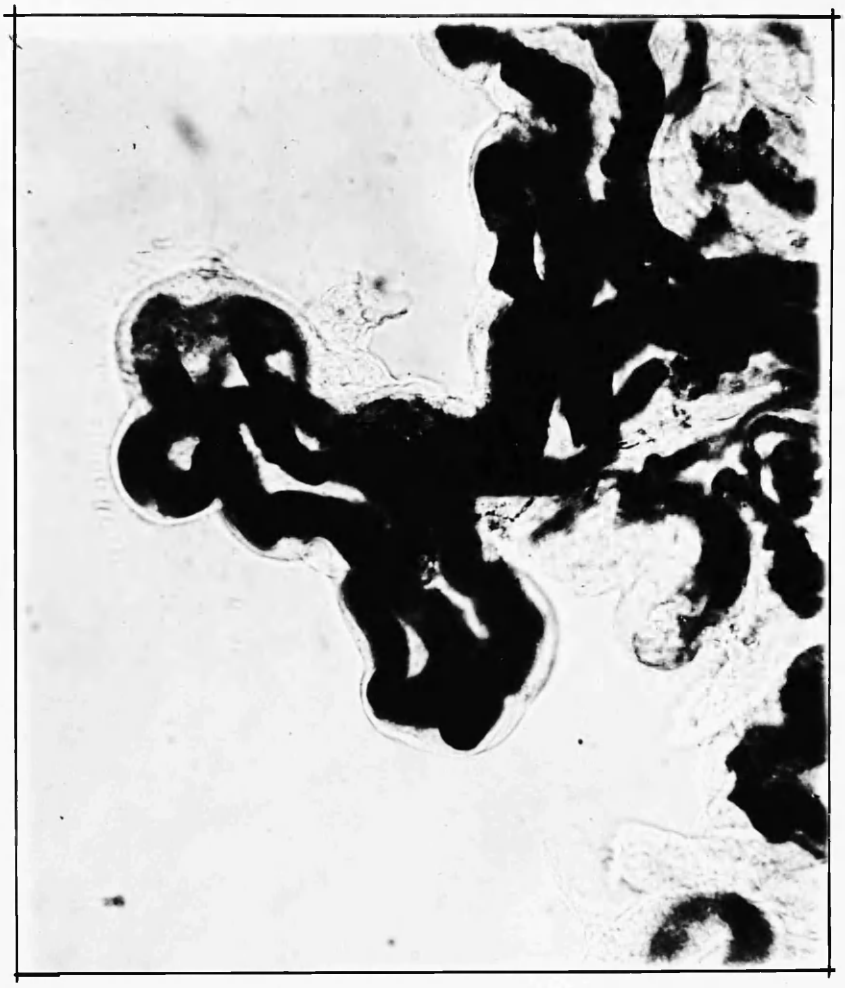

Figure No. 19. X 700.

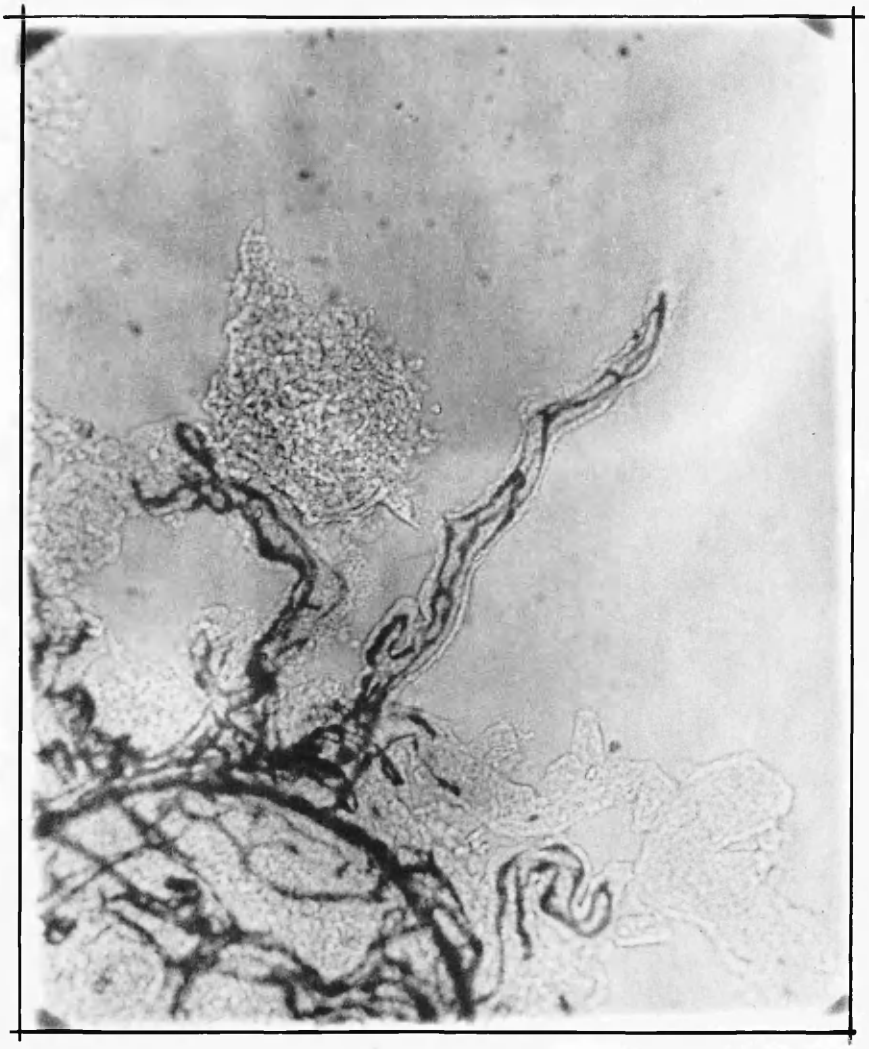

Figure No. 20. X 200.

present within it.

Figure 21. This villus shows very clearly the system of anastomosing vessels present. It will be seen that the vessels all arise from four parent vessels which enter the villus at its base.

THE ANATOMY OF THE VILLUS.

It has been shown that the convolutions of the capillary vessels in the villus are reproduced by projections of the covering syncytium. These syncytial projections are frequently large enough to constitute lobules and within them are the convolutions of the capillary vessels. Thus in the most complicated capillaries the villus is a multilobulated structure in three dimensions. The conception of a villus as a simple glove must be modified except in the very simplest capillaries. It becomes apparent that the convolutions of the capillary vessel, in three dimensions, ensures that the maximum surface area of foetal vessel wall is being displayed to the maternal blood. Its structure is shown by Figure 22.

Figure 22. This specimen shows very well

Figure No. 21. X 400.

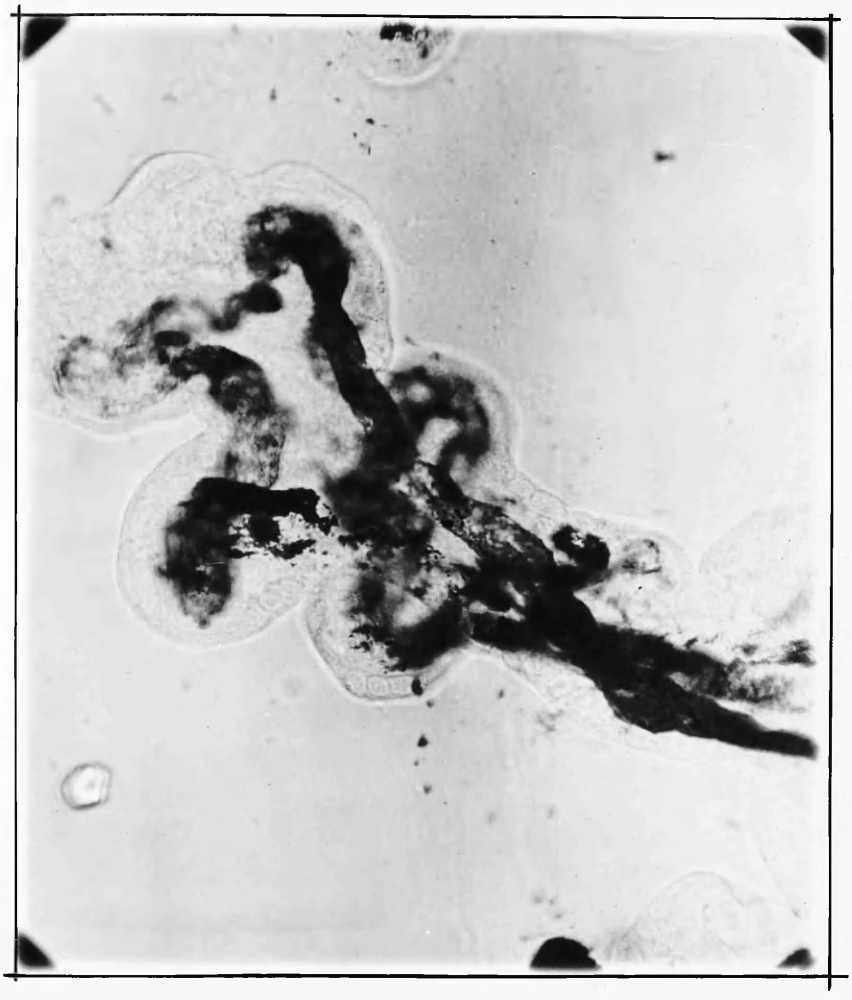

Figure No. 22. × 700.

the convolutions of a villus. The convolutions are large enough to constitute lobules each of which contain a complex loop of capillary vessels. It will be apparent that random histological section through the lobules would appear to show "villi" adhering together by syncytium.

THE DISPOSITION OF THE CAPILLARY BED.

It has been already pointed out that the disposition of the "fringe" region of the cotyledon is most dense nearest to the decidua and around the sides and least under the chorion. In other words the fringe is peripheral and not central. Since the "fringe" region is composed of villi and their parent vessels it follows necessarily that the capillary bed has the same disposition.

The studies of the capillary bed made by the digestion technique, reveal that the villus is a multilobulated structure with the lobules in three dimensions. Within the villus is an extremely long and complicated system of anastomosing vessels which run in three dimensions

and display the maximum surface area of vessel wall. The villi are peripheral rather than central, extremely numerous, and demonstrate in a very real fashion the extent of the capillary bed of the placenta. This in turn must indicate the tremendous foetal requirements of oxygen and other metabolites for its survival and growth.

The presence of lobules, all arising from the same villus explains in part the frequent finding of syncytial adhesion between villi. In histological section the "villi" will be frequently lobules and the syncytial adhesion between them the continuation of a common syncytium. Where "villi" or lobules arise from the same villus it will be possible, as pointed out by Stieve (1940)[72], to demonstrate vessels passing from one "villus" to another. This sharing of blood vessels only indicates the continuation of a common system of vessels within the villus proper.

PART TWO.

A STUDY OF PLACENTAL GROWTH.

Foreword

In Part One of this thesis the anatomy of the placenta was discussed at considerable length. This full discussion was deliberate and was intended to make clear the observations on placental growth which will be made in Part Two. The study of growth in any structure necessarily involves a study of its anatomy, and if this is known the process of growth can be more readily followed. This applies as forcibly to the placenta as to any structure. It is the intention in this study to follow the pattern of placental growth at several of its growth periods from the early weeks of pregnancy until full term at 40 weeks. At each of these growth periods the main features of placental anatomy will be presented and compared. By doing so the alterations in the anatomy of the placenta will be apparent and indicate the mode of its growth. In this study the embryological growth in the very early days of pregnancy has not been considered. It is beyond the scope of this study to make any such contributions.

Studies have already been made by many authorities including Hertig and Rock[40, 84] mainly, Teacher and Bryce[75], also Wislocki and Streeter,[85] Hamilton, and others.[37,38] The early development of the human embryo has been reviewed by Hamilton (1950).[37] Since the early development of the embryo necessarily includes also the first stages in the development of the placenta, it is proposed to give a short account of this process. The account will follow closely that given by Hamilton and will make more understandable the growth in the later weeks of pregnancy.

At seven days old the embryo is partially implanted into the decidua. This implanted portion of the trophoblast constitutes the embryonic pole. The free portion of trophoblast is termed the abembryonic pole. The implanted trophoblast has already become a thick proliferating layer, differentiating into syncytio-trophoblast and cytotrophoblast, and already invading the maternal decidua. By the ninth day the entire trophoblast is undergoing proliferation but this is most marked at the

embryonic pole. Spaces or lacunae are already present in the syncytio-trophoblast and are separate from each other, but contain little maternal blood. These spaces represent the earliest stage of the utero-placental circulation which has been observed. By the tenth day many lacunae contain maternal blood and communicate with each other and represent the beginning of a proper lacunar circulation. The syncytio-trophoblast is invading the maternal tissue by broad pseudo-podial outgrowths. The trophoblast layer has acquired, on its foetal surface, a lining of mesoblast and can now be termed the chorion. At the twelfth day the syncytio-trophoblast has proliferated rapidly and is invading not only the maternal endometrium but capillaries also. The cytotrophoblast is in much smaller amount, and consists mostly of a single layer of cuboidal cells.

From the thirteenth to the sixteenth day the syncytio-trophoblast, which lines the lacunar spaces, sends "streamers" into the endometrium. The cytotrophoblast again proliferates and

extends into the syncytium. These outgrowths of cytotrophoblast, covered by syncytium constitute the primary villi. These quickly acquire a core of mesoblast and become secondary villi. At a later stage blood vessels appear and the villus is now a tertiary or mature villus.

The later stages in the development of the human placenta are less well detailed because of lack of material. In the macaque monkey the process of placental development has been followed in detail by Wislocki and Streeter[85] until the 35th day. It is believed that the stages in development are closely applicable to man. It has been observed that by the seventeenth day in the macaque monkey, the cytotrophoblastic columns fuse at their extremities and form a trophoblastic shell or basal lamina. Between this and the uterine tissue is a layer of necrotic material which might be comparable to the Nitabuch layer of necrotic material which forms at this situation in the human placenta. In both man and macaque monkey the early chorionic villus is nodular and forms a club-shaped villous

sprout. It is believed that the lacunae in both species are formed by spaces forming in the trophoblast. The alternative method that they are formed by trophoblastic streamers enclosing areas of maternal tissue is considered to be less satisfactory.

It will be appreciated that between the end of this period and the formation of the definitive placenta at the twelfth week of pregnancy there is a considerable gap in knowledge with regard to the further development of the placenta. The growth of the placenta after the twelfth week is not any more clearly understood and there are extremely few observations in the literature. This lack of previous work is a testimony to the technical difficulties in the way of any such investigation. There are only two authorities who have made any observations on the macroscopic growth of the placenta. Spanner indicated that the human placenta did not grow in circumferential area during the second half of pregnancy but only increased in thickness. Stieve believed that

this was wrong. He believed that the placenta did increase by circumferential growth at its edge and based his belief on the fact that the placenta at term has a surface area of almost 30,000 square millimetres. The interior of the uterus at the fourth month has only a surface area of 20,000 square millimetres and could obviously not contain a full-time placenta. It follows necessarily that the placenta must grow in circumferential area in the second half of pregnancy! With regard to the mode of growth of the placenta there have been no published studies up to the present time, excepting of course the development of the embryo in the very early days of pregnancy. This has already been considered. Finn Bøe[10] (1953) has published several observations on the vascular growth of the placenta. He described in the arterioles and venules of the cotyledonary fringe a series of intercommunicating vessels between the arterial and venous circulations. In his opinion there was a system of four vessels in the vascular trunks at this

level. Two presumably arterial, and two venous in character. He considered also that this system of four vessels was continued into the capillary vessels of the villi. This reference to the finer vascular structure of the placenta appears to be the only observation of its kind in the literature. He employed indian ink to fill these fine vessels and teased the fringe apart to secure separate vascular trunks which would be suitable for observation. His results were excellent considering the technical difficulties with which he was confronted.

INTRODUCTION

The key to the study of placental growth after the first weeks of development lies in finding a method which would permit a full and detailed dissection of the placenta. The method should permit cotyledons to be dissected readily and completely from their neighbours. Thereafter an individual cotyledon must be fully dissected to reveal its complete structure, its length and its weight. The method must be flexible to permit the use of dyes to fill the

placental vessels and allow observations to be made on the finest vessels and capillary structures. The use of histological methods becomes less and less satisfactory as the placenta gets bigger. There is such a profusion of developing and dividing vessels that random tissue sections could not reveal the smaller vessels and the capillaries in their entirety. It will be shown later that the pattern of placental growth can only be understood if these structures are seen complete. Injection and corrosion techniques are not any more satisfactory. Quite apart from the labour involved in such a study, it would not be possible to fill cotyledonary vessels fully and casts obtained would be, of necessity, incomplete. Thus, the picture obtained of growth would be also incomplete. The most serious objection lies in the fact that the finest vessels would not fill completely and this area, as will be shown later, provides the solution to the precise mode of placental growth.

THE MODE OF INVESTIGATION.

The Rationale of Investigation.

In this study of placental growth trypsin digest has been employed to make possible a complete dissection of the placenta. Placentae have been examined from the sixth week of pregnancy until the 40th week. It was not found possible to study placentae earlier than the sixth week for a number of reasons. The decreasing use of abdominal hysterotomy as a therapeutic measure has prevented the use of early normal placentae. Also, placentae delivered vaginally at this early stage of pregnancy are frequently grossly incomplete or so obviously pathological as to be of little value. Although the absence of such early placentae is regrettable it has not interfered with the purpose of the investigation or affected adversely its findings. Indeed it will be demonstrated that the pattern of placental growth at the twelfth or subsequent week is so clear cut that reasonable deductions can be made of the growth in earlier weeks.

The Materials.

(A) Placentae. Seventy placentae at various growth stages were employed in this investigation. The earliest placenta examined had a maturity of six weeks and the oldest placenta examined was at term. In all cases the placentae had been delivered vaginally and the maturity was calculated from the first day of the last menstrual period. If a maturity date could not be obtained, for any reason, the placentae were rejected. Similarly, placentae which were incomplete or obviously pathological, were also not used. This insistence on reasonably normal material for examination meant a very high rejection rate, and many of the specimens obtained were not used. However, enough reasonably normal placentae were examined to ensure that the growth features obtained in the study were characteristic of normal growth and not evidence of any pathological condition present in the pregnancy. It must be pointed out that all of the early placentae were aborted material but in spite of this many of the

placentae, grossly at least, appeared to be quite normal. The seventy placentae examined were divided into two categories. In the first category, forty placentae were used to demonstrate the gross anatomy at various growth periods. In the second category thirty placentae were employed to demonstrate the anatomy of the smallest vessels and capillaries.

The placentae in category One were divided into the following growth periods.

MATURITY	NUMBER.
12 weeks	Three
16 weeks	Five
18 weeks	One
20 weeks	Two
24 weeks	Seven
28 weeks	Two
30 weeks	One
32 weeks	Four
34 weeks	Two
36 weeks	Two
40 weeks	Eleven
Total	Forty

The thirty placentae in category Two were examined at the following growth periods and the characteristics of the "fringe" area noted in each case.

MATURITY	NUMBER.
6 weeks	One
10 weeks	One
12 weeks	Four
16 weeks	Three
20 weeks	Four
24 weeks	One
25 weeks	Two
26 weeks	Two
28 weeks	Two
30 weeks	Two
36 weeks	One
40 weeks	Seven
Total	Thirty

Only fresh placentae were used and digestion was begun within a few hours of delivery. If any delay was anticipated the placenta was refrigerated in a deep-freeze cabinet until required. The object of using fresh material was to guard against any possibility of artefact by decomposition. It has been found by experience that deep-freezing by itself is an advantage since it haemolysis foetal blood and this assists its removal in the subsequent digestion.

The Rationale of the Digestion Technique.

In histo-chemistry it is the practice to use trypsin for the identification of protein. The material to be studied is digested with

trypsin in an alkaline-medium suitably buffered. Thereafter it is processed in the usual way and if a certain tissue component has disappeared it is certain that it was protein in nature. Also, in pathology, where areas of tissue necrosis are present, parenchymatous tissue disappears before connective tissue and blood vessels and this disappearance is related presumably to proteolytic digestion. In this fashion the idea was conceived of digesting the placenta and removing parenchymatous tissue whilst preserving connective tissue such as blood vessels. Since proteolytic enzymes are the most important trypsin was finally selected, after experimentation, as the most likely enzyme to employ. The conditions under which enzyme activity takes place were also investigated. A buffered environment is necessary for an enzyme and trypsin, for example, requires a medium with a pH of 8. In the case of the placenta, which contains such a complex variety of tissues, it was felt that any attempt to maintain a constant pH would be extremely difficult. It was decided therefore to

adopt a simpler technique and to renew the enzyme solution whenever it was necessary to obtain a more complete digestion.

In practice it has been found that parenchymatous tissue can be readily removed, leaving behind the connective tissue elements which are more resistant to trypsin. It is possible therefore by controlled digestion to remove decidua, chorionic epithelium, and maternal blood leaving behind the foetal vessels, chorion and umbilical cord. Subsequent work, however, has shown that the technique must be modified according to the type of vessel it is desired to study, and the duration of digestion watched carefully. If the main structure of the vascular tree is to be studied, digestion may be allowed to proceed unchecked, but removal of all support from the vessels, in this manner, renders them liable to damage and it is difficult to demonstrate the finer ramifications of the vessels. This is particularly so in relation to the terminal capillaries. These are extremely fragile and if not already attacked by

the enzyme may easily be swept away in any subsequent washing or handling unless extreme care is exercised. It has even been found possible to limit the digestion to the decidual layer leaving the villi complete with their covering of chorionic epithelium. This has greatly facilitated the study of the villus and its constituent capillary.

When digestion is completed the placenta is ready for dissection and this can be accomplished readily and quickly. The method will be described later.

The Technique of Injection.

For injection of the specimens following digestion polythene catheters were employed, of a diameter small enough to enter the umbilical arteries and veins. It is of advantage to cut the catheters straight across and not to a point. The vessel walls are thin and can be penetrated easily. A large hypodermic syringe of at least 50 ml. capacity was used for the actual injection, and finger pressure alone was sufficient to fill the foetal vessels.

A one per cent solution of a water soluble opaque dye made by Imperial Chemical Industries was found to be most satisfactory. "Monolite" for green, yellow, and red; "Monastral" for blue. The arteries and veins may be injected with any of these colours, but red for the arteries and blue for the veins are the most satisfying colours visually. These dyes can be used alone or dissolved in fifteen per cent gelatine solution.

The Digest Solution.

This consists of a one per cent solution of sodium carbonate and is used to immerse the whole placenta or lobe as required. Then to the alkaline solution is added sufficient trypsin powder (British Drug Houses) or liquor trypsin compound (Allen and Hanbury), to produce a one per cent solution of digest.

The Method of Digestion.

The method employed varies according to the variety of structure it is proposed to study, and this will be considered under the following headings.

(a) The Gross Anatomy.

(b) The Growth of the Placenta.

(c) The "Fringe" or Capillary Region.

(a) The Gross Anatomy.

A fresh placenta is washed carefully in cold running water to remove blood clot, and the foetal membranes pared off around the placental edge. The cord is cut short but should be three to four inches in length. The placenta is placed in a round glass container big enough to accommodate the whole placenta lying flat with the maternal surface downwards, and covered completely with the solution of digest, and a few drops of chloroform added. The chloroform reduces very considerably the foul odour which was such a feature of digestion previously. The container is covered and placed in an incubator where the placenta is incubated at 37°C. for a period of 36 - 48 hours. It is of advantage to inspect the rate of digestion frequently during the period of digestion because commercial trypsin varies in its activity and

digestion may proceed more rapidly than was anticipated. If allowed to proceed unchecked trypsin will digest away the whole placenta. When digestion is complete the placenta in its container is placed in a larger vessel or a basin into which a stream of cold water is led gently. The water should not run directly on the placenta. After a few hours the digested material will have been washed away. If it is considered that further digestion is necessary the placenta can easily be replaced in the incubator with fresh digest solution and digestion continued. When digestion is complete the placenta consists only of umbilical cord, chorion and cotyledons.

The specimen is next immersed in 10 per cent formol-saline for approximately one hour. This hardens the tissue somewhat, without producing distortion. Thereafter the specimen is immersed in warm water, the umbilical arteries and vein catheterised gently and gelatine solution coloured red and blue injected into them. It is usually enough to catheterise one artery

since the transverse communicating branch between them ensures that both arteries are adequately filled. About 150 ml. are required for each artery and vein. The veins being of larger calibre usually take more gelatine solution. To ensure the fullest penetration the gelatine should be at a temperature of 50° Centigrade. Injection is carried out rapidly and when completed the placenta is placed in a cold solution of 10 per cent formol-saline for some hours before being handled.

The placenta is now a permanent preparation and can be handled without any special care.

Each of the forty placentae in this series was treated in this way and thereafter dissected. In turn, each placenta was carefully dissected to separate the cotyledons from each other, a task which occupies several hours because of the very intimate way in which they are related to each other. Also the adhesions which many cotyledons, especially the smaller ones, show to the maternal surface of the chorion were separated carefully. When dissection was completed each cotyledon was

quite separate from the others and was a complete structure.

The cotyledons were then enumerated and divided into their three categories of large, medium, and small varieties. In some placentae the division between large and medium cotyledons is not clear cut and the separation in consequence is somewhat arbitrary in nature. However, the total count of large and medium cotyledons was accurate. In addition the primary vascular trunks giving origin to cotyledons show branching and it is difficult sometimes to decide whether the cotyledons which develop from such branching should be regarded as separate cotyledons or part of the parent cotyledon. Once again the decision whether to include them as separate cotyledons was made somewhat arbitrarily. Since the same procedure was followed with each placenta the counts are reasonably accurate. The small cotyledons are the most numerous and were counted for the sake of completeness, but in terms of actual bulk of placenta they form a very small part. The bulk

of the placenta is derived almost entirely from the large and medium cotyledons.

When enumeration was complete the placenta was spread out flat, foetal surface uppermost, and its longest diameter measured taking the most peripheral primary vascular trunks of the cotyledons as its true edge. These can readily be seen through the chorion taking origin from the large vessels on the foetal chorion. Thereafter the placenta was weighed. To ensure a reasonable conformity of results the placenta was roughly dried between layers of absorbent lint, and most of the moisture removed from it. The weights obtained are therefore not dried weights but each placenta was treated in a similar fashion and the weights are strictly comparable.

Finally, representative large, medium and small cotyledons were selected. These were weighed and their lengths noted (including the whole primary vascular trunk). The small cotyledons are of negligible weight and these have not been included in the results.

In carrying out these investigations care was taken to avoid excessive drying since it promotes distortions of the tissues and affects adversely the anatomical features.

(b) The Growth of the Placenta.

The placentae, at different growth periods, used in this series were digested in a similar fashion but the foetal vessels were not filled with gelatine. The cotyledons were separated from each other as before and large and medium cotyledons removed for further study. The separated cotyledon was carefully dissected into its sub-cotyledons, and the sub-cotyledons into their constituent vessels. In this way the structure of the cotyledon at different growth periods could be compared. Gelatine made dissection of these small vascular trunks rather difficult and was avoided for that reason. In addition the "fringe" area was removed from several cotyledons in order to make the division of the larger vascular trunks more obvious. This greatly facilitated the photography of the specimens. Histological studies of the vascular

trunks were undertaken at primary, secondary and subsequent divisions in order to observe the increase in the calibre of the vessels as they became more mature. The isolation, by dissection, of a vascular trunk at any level of division is quite readily performed in these cotyledons. In addition transverse serial sections of the vascular trunks were also carried out at different levels of division in order to observe the possibility of arterio-venous anastomosis at these levels.

These investigations of the development and increase in size of the cotyledon have made it possible to present a picture of placental growth.

(c) The "Fringe" or Capillary Region of the Cotyledon.

The technique necessary to study this region of the cotyledon required some modification of the standard technique.

When this region of the cotyledon was studied in the original series of placentae it was customary to inject only the artery and vein supplying a lobe of placenta. This lobe

was removed by sharp dissection and digested. The preparations of capillaries obtained from the lobe "fringe" suggested that a system of anastomosing vessels were present within the villus but they could not be seen with accuracy. In consequence the technique was modified and will now be described.

Each of the placentae at the different growth periods was washed with cold water gently to remove maternal blood. The umbilical vein was catheterised with a polythene catheter and 100 - 150 ml. of a 1% solution of the blue dye "Monastral" injected. This blue dye gives a very satisfying picture visually and being dense photographs very well. The placenta is then placed, maternal surface uppermost, in a round glass jar big enough to accommodate the whole placenta lying flat, covered with digest solution and incubated for not more than 24 hours. A longer period of digestion tends to remove the syncytium and makes a much less satisfactory preparation. When digestion is complete the digest solution is carefully siphoned off and

replaced by 10 per cent formol-saline. This makes the delicate "fringe" area harder and dissection is more easily accomplished. Small areas from the fringe at any depth can be removed by sharp dissection, placed in water and gently teased out. Finally the material is washed in acetone quickly and then placed again in cold water. Acetone removes much of the debris of digestion and gives a clear final preparation. The material is placed finally on a glass slide, warm gelatine mounting medium added and a stout coverglass placed over it. Pressure with the point of a hypodermic needle is exerted on the cover slip and the material is seen to flatten out. This pressure is continued until no more flattening is possible, and maintained until the gelatine medium hardens with cooling and prevents retraction of the spread out specimen. The employment of only one dye into the umbilical vein has improved greatly the injection of the capillary vessels. The entire system of anastomosing vessels in the villus has been revealed. The use of dyes into both

artery and vein prevented escape of fluid in the capillary vessels, from in front of the dyes, accumulation of fluid took place in the anastomosing vessels and prevented their demonstration. Placentae, at different stages of maturity, were treated in this fashion. From the fringe areas over the whole placenta, at each stage, about fifty preparations of capillaries were made and examined. Many placentae were treated in this fashion but the preparations rejected because of poor injections and detail. These rejected placentae are not in the present series which only refers to placentae which were satisfactorily injected. The preparation of capillary specimens was a slow and painstaking procedure and each placental fringe required several days for its complete survey.

In addition to the placentae, which were injected, a similar series was examined without injection of capillaries. The intention was to present the gradual increase in the bulk of the fringe and the change in the anatomical characteristics in this region with maturation.

This aspect of the investigation will be described later.

THE RESULTS OF THE INVESTIGATION.

This will be discussed under two headings as follows.

(A) Macroscopic growth.

(B) Microscopic growth.

(A) The Macroscopic Growth.

The details of this part of the investigation will be set down in sequence and commented upon shortly as each detail is described. At the end of this part a general comment on the macroscopic growth will be given.

The Diameter of the Placenta.

The placenta obviously, by naked eye, increases in size and bulk. Its shape in most instances remains round or oval. This implies that increase in the surface area of the placenta is accomplished by a uniform enlargement either peripherally, centrally, or both, and not by any localised portion.

The increase in the surface area is reflected in the increase in diameter of the

placentae at each of its growth periods. The diameter in all cases was the longest measurement obtained across the placenta, and was the distance between the most peripheral cotyledons. The actual point for measurement was the perforation of the chorion by the vascular trunks of the cotyledons selected. It was necessary to use such an arbitrary point since the placenta after digestion and dissection can be stretched quite readily to give an excessive measurement. Each placenta was treated in a similar fashion and the results are strictly comparable. At twelve weeks the diameter of the placenta may be as little as 8 cm. and by forty weeks will have risen to 20 cm. This was the largest diameter obtained. The diameter gradually rises during these twenty-two weeks of development, but there are considerable variations. For example at 28 weeks a measurement of 16 cm. was obtained, whilst at term there was a placenta of only 11 cm. This variation underlines the manner in which placentae at the same period of maturity

differ in size. At 24 weeks the largest placenta measured 15 cm. and the smallest 12 cm. At 40 weeks the range was even more extreme, from 11 cm. to 20 cm. This natural variation in size is familiar to all who examine placentae. The size, as observed clinically, is in no way related to performance during labour or pregnancy.

The diameters are set down, in detail, in Table A. It will be appreciated that the diameter of the placenta is not a very accurate guide to its maturity. However, with some exceptions the largest placentae are the most mature.

TABLE A.

No.	Maturity in Weeks.	Diameter in Cms.
3	Twelve	8 : 8.5 : 9.
5	Sixteen	8 : 9 : 10 : 10 : 10
3	Twenty	9 : 12 : 14
7	Twenty-four	12 : 12.5 : 13 : 13.5 : 14 : 14 : 15.
2	Twenty-eight	15 : 16
1	Thirty	12
4	Thirty-two	11 : 13 : 14 : 16
2	Thirty-four	11.5 : 14
2	Thirty-six	15 : 16
11	Forty	11 : 15 : 15 : 16 : 17 : 17 : 17 : 18 : 18 : 19 : 20.
40		

The Weight of the Placenta.

In this series the weight of the placenta was obtained after digestion and thorough washing in water. The placenta had also been injected, with coloured gelatine, into umbilical artery and vein, and then immersed in formol-saline for some hours. After digestion and washing, as already explained, only the umbilical cord, chorion and cotyledons remain. The maternal blood which usually increases the weight of the placenta considerably had been removed and it was considered that weighing after digestion would give a more reliable estimate of its true weight. The placenta was of course wet, but excess water was removed by squeezing between layers of lint. It is not claimed that the weight obtained was the true weight. Since each placenta was treated in a similar fashion the weights obtained are comparable. Excessive drying of the tissues was avoided to keep the placentae suitable for further examination and dissection.

It will be observed from Table B that the

weight of the placenta is a more reliable guide to its maturity than its diameter. The heaviest placentae were in the second half of pregnancy. The greatest weight obtained, 300 grams, was in a full-time placenta. It will be observed that there was one major exception. A placenta of twenty-four weeks maturity weighed 200 grams. This was, by far, the greatest exception and cannot be explained. The placenta appeared normal and the menstrual cycle of the patient was regular. This very heavy placenta may have indicated some pathological condition in pregnancy which was not recognised. There were several other exceptions. One placenta at twenty-eight weeks weighed 135 grams. which was heavier than a full term placenta of 125 grams. One placenta at term weighed only 60 grams, and will be commented on, because of its interest. There was no separation of this placenta into lobes. It consisted of a single lobe and its cotyledons were all closely opposed to each other. It was derived from a normal delivery at term with a living child.

It will be apparent that although the weight is a more accurate guide to maturity, it is not by any means very accurate. A more accurate guide is required and this will be demonstrated later.

The full details of placental weight are set down in Table B.

TABLE B.

No.	Maturity in Weeks.	Weight in Grams.
3	Twelve	20 : 30 : 30
5	Sixteen	20 : 20 : 30 : 30 : 40.
3	Twenty	30 : 35.5 : 50
7	Twenty-four	60 : 75 : 90 : 95 : 125 : 135 : 200.
2	Twenty-eight	125 : 135.
1	Thirty	65.
4	Thirty-two	70 : 150 : 165 : 175.
2	Thirty-four	50 : 90.
2	Thirty-six	150 : 150.
11	Forty	60 : 125 : 130 : 150 : 160 : 200 : 200 : 210 : 250 : 255 : 300.
40		

The Cotyledon Count.

The amount of dissection required to perform this count took rather a long time. Each of the forty placentae in this series was dissected in exactly the same way. To perform the dissection carefully required about one day for each

placenta. The placenta was first separated into its lobes and, in turn, each lobe dissected into its constituent cotyledons. The cotyledons are closely enmeshed with each other and their vessels must be separated. When the cotyledons were separated from each other they were counted in turn, noting the numbers of large, medium and small cotyledons present. The count for each placenta took several hours and particular care was taken not to count cotyledons twice over. This was prevented by covering with a flat metal plate in a progressive fashion, the cotyledons counted, until the whole placenta had been dealt with. The large and medium cotyledons were easily recognised and counted because of their bulk. The small cotyledons were extremely numerous and often very small and their enumeration tedious and difficult. The count for small cotyledons is not claimed to be extremely accurate. The total numbers of large and medium cotyledons are accurate. In some placentae there is not a striking size difference between these cotyledons and the

numbers obtained depends largely on the dissector. It can be said that although the numbers in each of these two categories may not be correct the total obtained is accurate. This has a very real bearing on the growth of the placenta since the larger cotyledons constitute the bulk of the placenta.

Table C records the cotyledon counts obtained from twelve weeks until forty weeks. From the Table it is apparent that there is no relationship between the total number of cotyledons and the degree of maturity of the placenta. It is also apparent that with few exceptions the number of cotyledons can be accommodated in the range, approximately, of 150 - 250 cotyledons. The exceptions were a placenta at 16 weeks which had only 109 cotyledons, a placenta at thirty-two weeks which had 112 cotyledons, and a placenta at term with 76 cotyledons only. The average number of large cotyledons was 15, medium cotyledons 48, and small cotyledons 127, in this series.

From Table C it can be seen that a

TABLE C.

THE COTYLEDON COUNT.

Maturity in Weeks.		Cotyledon Count.			
		Large.	Medium.	Small.	Total.
Twelve	20 grm.	14	90	60	164
	30 grm.	10	100	75	185
	30 grm.	12	110	65	187
Sixteen	20 grm.	6	50	109	165
	20 grm.	6	30	73	109
	30 grm.	20	50	100	170
	30 grm.	8	30	133	171
	40 grm.	21	64	112	197
Twenty	30 grm.	5	121	120	246
	35.5 grm.	20	50	90	160
	50 grm.	27	29	110	166
Twenty-four	60 grm.	11	55	201	267
	75 grm.	11	49	155	215
	90 grm.	13	46	152	201
	95 grm.	20	31	73	124
	125 grm.	17	47	128	182
	135 grm.	25	52	145	222
	200 grm.	23	90	136	249
Twenty-eight	125 grm.	12	55	157	224
	135 grm.	21	50	106	177
Thirty	65 grm.	12	28	189	229
Thirty-two	70 grm.	21	26	65	112
	150 grm.	15	42	87	144
	165 grm.	15	37	163	215
	175 grm.	13	29	109	141
Thirty-four	50 grm.	18	51	139	208
	90 grm.	16	41	131	188
Thirty-six	150 grm.	17	52	134	203
	150 grm.	16	39	164	219

(contd.)

TABLE C. (contd.)

THE COTYLEDON COUNT.

Maturity in Weeks.		Cotyledon Count.			
		Large.	Medium.	Small.	Total.
Forty	60 grm.	8	22	46	76
	125 grm.	20	35	75	130
	130 grm.	13	18	176	207
	150 grm.	9	27	193	229
	160 grm.	18	57	190	265
	200 grm.	9	27	215	251
	200 grm.	8	26	139	173
	210 grm.	27	34	123	184
	250 grm.	8	53	191	252
	255 grm.	5	41	189	235
	300 grm.	10	38	113	161

placenta at twelve weeks can have as many cotyledons as a placenta at forty weeks. In a similar fashion a full time placenta can have fewer cotyledons than a considerably less mature one. It is evident therefore that an increase in the total number of cotyledons is not a feature of placental growth from the early weeks until full time. A cotyledon count is therefore of no value as a guide to placental maturity. It was remarked earlier that the bulk of the placenta is derived from the large and medium cotyledons. The weight of the small cotyledons is negligible and can be disregarded as a significant contribution to placental weight. It follows from this that the weight of the placenta must be related to the large and medium cotyledons. This relationship between the weight and the total count of these two categories of cotyledons provides the best illustration of the fashion by which the placenta grows. This relationship has been termed by the writer the weight/count ratio and provides the most certain method of demonstrating

placental maturity. The weight/count ratio has been determined for placentae at their various growth stages and are set out, in detail, in Table D.

The weight/count ratio is seen to rise from 0.19 at twelve weeks to a maximum of 6.2 at forty weeks. Between these two extremes, with advancing maturity, there is a steady rise in this ratio. The only serious exception was a placenta at thirty-four weeks whose ratio was only 0.7. These figures indicate the pattern of placental growth. If the ratio rises as the placenta matures then, since the placental weight increases, the numbers of large and medium cotyledons with respect to each placenta must remain stationary. If this were not so the weight/count ratio would remain relatively unaffected, since both placental weight and numbers of cotyledons would rise in proportion as the placenta matures. It is clear therefore that increase in numbers of cotyledons is not the pattern by which the placenta increases in size. On the contrary the findings suggest

TABLE D.

Maturity in Weeks.	Weight in Grammes.	Cotyledon Count Large and Medium.	Weight/ Count Ratio.
Twelve	20	104	0.19
	30	110	0.27
	30	122	0.24
Sixteen	20	56	0.35
	20	36	0.55
	30	70	0.42
	30	38	0.78
	40	85	0.47
Twenty	30	126	0.23
	35.5	70	0.50
	50	56	0.89
Twenty-four	60	66	0.90
	75	60	1.20
	90	59	1.50
	95	51	1.8
	125	64	1.9
	135	77	1.7
	200	113	1.7
Twenty-eight	125	67	1.8
	135	71	1.9
Thirty	65	40	1.6
Thirty-two	70	47	1.5
	150	57	2.6
	165	52	3.1
	175	42	4.1
Thirty-four	50	69	0.7
	90	57	1.5
Thirty-six	150	69	2.17
	150	55	2.7

(contd.)

TABLE D. (contd.)

Maturity in Weeks.	Weight in Grammes.	Cotyledon Count Large and Medium.	Weight/ Count Ratio.
Forty	60	30	2.0
	125	55	2.2
	130	31	4.1
	150	36	4.1
	160	75	2.1
	200	36	5.5
	200	34	5.8
	210	61	3.4
	250	61	4.0
	255	46	5.5
	300	48	6.2

that increase in weight and size is brought about by a progressive increase in size and weight of the same cotyledons. If the same cotyledons, within normal limits, are the same at twelve weeks as they are at full term then it also follows that the maternal vessels supplying them must also be the same. The findings would infer that the uterus and the placenta grow together and at the same rate. The popular impression that the placenta grows like a "fungus" across the decidua and acquires new maternal vessels on its way is hardly tenable. It would be to the advantage of the foetus for its placenta to establish a maternal blood supply early in pregnancy, and to maintain this relationship and develop it during pregnancy. The alternative view of a placenta acquiring a maternal blood supply haphazardly as it grows would diminish the security of the foetus and be much less satisfactory for its continued development. The growth of the cotyledons is illustrated in the next paragraph and strongly reinforces this view of the placental growth pattern.

The Growth of the Cotyledon.

The growth of the cotyledon which takes place during pregnancy will be considered under two headings.

1. The Increase in Weight.
2. The Increase in Length.

1. The Increase in Weight.

The cotyledons which illustrate this increase were obtained from the forty placentae, at the various maturities detailed in the preceding section. From each of these placentae representatives of large and medium cotyledons were selected. These were removed, along with the primary vascular trunk, by cutting through the vascular trunk immediately after it had perforated the chorion and entered the placenta. In general the largest cotyledons were taken in order to demonstrate the increase in size in as striking a manner as possible. The selected cotyledons were dried gently by pressure between layers of lint. In this way excess moisture was removed but without

TABLE E.

THE GROWTH OF THE COTYLEDON

1. THE INCREASE IN WEIGHT

Maturity in weeks.	Weight of Placenta in Grammes.	The Weight of the Cotyledon in Grammes.	
		Large.	Medium.
Twelve	20	1.0	0.0666
	30	1.5	0.15
	30	1.0	0.17
Sixteen	20	0.848	0.29
	20	2.94	0.18
	30	0.89	0.24
	30	0.72	0.17
	40	0.44	0.145
Twenty	30	2.0	0.130
	35.5	1.34	0.64
	50	1.99	0.72
Twenty-four	60	2.89	0.79
	75	3.28	0.42
	90	6.575	0.637
	95	4.78	1.31
	125	6.98	1.17
	135	4.866	0.80
	200	4.5	0.39
Twenty-eight	125	3.01	0.712
	135	4.0	2.0
Thirty	65	7.0	1.50
Thirty-two	70	4.53	0.36
	150	7.36	1.58
	165	10.42	1.02
	175	6.05	0.36
Thirty-four	50	1.71	0.54
	90	4.39	2.15

(contd.)

TABLE E. (contd.)

THE GROWTH OF THE COTYLEDON

1. THE INCREASE IN WEIGHT

Maturity in weeks.	Weight of Placenta in Grammes.	The Weight of the Cotyledon in Grammes.	
		Large.	Medium.
Thirty-six	150	5.06	0.987
	150	5.679	2.20
Forty	60	7.11	0.72
	125	6.02	0.8519
	130	5.90	1.19
	150	6.17	1.05
	160	5.53	0.50
	200	13.28	5.28
	200	4.09	1.01
	210	7.07	2.42
	250	2.93	2.76
	255	9.18	5.69
	300	14.21	5.46

drying them excessively. The cotyledons were then weighed and the results are given, in full, in Table E. It is emphasised that the weights obtained from large and medium cotyledons at the stated growth periods are the weights of the selected cotyledons. They are not average weights of all the large and medium cotyledons examined.

The results in Table E are of especial interest because they demonstrate in a most striking way, not only the capacity of placental tissue to increase and meet the needs of the developing foetus, but also the tremendous needs of the foetus for its development. It will be seen that a large cotyledon weighed 1.0 gramme at 12 weeks and by full term at 40 weeks one large cotyledon weighed more than 14 grammes. This increase of fourteen times is exceptional but it does underline the opening remarks in this paragraph. Between these two extremes it can be seen that there is a progressive increase in weight with advancing maturity. There are, of course, exceptions. A cotyledon at 16 weeks

weighed 2.94 grammes which was as much as a large cotyledon weighed in one full term placenta. Also, at thirty-two weeks a large cotyledon weighed 10.42 grammes, and this weight was very much greater than most of the weights obtained in full time placentae. In general it was found that where cotyledons are heavy, their numbers are fewer. The reverse was, of course, also found. This relationship must, of necessity be present. If it were not present the placentae with the greatest number of cotyledons would be the heaviest, and the weight/count ratio no longer show, so clearly, its characteristic rise from twelve weeks until full term at forty weeks. There would appear to be a special relationship, in each placenta, between the total numbers of large and medium cotyledons and its weight. It is uncertain which influences are at work in determining this relationship. Genetic inheritance obviously plays some part, in a normal pregnancy, by influencing the size and weight of the foetus and determining the demands which will be made on the

placenta for foetal development and growth.

2. The Increase in Length.

The increase in weight of cotyledons, with advancing maturity, which has been demonstrated in the previous section, is accompanied by a corresponding increase in length. At each of the maturity periods considered the cotyledons were measured and the findings obtained are set down in detail in Table F.

The cotyledons for this part of the investigation were the same cotyledons which had been weighed already, and whose weights are recorded in Table E. These cotyledons were still moist and could be readily dissected. The amount of dissection was limited to a separation from each other of the divisions which form the sub-cotyledons. The cotyledon was then allowed to lie flat and the greatest length from the start of the primary trunk to the capillary fringe was measured. The "fringe" area was not dissected out. The small vascular trunks in this region show the curved "downwards

TABLE F.

THE GROWTH OF THE COTYLEDON

2. THE INCREASE IN LENGTH

Maturity in weeks.	Weight of Placenta in Grammes.	The Length of the Cotyledon in cms.	
		Large.	Medium.
Twelve	20	3	2.5
	30	3	3
	30	2	1.5
Sixteen	20	3	2.5
	20	3.5	5.0
	30	2.0	1.5
	30	3.5	3.0
	40	1.5	1.0
Twenty	30	2.5	2.0
	35.5	4.0	3.5
	50	2.5	2.0
Twenty-four	60	4.0	3.0
	75	4.0	4.0
	90	2.5	2.5
	95	3.5	3.5
	125	3.5	2.75
	135	2.5	2.0
	200	5.0	3.5
Twenty-eight	125	4.0	3.0
	135	3.0	2.5
Thirty	65	2.5	2.0
Thirty-two	70	4.0	5.0
	150	3.0	2.5
	165	4.5	3.0
	175	5.0	4.0
Thirty-four	50	4.0	3.0
	90	3.0	2.0

(contd.)

TABLE F. (contd.)

THE GROWTH OF THE COTYLEDON

2. THE INCREASE IN LENGTH

Maturity in weeks.	Weight of Placenta in Grammes.	The Length of the Cotyledon in cms.	
		Large.	Medium.
Thirty-six	150	4.0	4.0
	150	5.0	3.5
Forty	60	4.5	3.5
	125	6.0	4.0
	130	9.0	8.0
	150	4.5	4.5
	160	4.0	3.0
	200	7.0	6.0
	200	7.0	4.0
	210	4.0	4.0
	250	6.0	4.0
	255	7.5	4.5
	300	6.0	4.0

and upwards" course or "chandelier" arrangement of Spanner and if made to lie straight increase very markedly the length of the cotyledon. It was considered that the length of the cotyledon should be obtained in the form in which it occurs in life, and not after an artificial dissection. Each cotyledon was investigated in the same fashion and the measurements are quite comparable.

The measurements obtained and set down in Table F show that increase in length of the cotyledon occurs with increasing maturity. The increases are not so dramatic as the weight increases, although in the fortieth week of pregnancy a large cotyledon measured 7 cm. as compared with 1.5 cm. at sixteen weeks and 2 cm. at twelve weeks. This represents a very considerable increase in length. The Table also shows that there was not such a marked difference in length between the large and medium cotyledons. This should be compared with the markedly greater weight of the large cotyledon. The reason for this disparity

between weight and length increases is due to the fact that a measurement of length does not accurately reflect the increase of bulk in the cotyledon. The medium cotyledon may be as long as a large cotyledon but it is a much less bulky structure. The medium cotyledon does not possess the same numbers of secondary and subsequent branches of the large cotyledon. In addition the development of its fringe is always less. However, the Table does show that increase in length of the cotyledon occurs as the placenta matures. This increase in the size of the cotyledon underlines once again the increasing needs of the foetus for growth and development, as it matures.

The increase in the bulk of the cotyledon can be shown in the following fashion. It follows that as a cotyledon increases in bulk the vessels supplying it will also become larger. This enlargement in the vessels will be reflected by their increasing diameters. To demonstrate this enlargement large cotyledons were selected from placentae at 12, 16, 20, 24,

30, and 40 weeks of pregnancy. Each cotyledon was dissected into its secondary branches and in turn the tertiary and subsequent branches were also dissected free from each other. At each level of division the vascular trunk was freed from any smaller branches which might be present, and thereafter a segment of each vascular trunk removed. These segments were fixed, and transverse sections of the trunks cut as in an ordinary histological preparation. The cut sections were stained with aniline methylene blue and mounted. Thereafter, at each level of division of the trunks, the calibre of the arteries was measured with a stage micrometer. In this way it was possible to demonstrate that with increasing maturity the diameters of all the arteries in the vascular trunks increased with maturity. The measurements obtained are recorded in Table G.

From the table it is apparent that each cotyledon is having an increasing volume of blood circulating through it, as it gets bigger. This is most apparent when the diameter of a

TABLE G

THE DIAMETER OF THE FOETAL ARTERIES

Maturity in Weeks.	Primary Division in mm.	Secondary Division in mm.	Tertiary or Subsequent Division in mm.
Twelve	0.28	0.21	0.14
Sixteen	0.56	0.42	0.14 : 0.07
Twenty	0.70	0.28	0.14
Twenty-four	1.4	1.12	0.56
Thirty	1.4	0.98	0.70
Forty	5.0	3.0	2.0

primary trunk at 12 weeks, 0.28 mm., is compared with a corresponding diameter of 5 mm. at forty weeks. This amounts to an increase of twenty times in the diameter of the same vessel, and by inference indicates a similar increase in the volume of circulating blood at any instant. Similar but smaller increases in diameter are also seen in the secondary and subsequent vascular trunks. There can be little doubt, from these figures, how greatly the bulk of a cotyledon must increase during pregnancy. This increase indicates in turn the increase in foetal blood passing through the cotyledon at any unit of time.

The following calculations are intended to express this increase in a mathematical fashion. The figures obtained are, of course, only approximate but they do serve to illustrate the tremendous growth of the placenta during pregnancy.

If the diameter of the artery in the primary vascular trunk at 12 weeks is 0.28 mm., the surface area of the vessel will be 0.0616

sq. mm. Similarly, if the diameter of the artery in the primary vascular trunk at 40 weeks, is 5 mm., the surface area of the vessel will be 19.6 sq. mm. This represents an increase in surface area of 323 times!

The volume of the cotyledon can be calculated if it is assumed to have the shape of a cylinder. This is only an approximation, but the figures obtained are most instructive. For example, if the cotyledon at 12 weeks has a vessel surface area of 0.0616 sq. mm., and a length of 20 mm., its volume will be 1.848 cu. mm. Similarly, a cotyledon at term with a surface area of 19.6 sq. mm., and a length of 50 mm., will have a volume of 970 cu.mm. This represents an increase in volume of 524 times from twelve to forty weeks!

The theoretical volume of the placenta at these maturities can also be calculated.

For example if a placenta at 12 weeks has 100 large and medium cotyledons then the total volume of the placenta will be 184.8 cu. mm. This is assuming that each cotyledon

has the same volume.

Similarly, a placenta at term which has 50 large and medium cotyledons will have a total volume of 48,500 cu. mm. This represents an increase in placental volume of 208 times!

The results are set down in detail in Table H.

An increase in volume of the cotyledon, of 524 times, from the twelfth to the fortieth week indicates a tremendous production of vascular tissue on the part of the placenta. The increase in the diameter of the artery is not just a dilation of the vessel. The muscular and other layers of the vessel wall increase also in thickness with advancing maturity. In certain of the histological sections of the vascular trunks, the hypertrophy of the muscular coat is most apparent and the vessel lumina appear comparatively small. It was for this reason that the diameter of the vessels was taken to include the thickness of the wall rather than just the lumen itself.

The calculations on which the surface areas

TABLE H.

THE THEORETICAL VOLUME OF THE COTYLEDON.

MATURITY IN WEEKS.	LENGTH OF COTY-LEDON. (mm.)	DIAMETER OF ARTERY IN PRIMARY VASCULAR TRUNK. (mm.)	CROSS SECTION OF ARTERY IN PRIMARY TRUNK. (sq. mm.)	VOLUME OF COTY-LEDON. (cu. mm.)
12	20	0.28	$\pi \times (\frac{.28}{2})^2$ 0.0616	$\pi \times (\frac{.28}{2})^2 \times 20$ 1.848
40	50	5.0	$\pi \times (\frac{5}{2})^2$ 19.6.	$\pi \times (\frac{5}{2})^2 \times 50$ 970

Increase of cross section vessel surface area: x 323

Increase of cotyledon volume: x 524.

THE THEORETICAL VOLUME OF THE PLACENTA.

MATURITY (weeks)	VOLUME OF COTYLEDON. (cu. mm.)	NUMBER OF COTYLEDONS.	VOLUME OF PLACENTA (cu. mm.)
12	1.848	100	184.8
40	970	50	48,500

Increase of placental volume: x 208

of the vessels, and the volumes of the cotyledons are based, are set down in Table H. It should be stressed again that the calculated volumes are only an approximation.

The macroscopic evidence of growth of the cotyledon are to be seen in Figures 23, 24 and 25. These show individual cotyledons at varying maturities from the 12th week until the 40th week. The cotyledons are all at the same magnification and the increase in size is readily apparent.

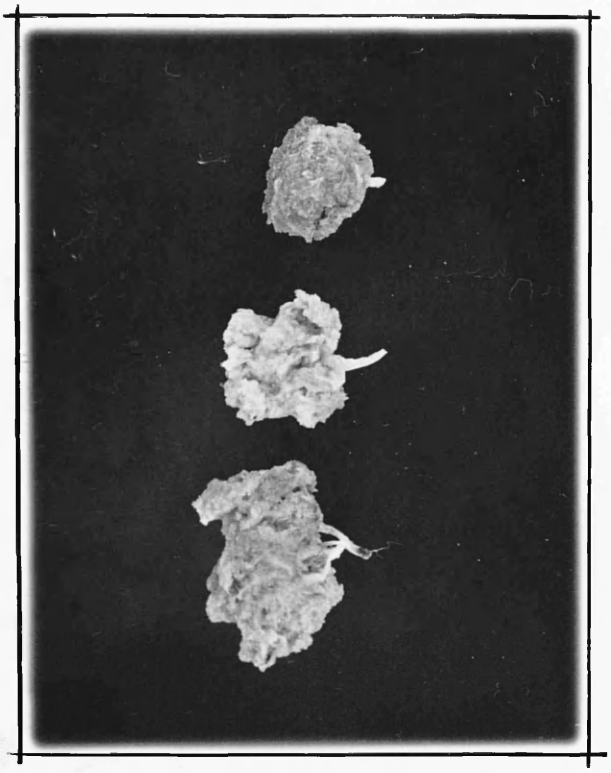

Figure No. 23. Life size.

From above downwards are shown cotyledons at maturity of 12, 16 and 20 weeks.

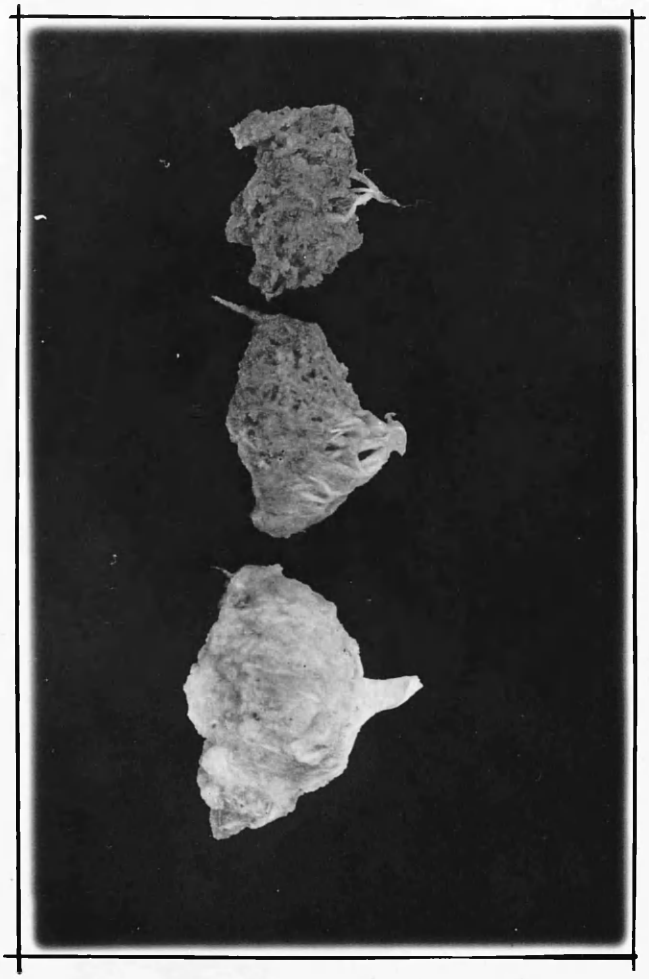

Figure No. 24. Life size.

From above downwards are shown cotyledons at maturity of 20, 24 and 28 weeks.

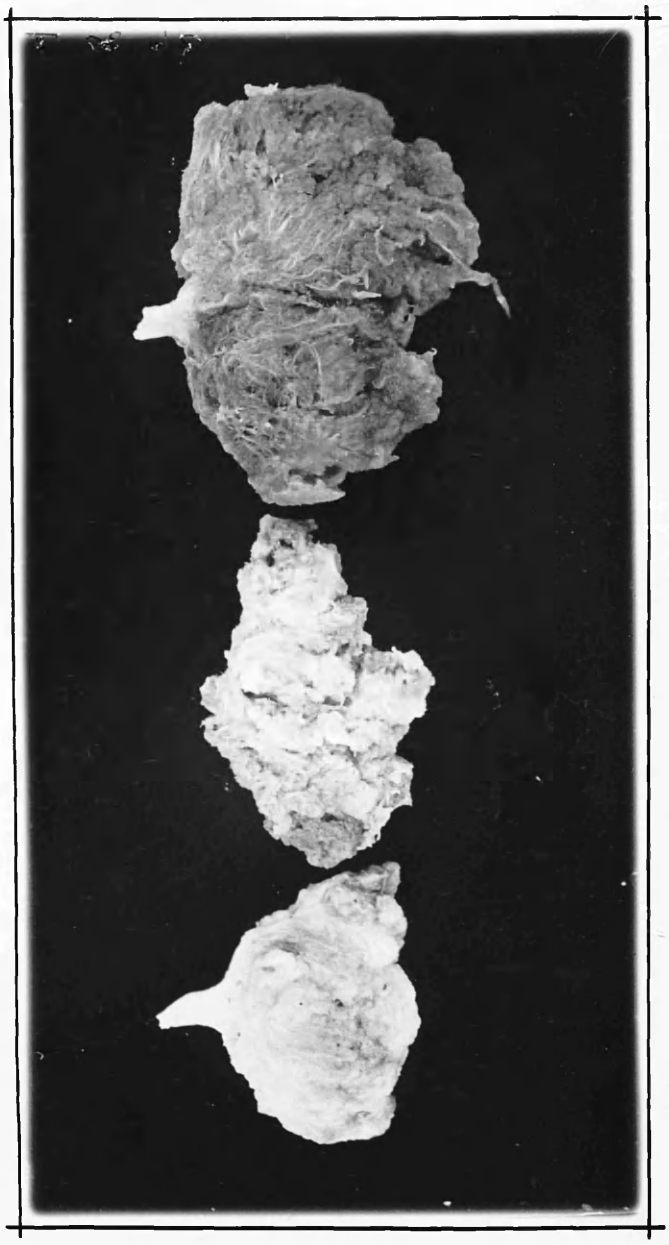

Figure No. 25. Life size.

From below upwards are shown cotyledons at maturity of 28, 36 and 40 weeks.

COMMENT.

The macroscopic growth of the placenta has been investigated in considerable detail. It has been shown, by the use of a digestion technique with trypsin, that full dissection of placentae is possible at all stages of maturity. This full dissection has permitted observations to be made which were not possible by previous techniques. It has permitted the weight of the placenta to be ascertained; the separation of individual cotyledons at varying stages of maturity and their enumeration; and the weighing and measuring of individual cotyledons. Such observations are essential before it is possible to investigate placental growth.

It has been shown by weighing forty placentae at various stages of maturity from the twelfth week until full term at forty weeks, that the placenta steadily increases in weight as it matures. Within limits, the heaviest placentae are found in the second half of pregnancy and the heaviest of these are

found in the last four weeks of pregnancy. The placental weight was obtained after digestion when the maternal blood within it had been removed. The quantity of maternal blood within any placenta varies in amount and must influence the weight of a placenta quite considerably. However, it is clear from the weights obtained that placental weight is not an accurate measure of its maturity. There were a number of placentae of considerably greater weight than a mature placenta and yet, were comparatively immature. For example, a placenta at 24 weeks maturity weighed 200 grammes, which was much more than several placentae at term. As in the case of placental weights, the diameter of the placentae increased with maturity and the biggest placentae were generally the most mature. There was considerable variation and the diameter of the placenta cannot be considered an accurate indication of maturity. The variation in size and weight which occurred in this series is a confirmation of the observed variations which

occur among placentae of similar maturities. In normal pregnancy the size and weight do not appear to be related to placental performance. It is not possible to state clinically that a small placenta at term is less efficient than a large one or vice versa.

The cotyledon count has been described and the numbers of cotyledons at the various maturities set down in detail. It has been shown that the large and medium cotyledons constitute the bulk and weight of the placenta. The small cotyledons are of insignificant importance in this respect. The total number of cotyledons in a placenta falls within the range of 150-250 cotyledons, and of these, perhaps ten are large, fifty of medium size and the remainder small cotyledons. The cotyledon count varies very widely. It is not related to maturity and cannot therefore be a means of assessing its maturity. Placentae at 12 or 20 weeks can have as many cotyledons as those at 40 weeks. It is apparent therefore that the cotyledon count does not rise with increasing

maturity. This finding implies that the placenta relies on a fixed number of cotyledons for its growth, and the cotyledons at term are the same ones as were present at twelve weeks or earlier. Thus, placental tissue loss cannot be made good. On the other hand, as already shown, the blood supply of a cotyledon is independent of its neighbours and the destruction of one cotyledon need not affect the others. It is apparent that there is both advantage and disadvantage in this method of growth.

It has been shown that the only reliable index of placental maturity is the weight/count ratio. This ratio is obtained by dividing the weight of the placenta by the numbers of large and medium cotyledons in each placenta. This ratio has been shown to rise from 0.1 at twelve weeks to 5 or more at forty weeks. During pregnancy the ratio shows a steady rise, apart from a few exceptions. The most mature placentae have the highest ratio numbers. This rise holds good no matter how many cotyledons are present or how much the weight varies, in

each placenta. There is evidently a most intimate relationship between placental weight and number of cotyledons. The mechanism or mechanisms which might control or modify this relationship is not known. The actual factors which produce placental growth are also quite unknown. It is possible to consider several likely influences but these considerations are purely speculative and will remain so until much more is known about the process of growth generally. Present day ideas while rightly emphasising the metabolic and other needs of the growing foetus have, in the opinion of the writer, tended to obscure the needs of the placenta. The placenta must make, during pregnancy, a tremendous increase in its volume. The theoretical increase of 200 times makes it quite clear that the needs of the placenta must be as great as those of the foetus.

The physiological load which is imposed on the placenta, requiring it to increase its volume by two hundred times, may well be the determining factor in the production of certain

abortions and premature labours. This is quite distinct from pregnancy complicated by disease. It is clear that this growth process can also be modified by disease and especially the diseases of pregnancy. The large placenta in erythroblastosis foetalis, and the small placenta in severe and prolonged pre-eclampsia illustrates how disease can modify placental increase.

A factor of some importance which will be referred to again is the dependence of the placenta on a fixed number of cotyledons for its growth. The inference which has been made already, assumes that, since the cotyledons are the same during pregnancy, the maternal blood supplying each cotyledon must come from the same maternal vessels. If this inference is correct the placenta and uterus grow at the same rate throughout pregnancy. This arrangement would ensure a continuity of maternal blood throughout pregnancy and would be an eminently safer method of ensuring foetal survival. The theory of the placenta growing

like a "fungus" across the uterus and acquiring maternal blood from maternal vessels in a haphazard fashion is much less attractive physiologically. The great concentration of maternal vessels under the placental site is a further proof that the maternal blood supply is steadily built up during pregnancy. Figures 26 and 27 illustrate this point.

The macroscopic growth of the placenta has been demonstrated by noting the increases of length and weight of individual cotyledons with maturation. The increases of placental diameter and weight have also been demonstrated. It has been shown that although the placenta and its cotyledons steadily increase in size and weight, the numbers of cotyledons remain relatively unchanged. It becomes clear that these increases are obtained by the growth of the same cotyledons during pregnancy and not by the formation of new cotyledons.

In the next section the macroscopic pattern of cotyledonary growth will be discussed, and the visible evidences of such growth

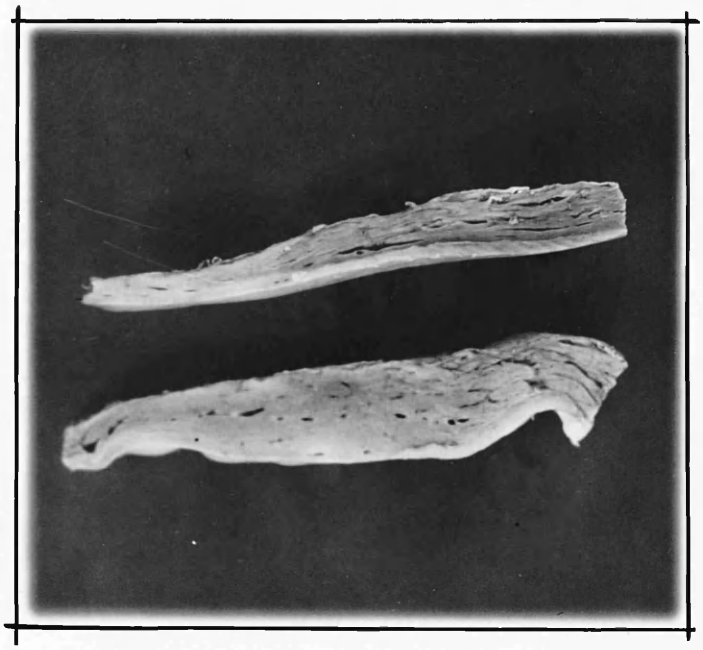

Figure No. 26. Life size.

In each strip of uterine muscle the placental site is on the right and in this area the maternal vessels are much more evident.

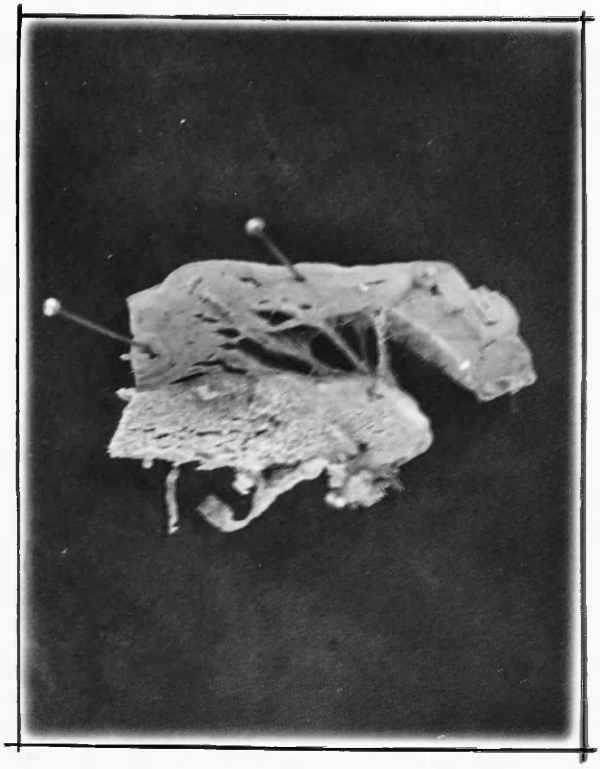

Figure No. 27. Life size.

demonstrated.

THE MACROSCOPIC GROWTH PATTERN OF THE COTYLEDON.

The Growth of the Cotyledon.

The growth pattern of the cotyledon from the early weeks of pregnancy until full term was demonstrated by selecting typical cotyledons at each of the chosen growth periods. These cotyledons were taken from ten placentae which had been digested and thereafter dissected. The placental vessels were not filled with dye or gelatine. The reason for avoiding 'filler' was to make photographic reproduction easier and produce more striking anatomical specimens. In each placenta after digestion, the cotyledons were dissected free from each other and typical large cotyledons were selected. These were placed in formol saline and after a few hours when firm enough were completely dissected into their constituent vessels. They were then replaced in formol-saline for 24 hours. During this period in formol-saline the vascular trunks of the cotyledon become decolourised and

make better specimens for photography. If these cotyledons at the chosen growth periods are examined and compared they are seen to increase steadily in size and bulk with maturation. The dissected cotyledon can be laid out flat and the structure of the cotyledon noted. It is seen that the structure of the cotyledon at twelve weeks, for example, is no different from the cotyledon at forty weeks. There is at twelve weeks, as at term, a primary vascular trunk, containing the parent artery and vein. These have been derived from the parent vessels on the foetal surface of the chorion. In each cotyledon the subsequent division of the primary vascular trunk follows two main patterns. At the primary division, two or three secondary vascular trunks may be produced and this has the effect of partitioning the cotyledon into a small number of sub-cotyledons. This type of division is most often seen in the "dispersed" type of placenta. On the other hand the primary division may produce a larger number of secondary divisions,

perhaps six or more, and the number of sub-cotyledons is correspondingly increased. This type of division is more commonly seen in the "magistral" variety of placenta. It should be stressed that many cotyledons, fall between these two varieties and no clear distinction can be made. This accords with variation in the arrangement of the main foetal vessels on the chorion. Although many placentae are either "dispersed" or "magistral" in arrangement, others fall between these two varieties. At the primary division artery and vein divide at the same time, and the secondary vascular trunks contain artery and vein. The diameters of the vessels are less than in the primary trunk vessels. The secondary vascular trunks, in each cotyledon, again divide after an interval and the mode of division appears to be the same in each variety. The cotyledon with the "magistral" type of division, produces more sub-cotyledons and are therefore more difficult to display on one plane, than the "dispersed" variety which has fewer sub-cotyledons. For

this reason they make less pleasing specimens and photographs. The secondary divisions produce tertiary divisions and each contain an artery and vein running side by side. Their diameters are again smaller than the parent trunks in the secondary divisions. The cotyledon is, by this level of division, clearly divided into a number of sub-cotyledons and of considerable bulk. It should be made clear that in life the sub-cotyledons are all closely related to each other and produce the familiar homogeneous appearance of the complete cotyledon. It is only after dissection that the division of the cotyledon into sub-cotyledons becomes apparent. The tertiary divisions divide and the number of divisions produced have become very great. The fringe area has been reached and the subsequent fate of the vascular trunks is best studied in microscopic preparations. At this level of division the arteries and veins again run side by side and their diameters are correspondingly reduced. These small divisions produce the final arterioles and venules which

bear as lateral projections the capillary vessels. The structure of the "fringe" area will be demonstrated later. In small cotyledons the "fringe" area can be produced after a much smaller number of divisions, but the general structure of these cotyledons is not any different from the larger cotyledons.

Although the structure of the cotyledon, at least in its larger divisions, is not any different at twelve weeks than it is at forty weeks. It is apparent that, with growth, important changes are taking place. As they grow, the primary and subsequent vascular trunks become longer and thicker and the vessels within them share this increase. In addition the "fringe" area increases not only in depth but in density. However, at each stage of maturity the cotyledon appears no different from its less or more mature counterparts. It is only when these cotyledons of varying maturity are compared that the changes described become obvious. In brief it may be said that at each stage of maturity

cotyledons appear complete and mature. There is nothing in their gross structure which would label them as immature or mature, apart from size and bulk. The general structure of the dissected cotyledon is illustrated by Figures 28, 29, 30, 31, 32 and 33.

Figure 28. This shows dissected cotyledons at 12 and 16 weeks maturity. It will be seen that each have the same basic structure of primary trunk, division into secondary trunks, and these thereafter sub-dividing until the "fringe" area is reached.

Figure 29. A dissected cotyledon at 20 weeks is seen showing exactly the same features as in Figure 28.

Figure 30. A cotyledon at 20 weeks is compared with a cotyledon at 24 weeks maturity. The cotyledon at 24 weeks shows a division of the primary trunk into a large number of secondary divisions. This type of cotyledon is more difficult to display, the large number of secondary branches cannot be readily displayed on one plane and some tend

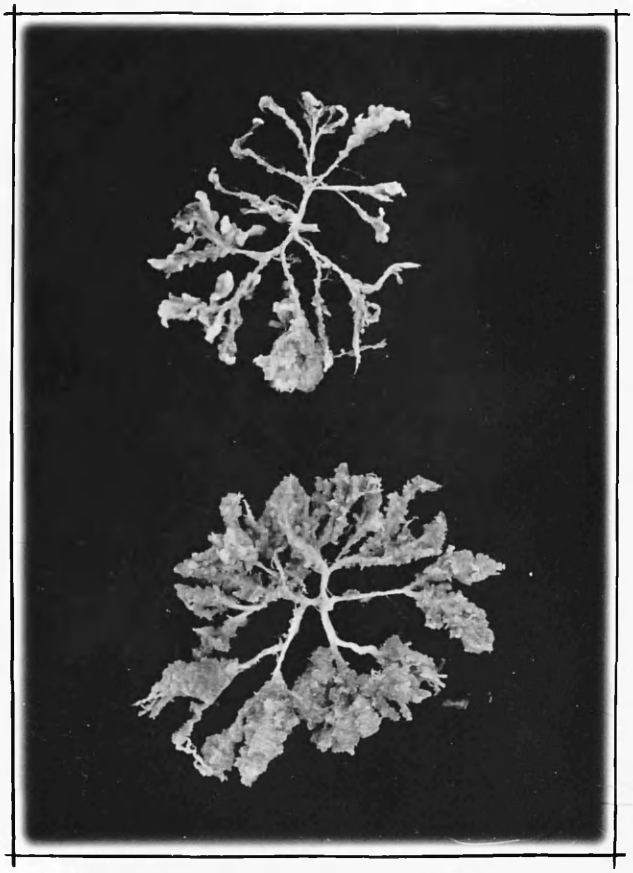

Figure No. 28. Life size.

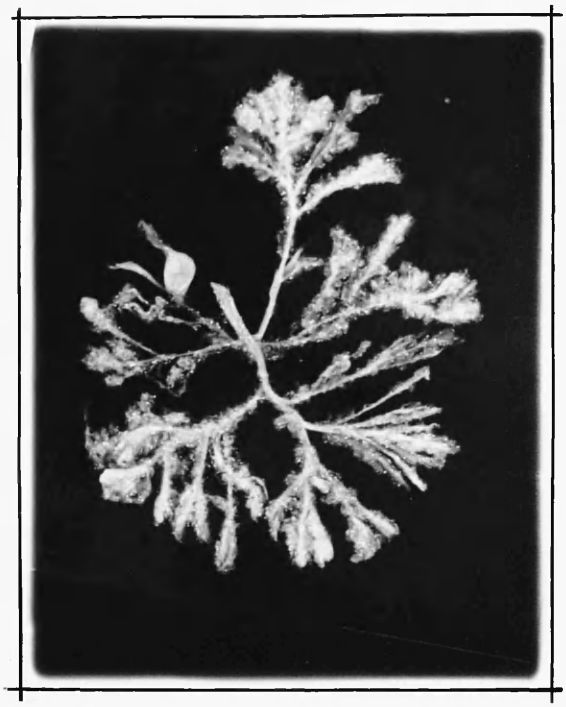

Figure No. 29. Life size.

to get hidden by the others.

Figure 31. A cotyledon at 24 weeks is compared with a cotyledon at 28 weeks maturity. The increase in size is apparent and the large number of divisions produced by the primary trunk at 28 weeks is readily apparent.

Figure 32. This shows a cotyledon at term with the "fringe" region removed. This has been done to make the primary and subsequent divisions more readily visible. The cotyledon at term has a large "fringe" area which obscures the smaller divisions. The general form of the mature cotyledon is not in any way different from the structure of the cotyledon at twelve or sixteen weeks. This type of division of trunks is seen most commonly in the "dispersed" type of placenta.

Figure 33. The increasing bulk of the cotyledon is illustrated from twelve to thirty-six weeks maturity. The increase in the bulk and depth of the "fringe" area is readily apparent.

The growth of the cotyledon and the

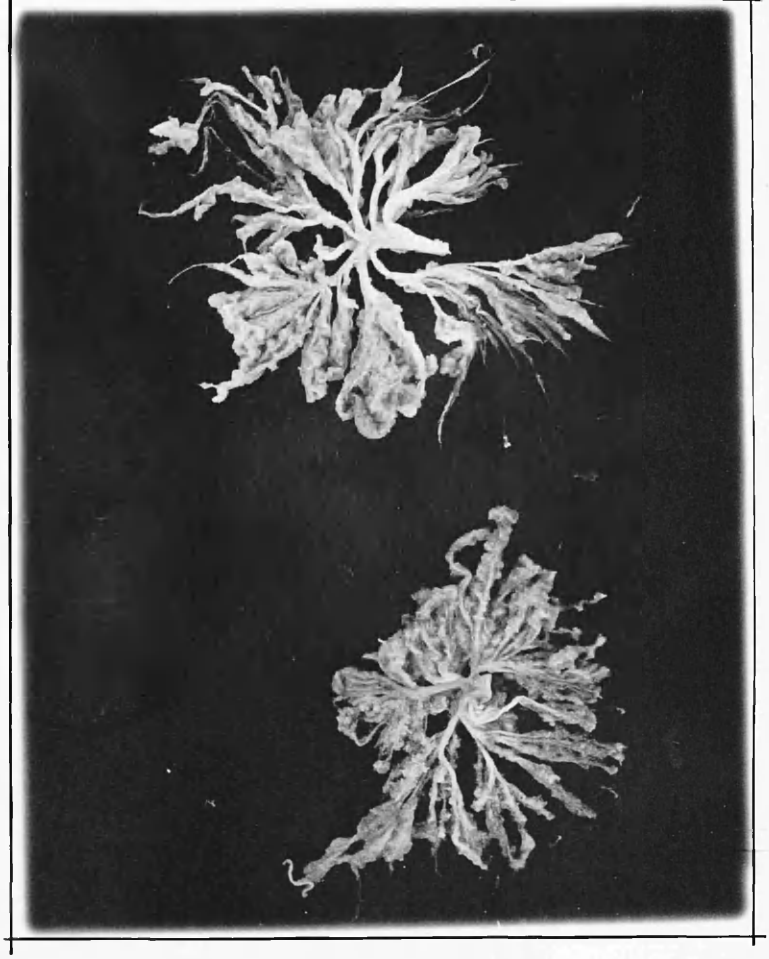

Figure No. 31. Life size.

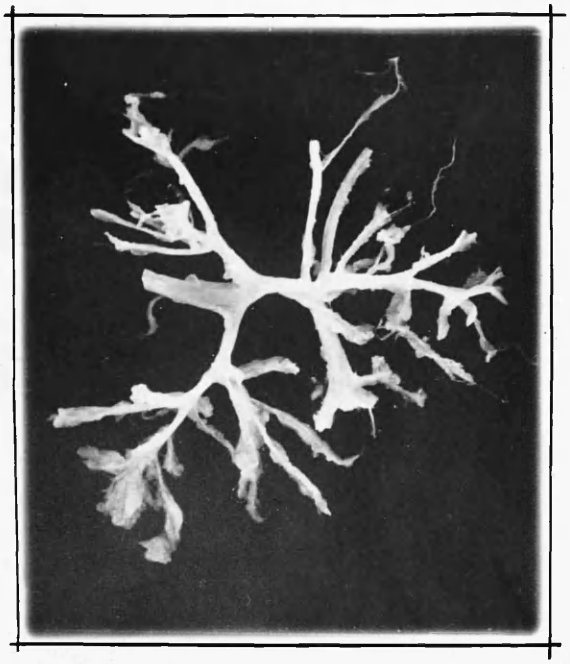

Figure No. 32. Life size.

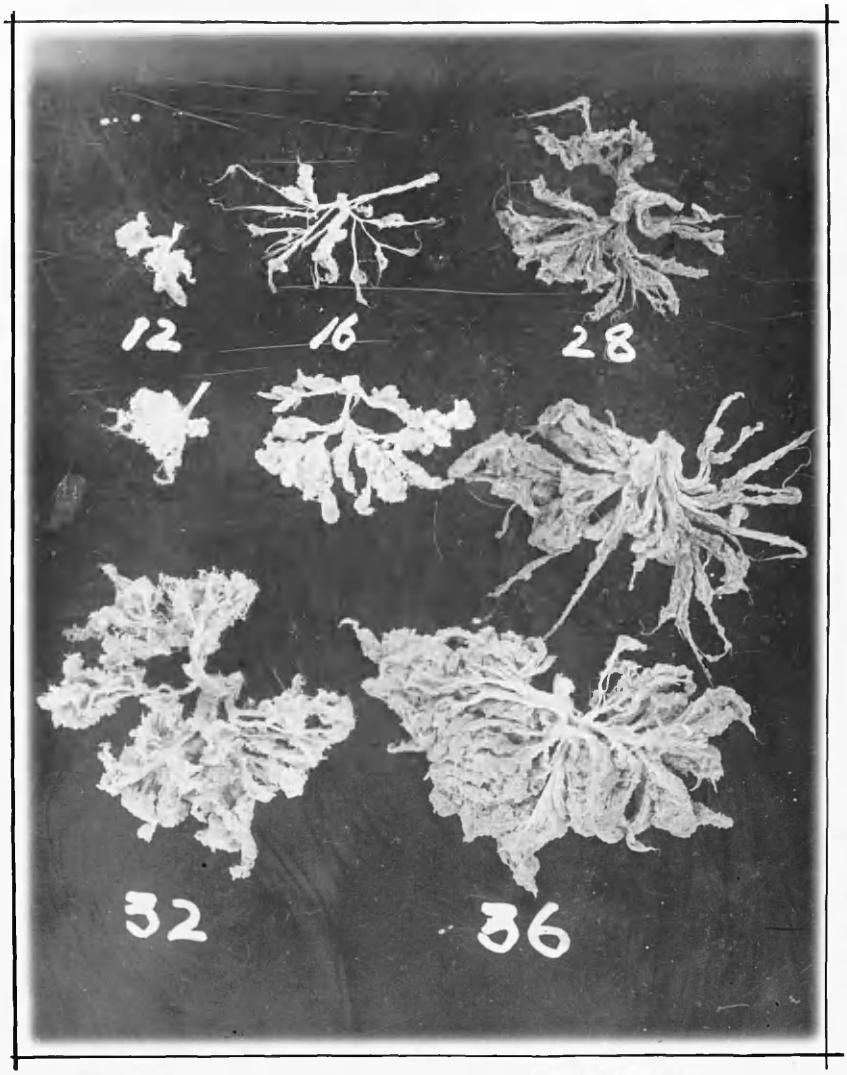

Figure No. 33. Half life size.

development of the "fringe" region is illustrated also by Figures 34, 35, 36 and 37.

Figure 34. A partially dissected cotyledon at twelve weeks is compared with a cotyledon of similar maturity where the "fringe" region has been more completely teased out.

Figure 35. Two cotyledons of sixteen weeks maturity are shown. The "fringe" area has been more completely dissected out and the increase in the length of the cotyledon is most apparent. The increase in length not only reflects growth, it also indicates the "chandelier" arrangement of the most peripheral vessels. These curved vessels at the "fringe" when straightened out are of considerable length.

Figure 36. This shows two cotyledons at twenty-four weeks maturity. The bulk of the cotyledon has increased and the "fringe" is larger and denser, when compared with Figure 35.

Figure 37. The increase in the "fringe" area from twelve to twenty weeks is seen.

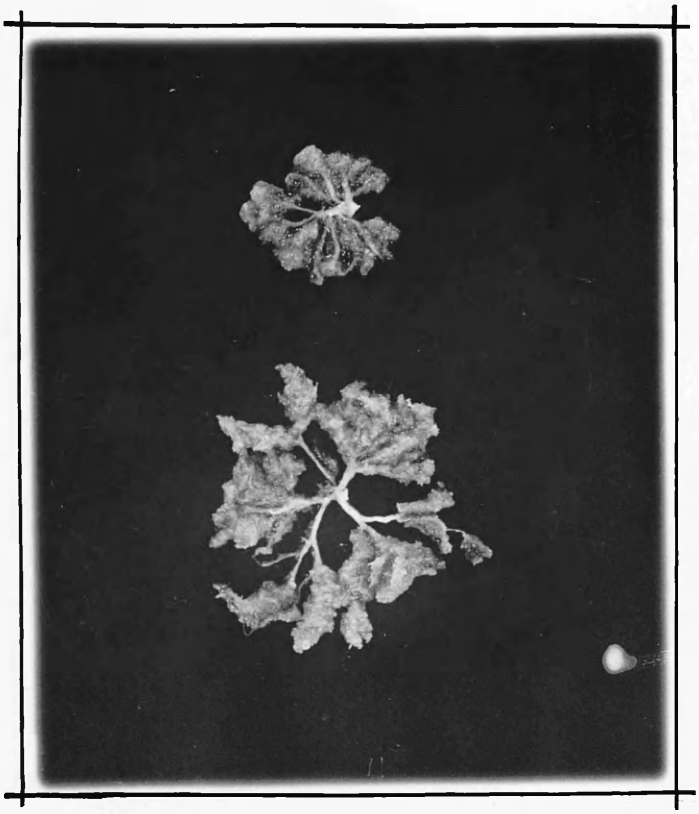

Figure No. 34. Life size.

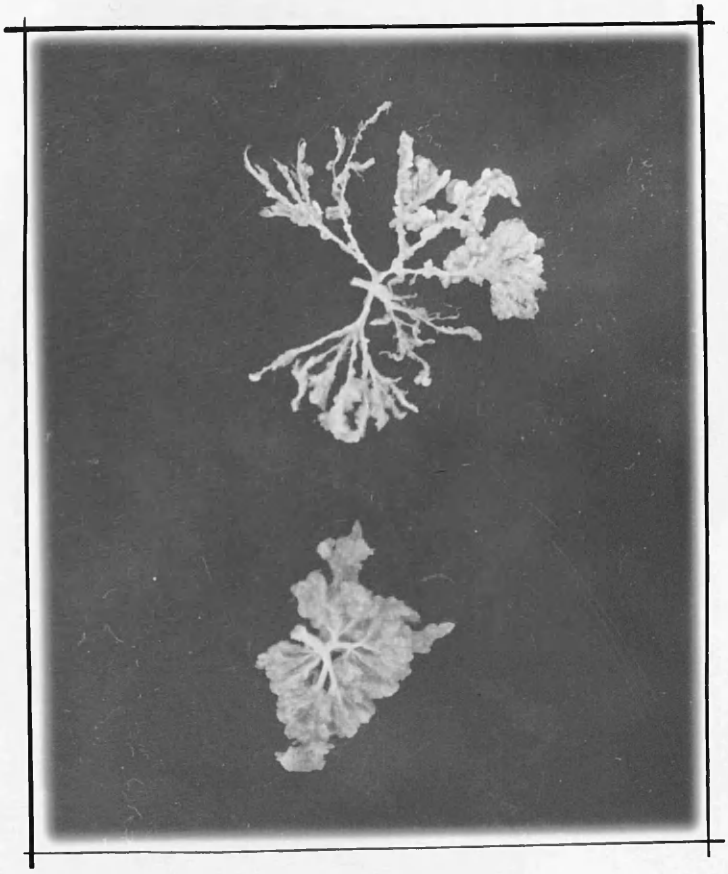

Figure No. 35. Life size.

Figure No. 36. Life size.

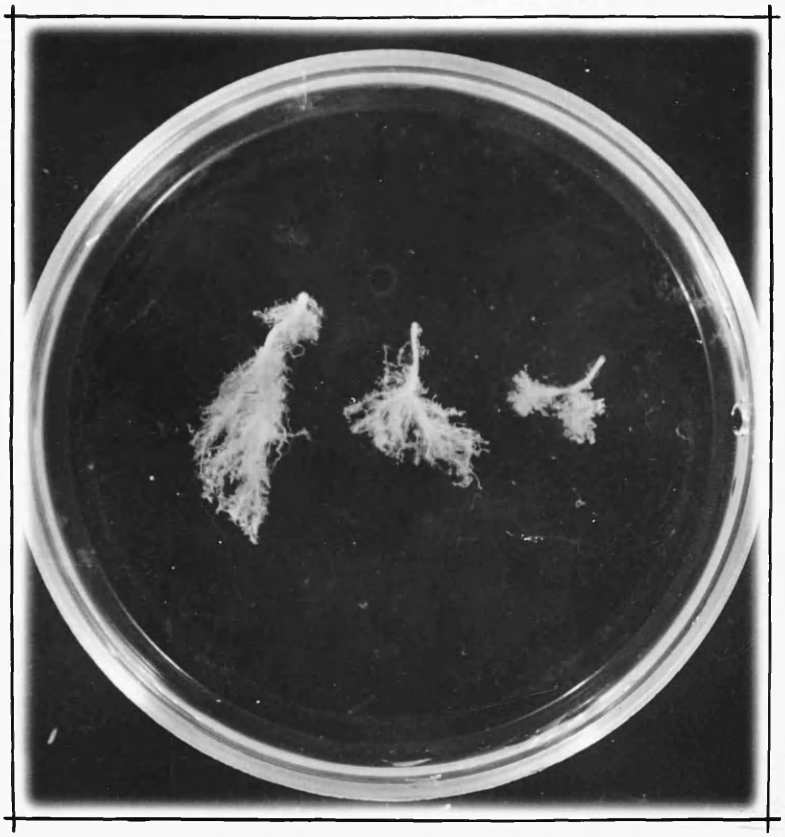

Figure No. 37. Life size.

Each specimen was taken from the terminal region of a sub-cotyledon and floated out in water. The "fringe" has increased not only in depth but in density.

THE MICROSCOPIC GROWTH OF THE PLACENTA.

THE GROWTH OF THE FRINGE REGION.

Foreword.

It has been shown that the fringe region increases in depth and density as the cotyledon becomes more mature. To the naked eye there is no change in the appearance of the fringe except that it is becoming greater and therefore much more prominent in appearance. This similarity in the appearance of the fringe is not borne out when it is examined under higher magnification. At each of the growth periods the characters of the structures composing the fringe are changing and maturing. The change from immature to mature fringe is not clear cut and dramatic. On the contrary the change is subtle and even at full-term structures can be seen, admittedly in smaller amounts, which were present at twelve weeks maturity or earlier.

The growth of the fringe region was studied in two separate ways.

1. Uninjected and uncoloured fringe material.

This unstained material was removed from the cotyledonary fringes of the ten uninjected

placentae which had already been used to demonstrate the gross growth and structure of the cotyledons. The earliest placenta studied was six weeks old and the most mature forty weeks old. From the fringe region specimens were obtained from these placentae in the usual fashion and mounted for examination.

2. Injected fringe material.

This material was obtained from the cotyledonary fringes of the twenty injected placentae. The maturities of these placentae ranged from twelve weeks until term. From the fringe regions of each of these placentae, specimens were removed and mounted in the usual way.

1. Uninjected and Uncoloured Fringe Material.

The change in the characters of the fringe, as it matures, will be described most suitably by indicating the types of structures found at the various growth periods.

At six weeks maturity the fringe region is a comparatively simple structure. It is produced by the division and redivision of the

primary and subsequent vascular trunks as in the more mature cotyledon. The fringe is composed of a number of bulbous structures, closely related to each other. They are of varying length and thickness. Some are long and tapering with a characteristic bulbous tip. Some, on the other hand, are short and thick with a rounded head and a constricted base. This short type of structure is the most prominent at this stage. The bulbous structures produce the further growth of the cotyledon and fringe and will be termed, in this account, the "growing ends". The growing ends are semi-transparent and difficult to photograph in consequence. The application of ordinary histological techniques to demonstrate them has been disappointing. Such techniques distort and break up these delicate structures and no satisfactory method has been found as yet to reveal them more clearly. They appear to consist of an outer coat of syncytiotrophoblast, lined possibly by cytotrophoblast and possessing a central core

of mesoderm. Vascular channels are present within and these are often outlined by foetal blood within them. The growing ends resemble the "streamers" of syncytium seen in the early days of placental growth. They resemble also, the club-shaped structures which were demonstrated by Braxton Hicks[41] many years ago. He believed that they were responsible for entering the decidua and fixing the placenta.

The growing ends are shown in low magnification in Figures 38 and 39, and in higher magnification in Figures 40, 41 and 42. Figures 40 and 41 demonstrate the long slender "growing end" and the characteristic bulbous tip. Figure 42, in contrast shows a shorter and generally more bulbous type of growing end. The vascular channels within are outlined by foetal blood and demonstrates their number and complexity.

At ten and twelve weeks maturity the growing ends remain unaltered in structure except that they increase in number and length. The fringe becomes more dense and larger. At

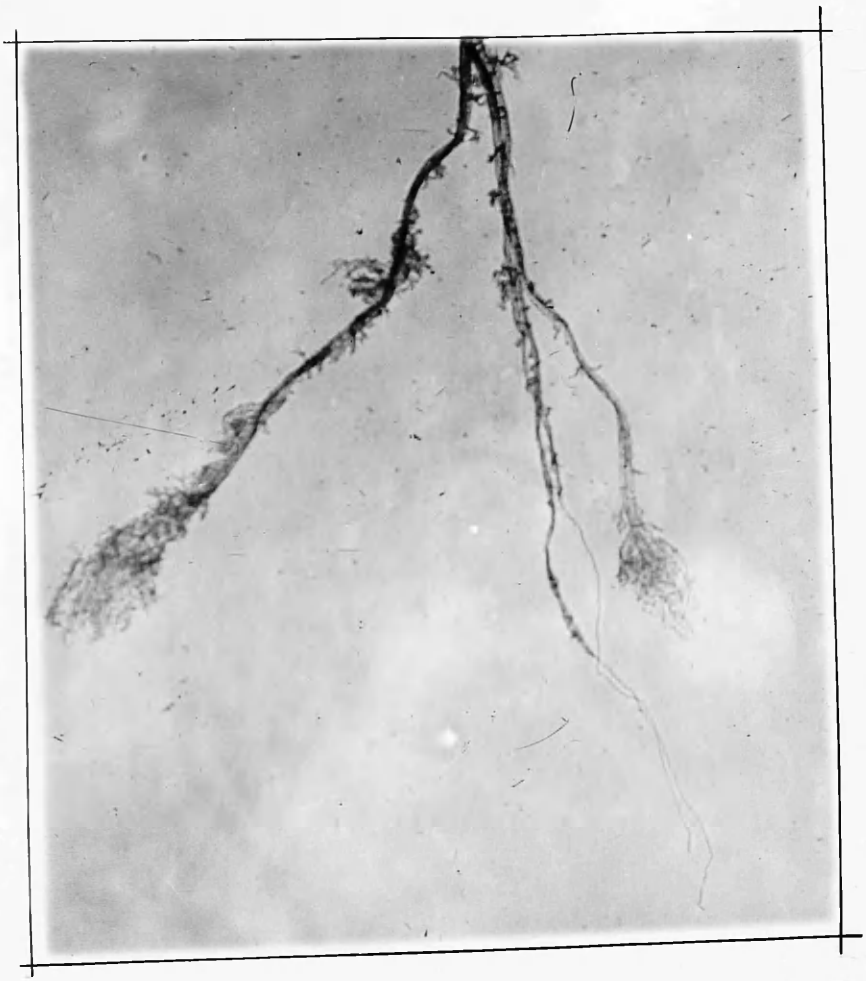

Figure No. 38. X 80.

Figure No. 39. X 200.

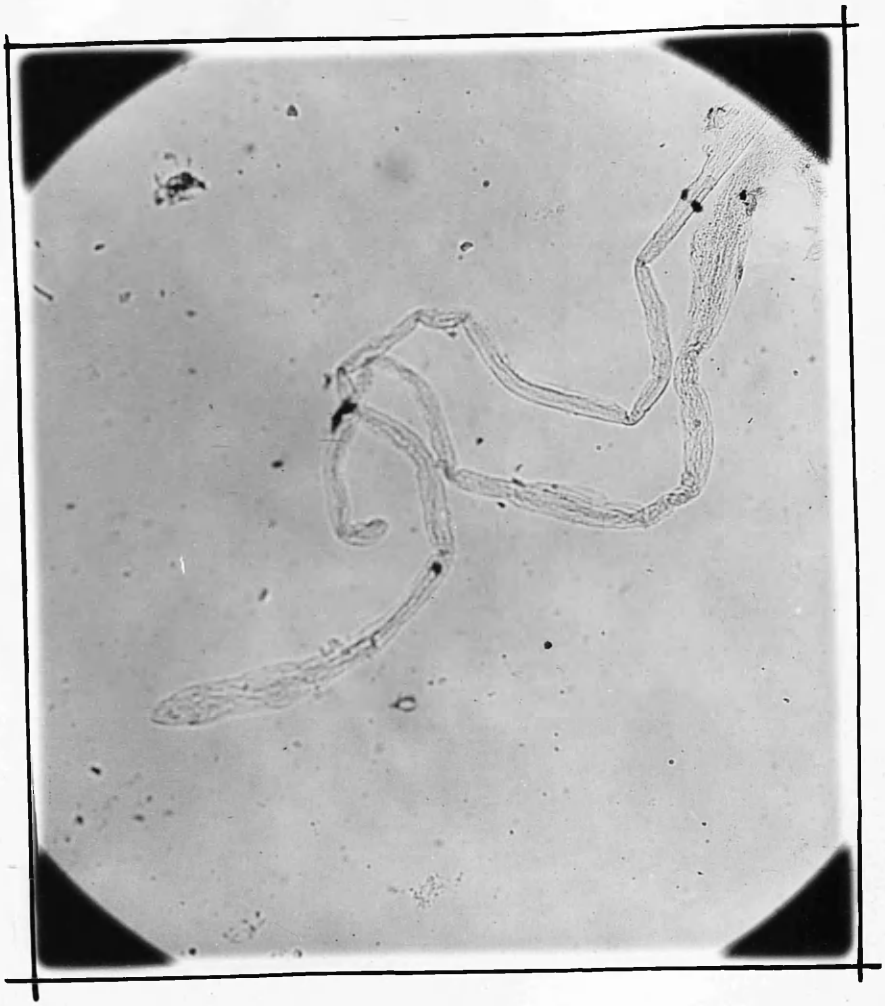

Figure No. 40. X 200.

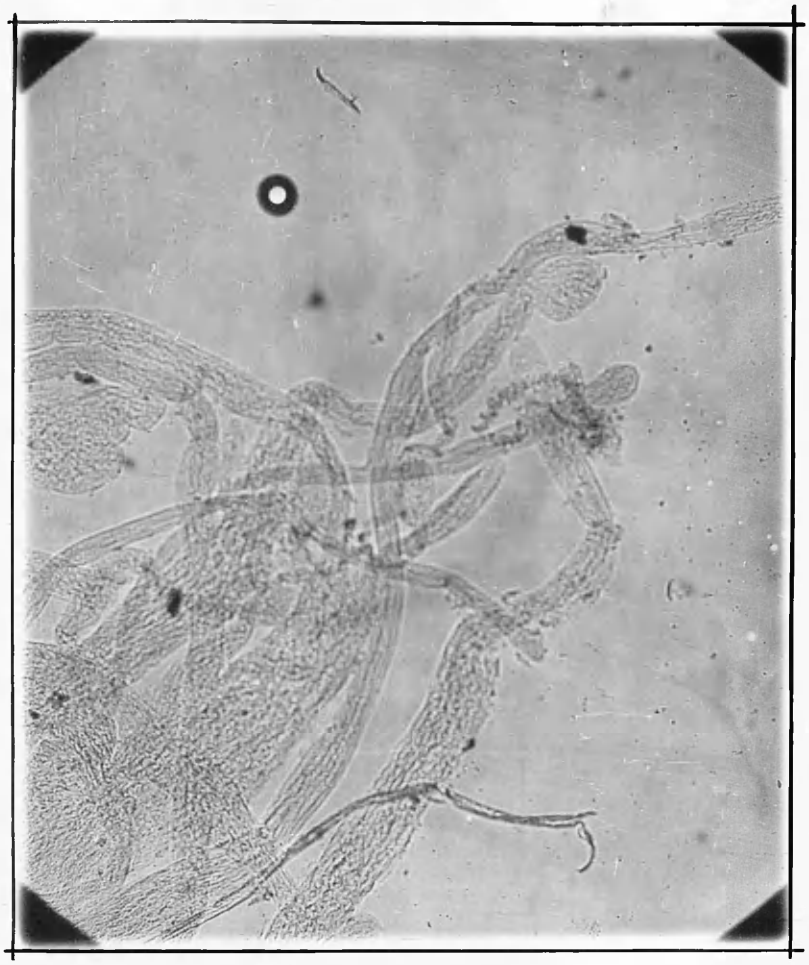

Figure No. 41. X 200.

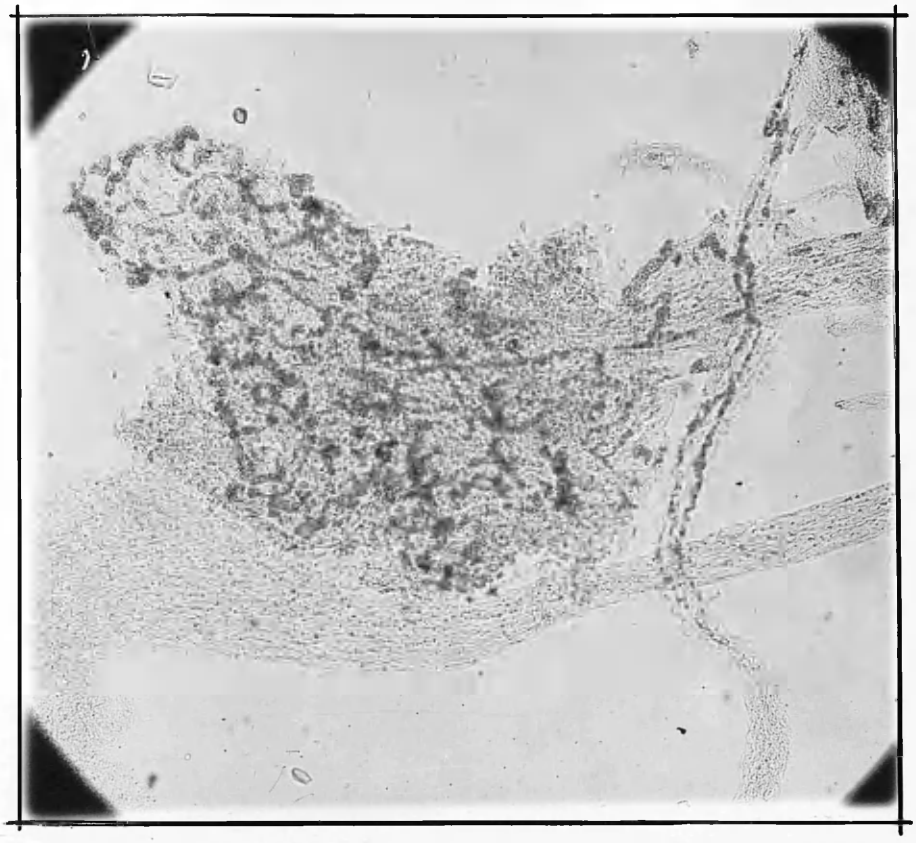

Figure No. 42. X 280.

sixteen and twenty weeks the appearance of the growing ends begins to alter, the change is a subtle one as stated already. The growing ends are manifestly longer and bigger. The short bulbous varieties are less numerous, although they are still present. Instead, the predominant growing end is a long sturdy projection and it is rational to assume that they have been derived from the growing ends seen in earlier placental fringes. In addition many of the growing ends are not simple tubular structures any longer. They are beginning to push out small simple rounded projections along their free borders, and are often showing a division into two or more sub-divisions at their extremities. These developments are seen in Figures 43 and 44.

At twenty-four and twenty-eight weeks maturity the development of the growing end has continued and increased. The lateral rounded projections have increased in size, lengthened and themselves constituting small growing ends. The parent growing ends have, at the same time

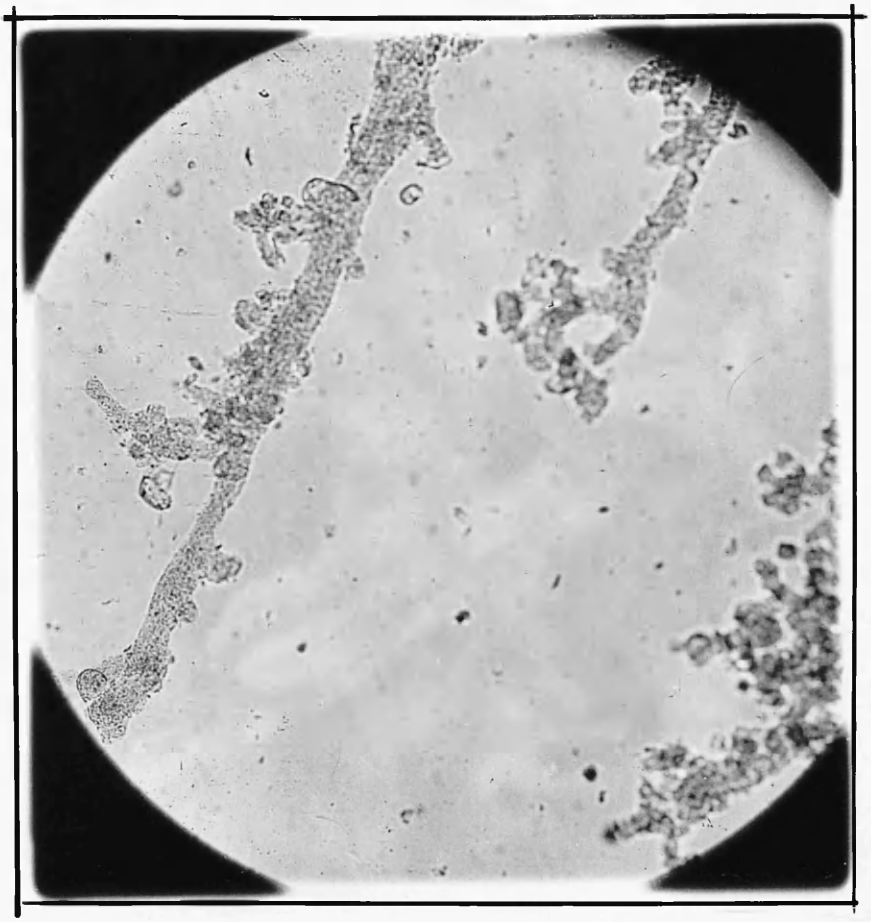

Figure No. 43. X 200.

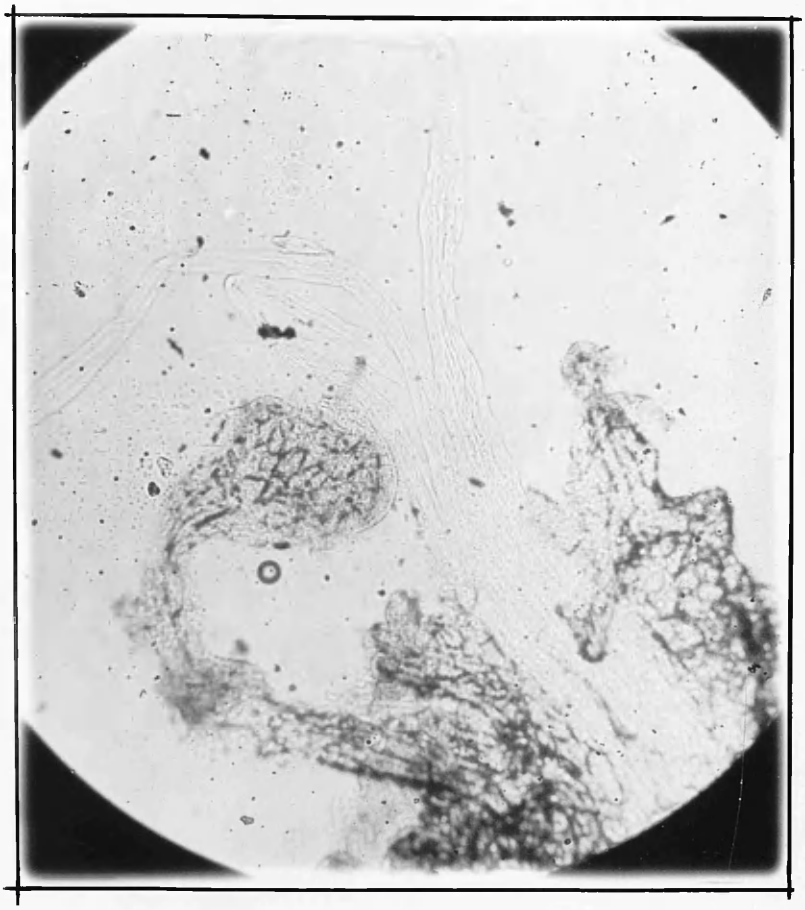

Figure No. 44. X 200.

steadily increased in length and width and in their less peripheral regions are quite robust structures. Lateral projections are borne at all levels of the parent growing end, but are naturally smaller in length and bulk as the extremity of the parent growing end is reached. In addition many of the parent growing ends have a somewhat bulky tip, not unlike these described already in less mature placentae. The increase in the bulk and number of growing ends has increased noticeably the density of the fringe. It must be repeated at this point that at this stage of development all the varieties of growing ends already described are still present in the fringe area.

In the succeeding weeks, until term is reached, the development is an exaggeration and multiplication of that already described. The growing ends continue to lengthen whilst at the same time becoming in their proximal parts stout and robust structures. The lateral projections are now of considerable size and equal to the parent growing ends which produced

them originally. They show also, as they lengthen, small rounded projections and these very obviously are also becoming growing ends. Undoubtedly in their turn, as the placenta matures, these will lengthen, become more robust, and produce growing ends. This continual production and growth of growing ends is well illustrated by Figure 45. The tip of the original growing end can still be seen. The daughter growing ends are themselves of considerable size and have already produced small lateral growing ends. The increase in the numbers of growing ends is reflected in the increasing density of the fringe. Figure 46 shows the fringe from a placenta at term and the density of growing ends is most striking. In the last few weeks of pregnancy the growth appears to slacken. Growth is still taking place, but the growing ends are usually small blunt projections in their most peripheral regions. The long tubular projections are still seen, even at term, but are not numerous. The blunt extremities of the growing ends seen in

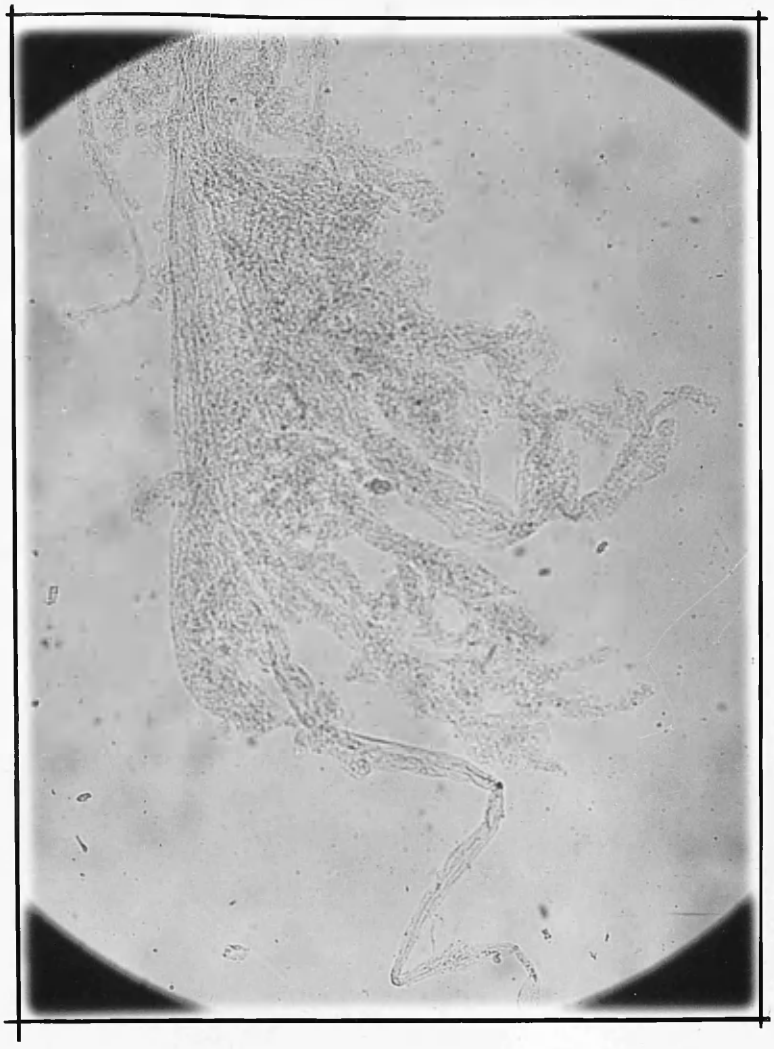

Figure No. 45. X 200.

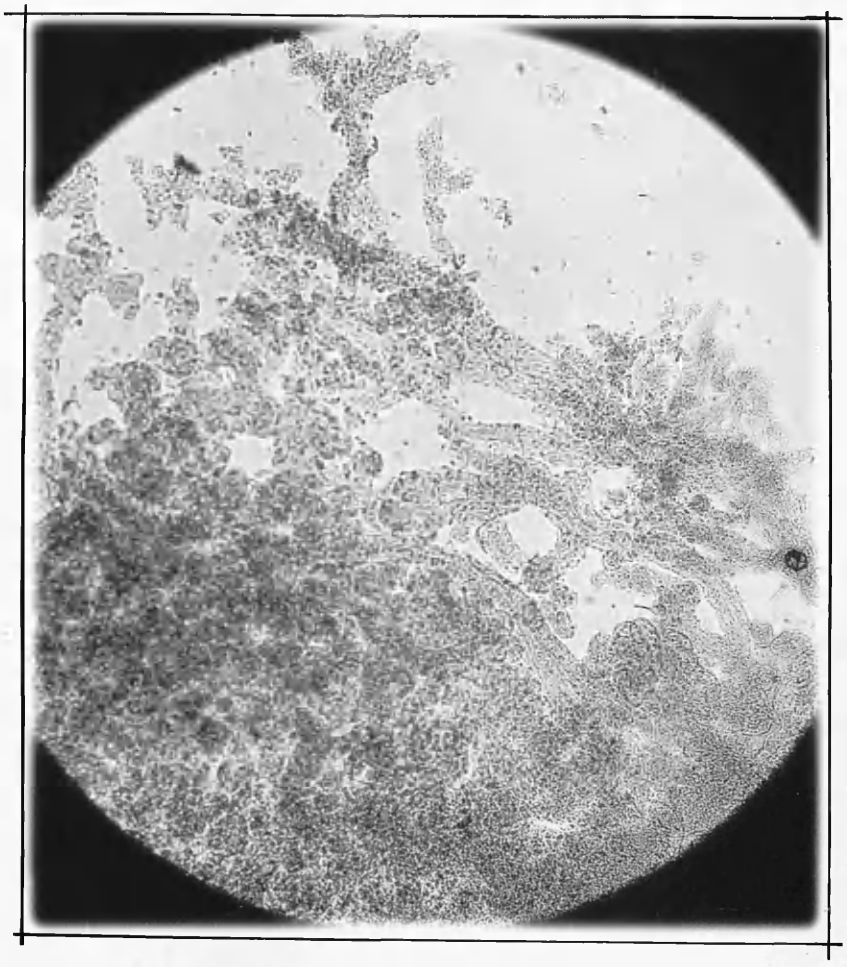

Figure No. 46. X 200.

the last few weeks, produce, when injected with dye, the familiar appearance of mature placental capillaries. These structures have already been described in Part One and will be studied again in greater detail in the next section.

The description of the changes in the structure of the fringe which has been given, provides a clue to the origin of the placental capillaries. The placental capillary, seen in the mature placenta, represents the bulbous tip of a growing end. This tip is not unlike that seen in less mature placenta but the appearances suggest that at or near full term growth is beginning to slacken in rate and amount. The anatomy of these structures is better understood in injected specimens and will be discussed in the next section.

2. Injected Fringe Material.

The description given in the previous section of the structural changes in the "fringe" region can be regarded as a prelude to the full investigation and understanding of placental growth. This full investigation is

only possible with injected placentae. It is only with a suitable dye filling the smallest foetal vessels that an appreciation of their structure and development can be obtained.

Twenty placentae with maturities from twelve weeks to full term were investigated. Each placenta, after digestion and washing, was injected with a suitable dye through the umbilical vein. The whole placental fringe area was subjected to close examination and not less than fifty preparations were made from each placenta. The photographs, which will be seen, represent the best preparations obtained from these placentae. The best preparations were selected in order to present as striking a picture as possible of the growth processes.

The fringe material obtained will be examined and discussed under the following headings.

A. THE GROWTH OF THE GROWING END.

B. THE ORIGIN OF THE GROWING END.

A. THE GROWTH OF THE GROWING END.

At twelve weeks maturity the fringe of the cotyledon is composed of growing ends of two varieties. There is a long slender growing end, and a shorter blunter and much thicker variety. The blunt variety is the most common and forms a very characteristic feature of the early fringe.

This short and blunt growing end, has a bulbous tip with a constricted base and is packed full of vessels of different diameters. It is possible to discern that some of the vessels are quite robust, but the majority are of much smaller calibre. They are joined by a numerous system of anastomoses and this is particularly marked at the bulbous tip. Precise examination of these vessels is not possible because of their density. Even at this early stage, the free edges of the growing ends show small rounded projections. The characteristics of this blunt growing end is well seen in Figure 47.

The long slender growing ends show many

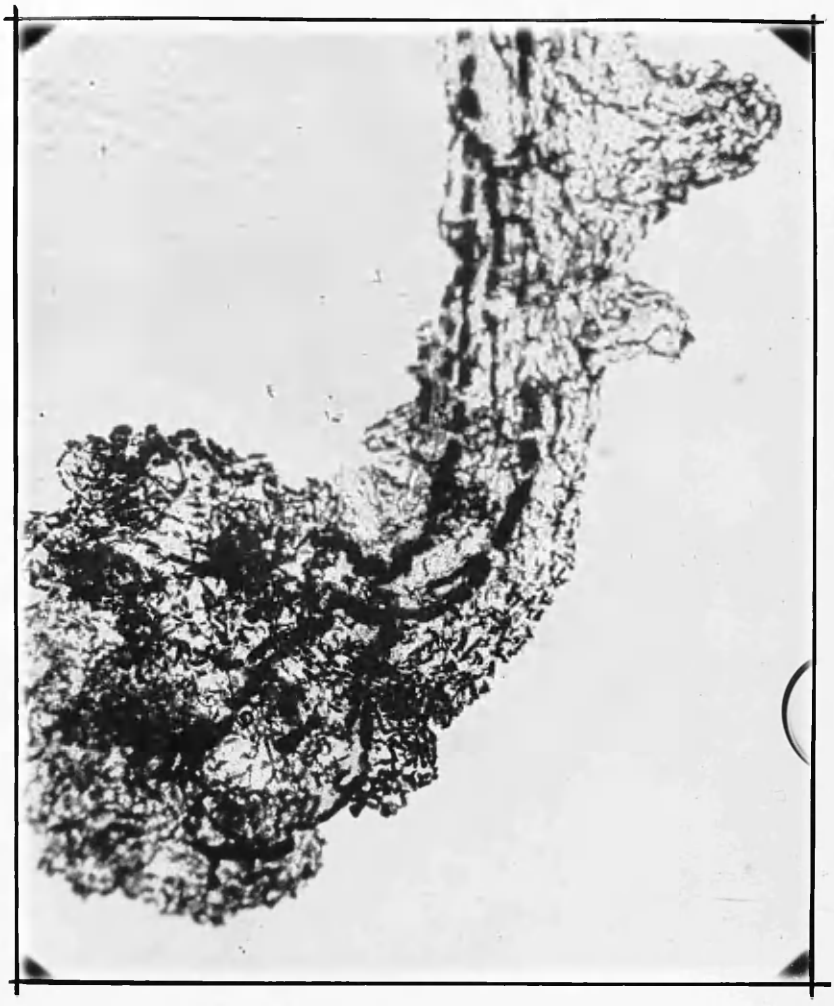

Figure No. 47. X 280.

fewer vessels, but it is obvious that a system of anastomosing vascular channels runs the whole length of the growing end and is particularly dense at its bulbous tip. It is uncertain how many vascular channels run the length of the growing end but there appears to be two main channels with a recurring system of anastomosing vessels around them. At some areas there would appear to be four vessels concerned in the anastomosis. It is certain that all these vascular channels are in free communication with each other. If the bulbous tip is very elongated the dye usually fails to reach it and the appearances suggest that vessels may have not yet formed in these areas. However this is not by any means certain. The absence of dye might merely indicate imperfect penetration. The slender growing ends are illustrated by Figures 48, 49 and 50.

These photographs show very well the system of anastomosing vessels indicating that an arterio-venous anastomosis is present. In addition numerous rounded projections are

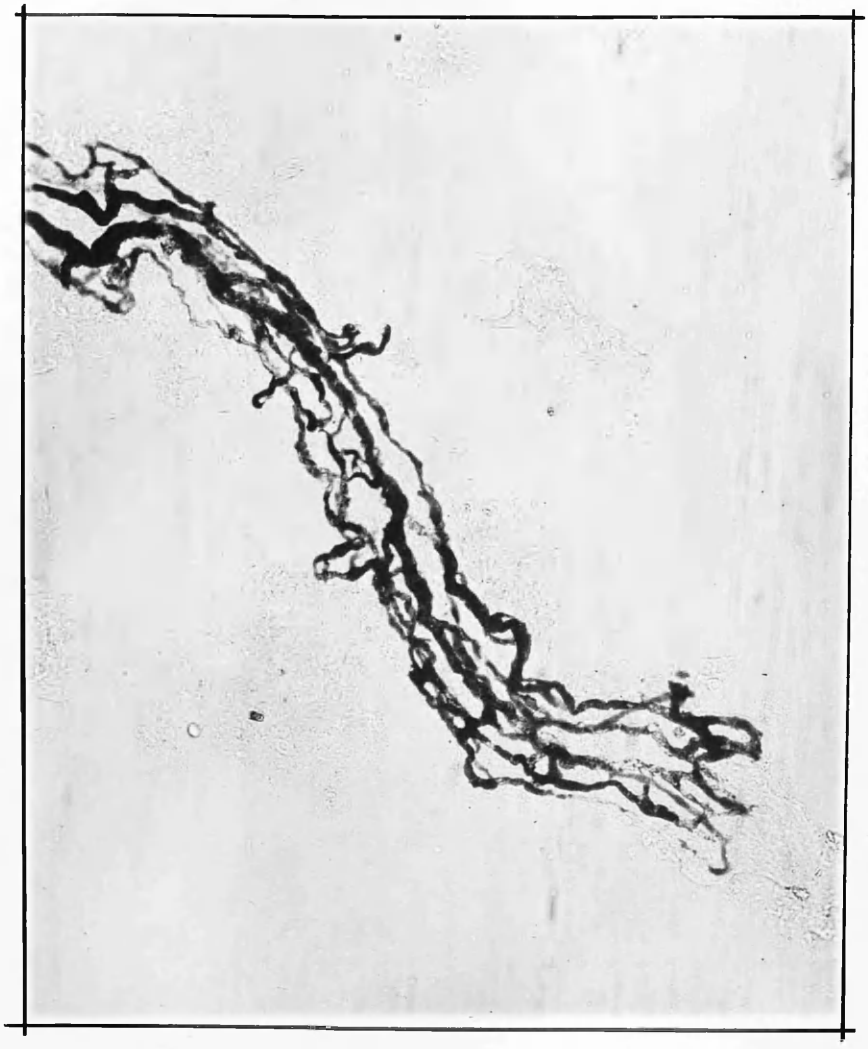

Figure No. 48. X 280.

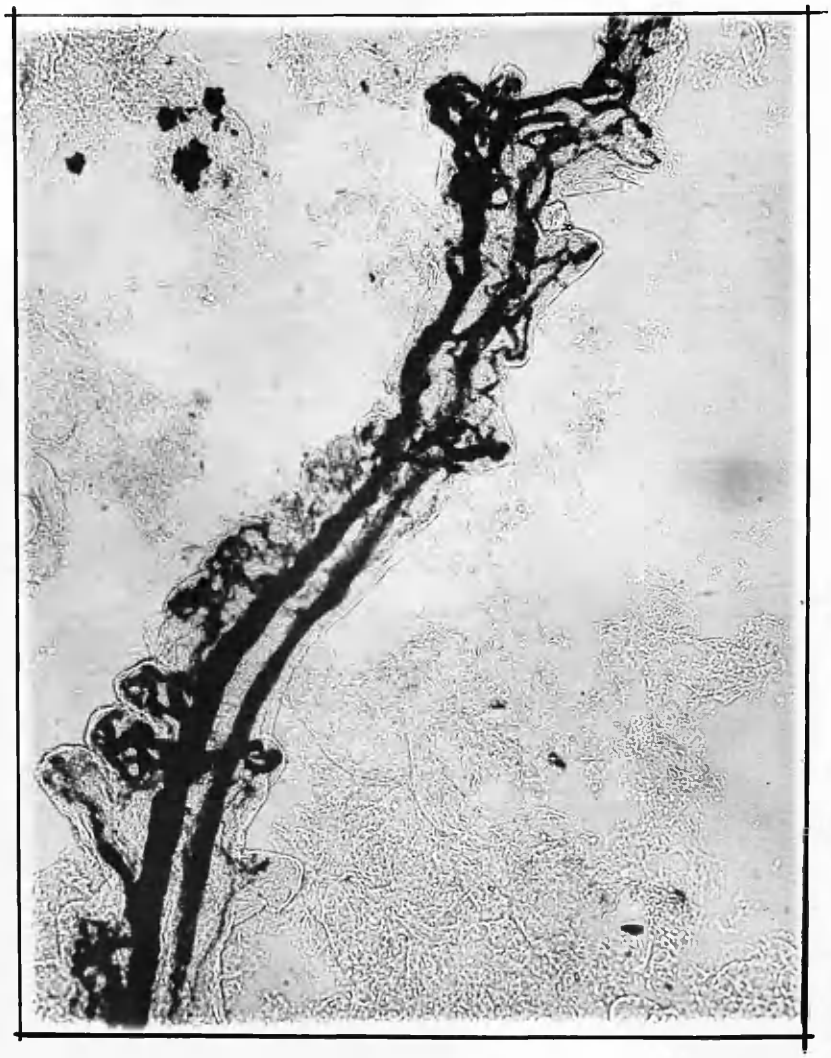

Figure No. 49. X 280.

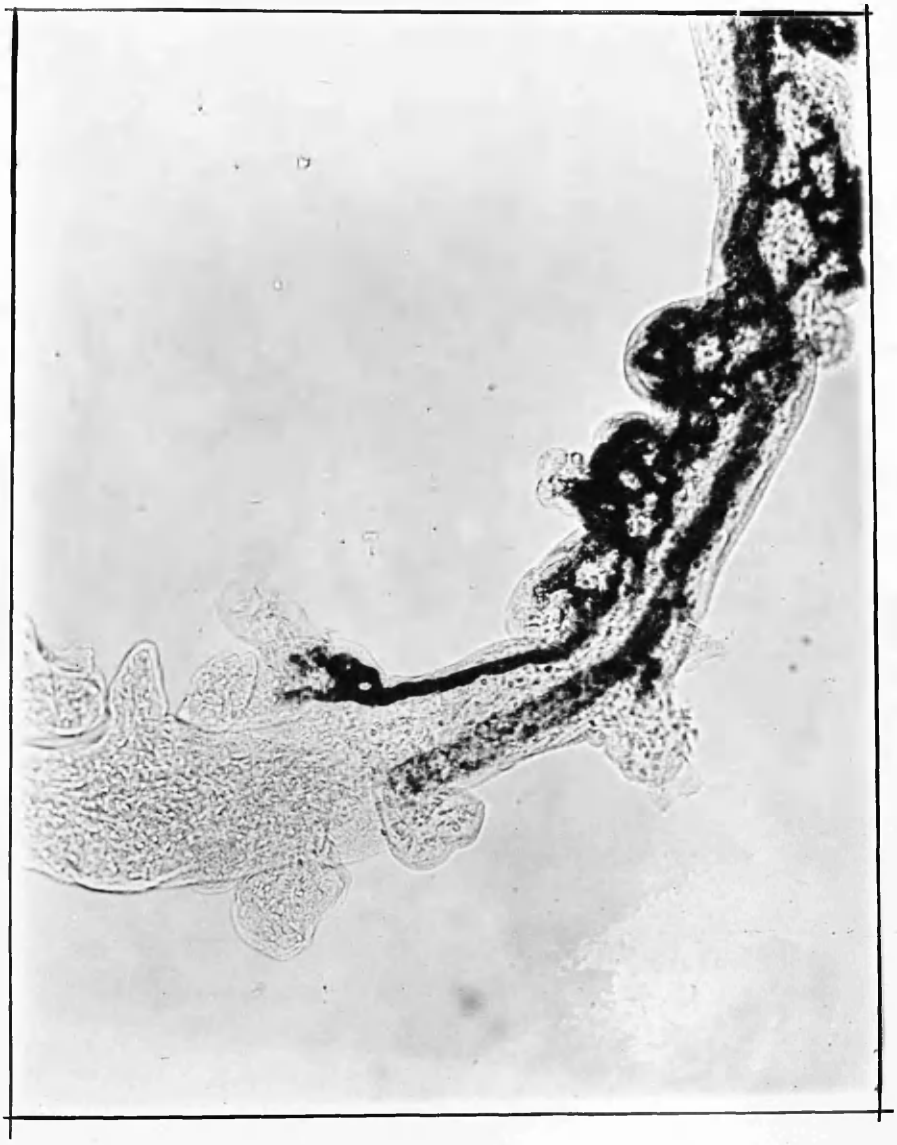

Figure No. 50. X 280.

present, and in most instances they can be seen to be occupied by vessels. In some cases there is only a single vascular channel, but in others there is already a system of anastomosing vessels.

In Figure 50 the dye has failed to reach the bulbous tip of the growing end but this probably indicates imperfect penetration of the dye. A segment of growing end is shown in higher magnification in Figure 51. The extent of anastomoses is well seen.

The two types of growing end persist, and can be seen even when the placenta is twenty or more weeks old. The disposition of the two varieties changes however. The slender variety becomes more numerous, and at the same time the short growing end is seen to be longer and less broad. It seems fairly certain that the slender growing end is derived from the shorter variety by growth, and especially growth at its bulbous tip. This growth is illustrated by Figure 52. The tip of the short growing end has divided into two "streamers" of syncytium and these have

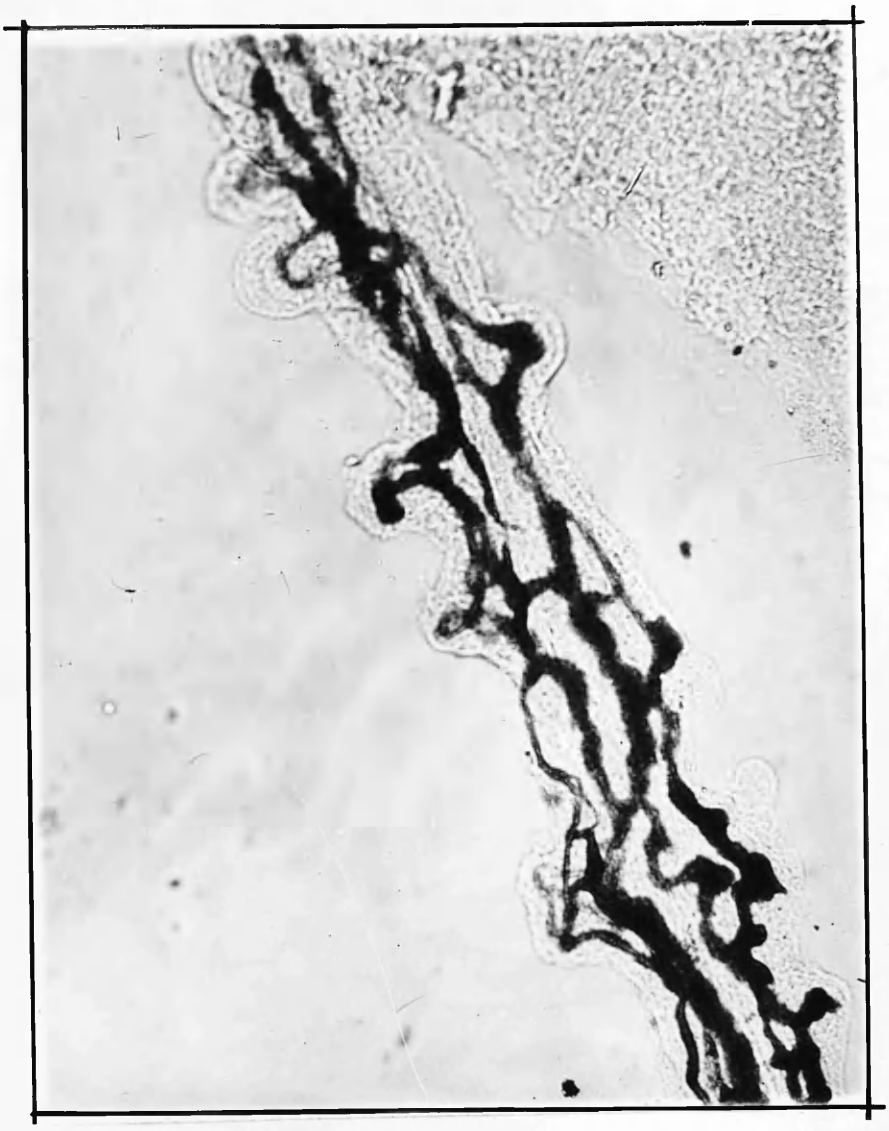

Figure No. 51. X 400.

Figure No. 52. X 280.

not filled with dye. Proximal to this region the system of anastomosing vessels is well seen. Two distinct projections of syncytium are also present and both are already filled with many intercommunicating vessels.

The bulbous tip of the growing end often divides into numerous syncytial streamers, and in Figure 53 such a division has taken place into three distinct growing ends. As already pointed out these have not filled with dye.

In some growing ends the growth appears to be more uniform and the growing end will lengthen while retaining its complex system of anastomosing vessels. This is illustrated by Figure 54. It will be apparent that the growing end is of considerable magnitude. Several syncytial projections are present, and one on its upper border is of considerable size and itself assuming the characteristics of a growing end. The system of anastomosing vessels within is already complex and the whole structure rather resembles a mature capillary and villus.

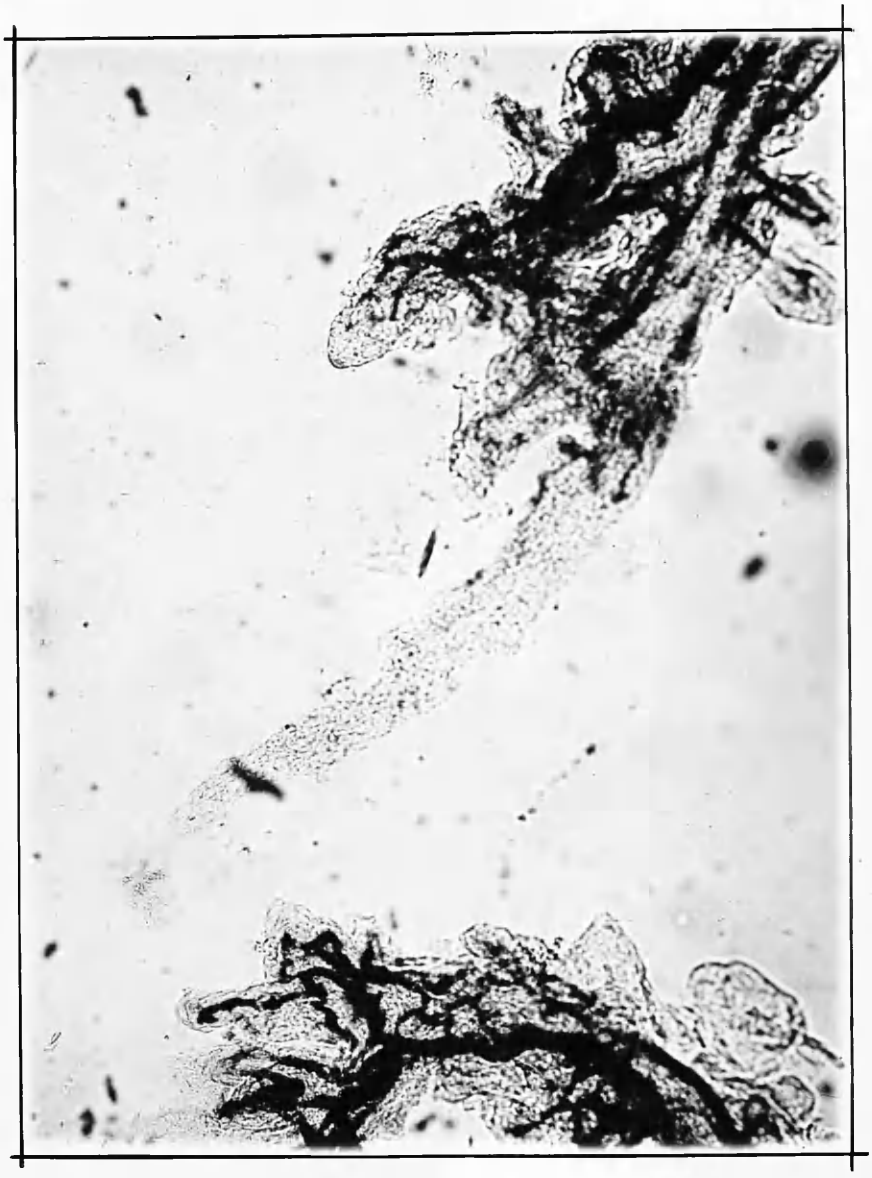

Figure No. 53. X 280.

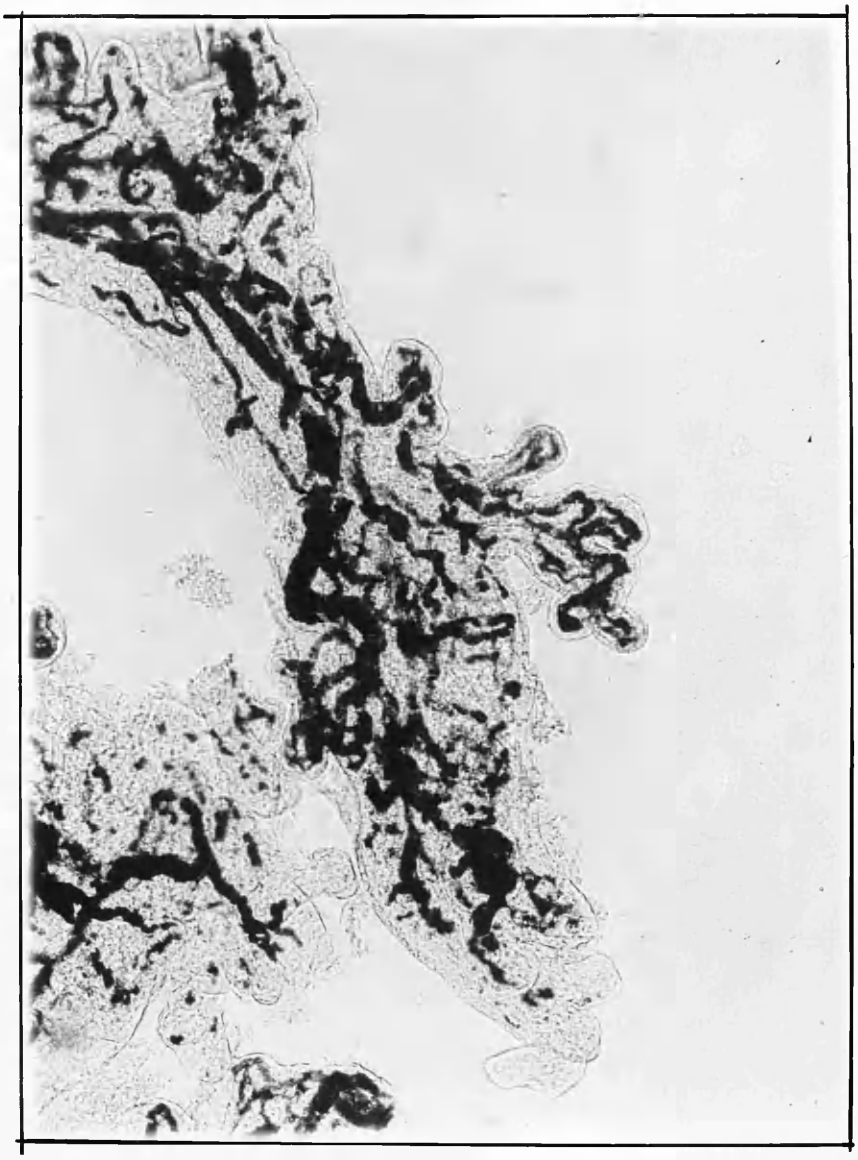

Figure No. 54. x 280.

Subsequent growth after the twentieth week continues the same pattern. Growing ends are becoming larger, more robust and bearing a succession of small growing ends along their lateral surfaces. The short robust structure is only seen at the extreme tip of the growing end and the complex anastomoses of vessels within the tip is much less involved. The vessels are less numerous and the numerous vascular connections more readily followed. Figures 55, 56, 57 and 58 illustrate these changes. Figure 55 demonstrates a growing end bearing a succession of daughter growing ends along its free margins. Several of these small structures already contain a complex of vessels within the syncytium.

Figure 56 demonstrates particularly well the complex vascular anastomoses within the tip of the growing end. Terminal structures like these described are seen at all stages until term. Gradually, however, the terminal vascular structures become modified and assume, with the enclosing syncytium, the shape of

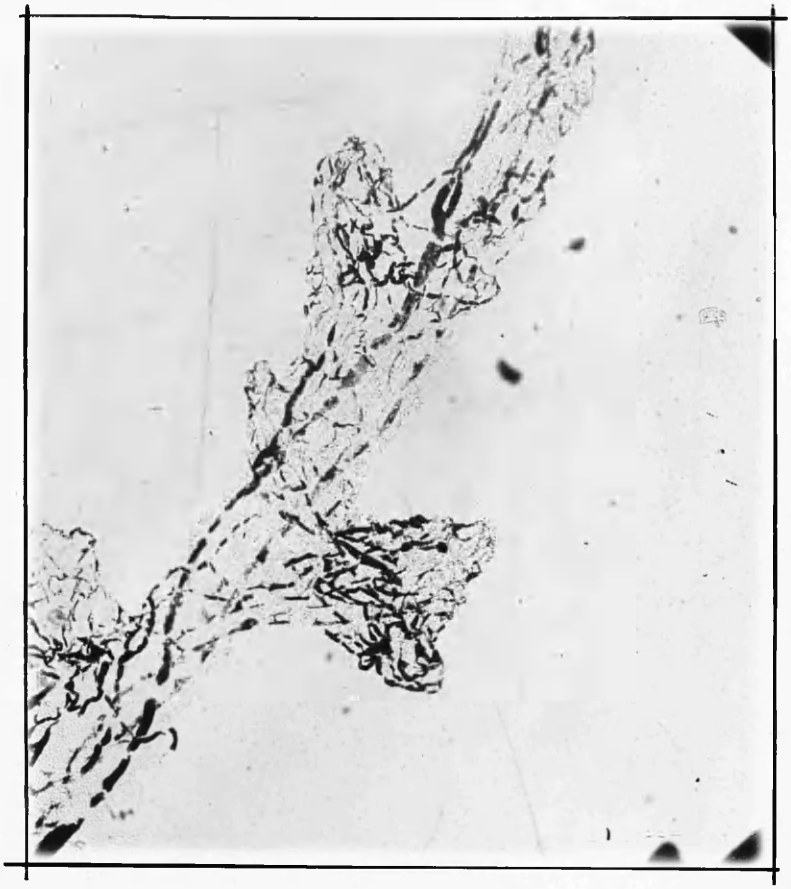

Figure No. 55. X 280.

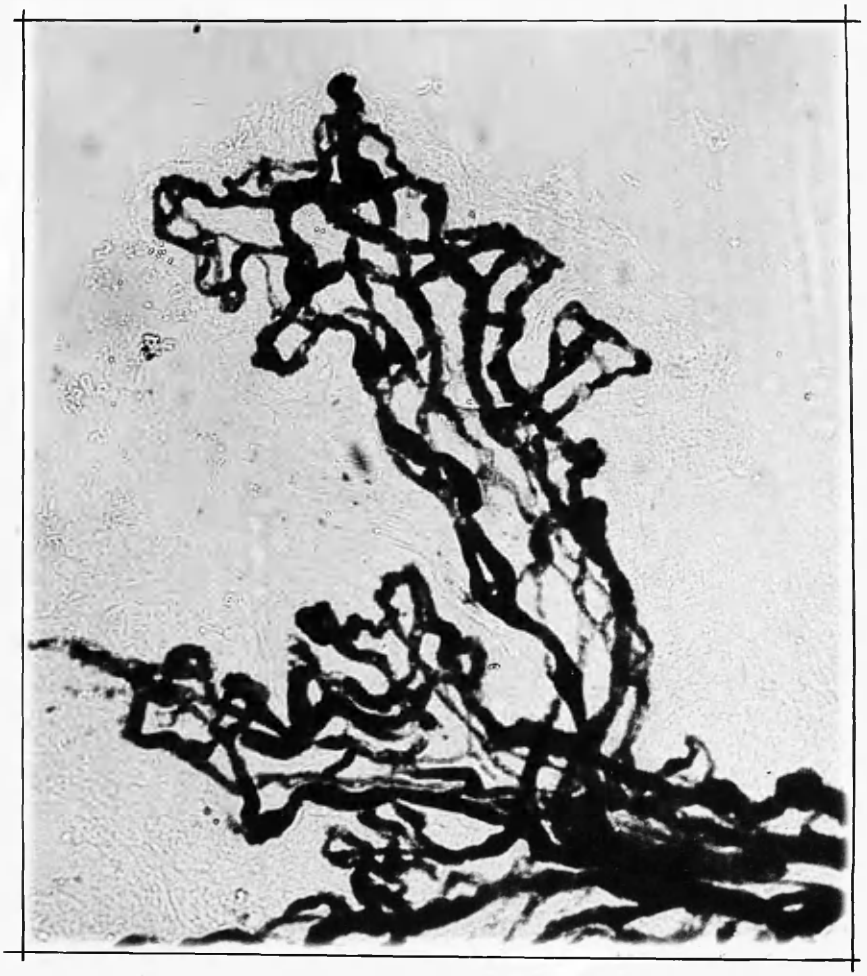

Figure No. 56. X 400.

structure associated with adult capillaries and villi. It must not be assumed that the adult form of villi are only seen near full term. Villi with adult shapes can be seen much earlier, for example at 20 weeks as shown by Figure 57. The Writer has emphasised already that there is no hard and fast line between different structures in the development of the growing end. There are, as it were, only trends in these developments.

Figure 58 illustrates the type of villus seen, most commonly, at or near term. As already explained, such villi represent the extreme tip of the original growing end. Growth as evidenced by the simplicity of the vascular pattern within the villus is slackening but still taking place. This is demonstrated by the numerous small daughter growing ends borne laterally.

The growth of the growing end has been presented somewhat artificially in order to present as clear a picture as possible. It should be appreciated that as the parent

Figure No. 57. X 280.

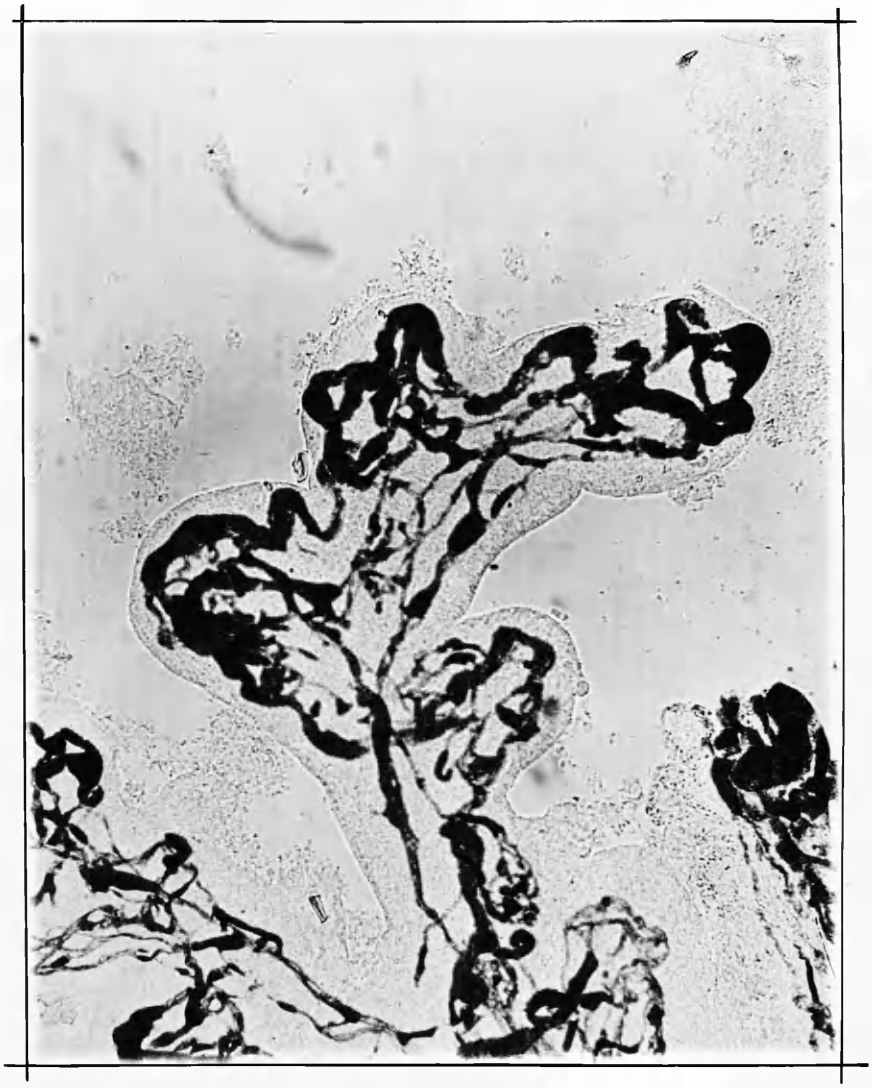

Figure No. 58. X 400.

growing end develops, the daughter growing ends are also developing in much the same way. These obscure the parent growing end and, of course, at the same time increase the density and size of the fringe. The only part of the parent growing end which is seen clearly in the latter weeks of pregnancy is its extreme tip which is still present above the heads of the daughter growing ends developing alongside. The origin of the growing end will be considered in the next section.

B. THE ORIGIN OF THE GROWING END.

The origin of the growing end and its subsequent development is a most interesting subject for study. Not only for itself but because it explains so many of the features of placental anatomy which have been so far obscure.

It was stated previously that the growing ends seen in early placentae showed along their lateral margins small rounded projections of syncytium. These initially appear as a "peaking" of the syncytium but quickly the

rounded form is assumed. At first the "peaking" of the syncytium is free from vessels, but almost at once a vessel opposite the projection begins to arch and move into the syncytial projection. This vascular development is derived from one of the vascular channels, anastomosing along the whole length of the parent growing end. The vascular arch within the syncytium is single at first but quickly other vascular channels opposite the syncytial projection begin to move inside. This has the effect of filling the syncytial projection, which is now rounded in form, with its own system of anastomosing channels. This rounded projection is now a small growing end in its own right.

These developments are illustrated by Figures 59, 60, 61 and 62. Figure 59 shows a parent growing end and a number of different stages are present in the development of the daughter growing ends. These range from a simple elevation of syncytium to a rounded structure containing its own system of

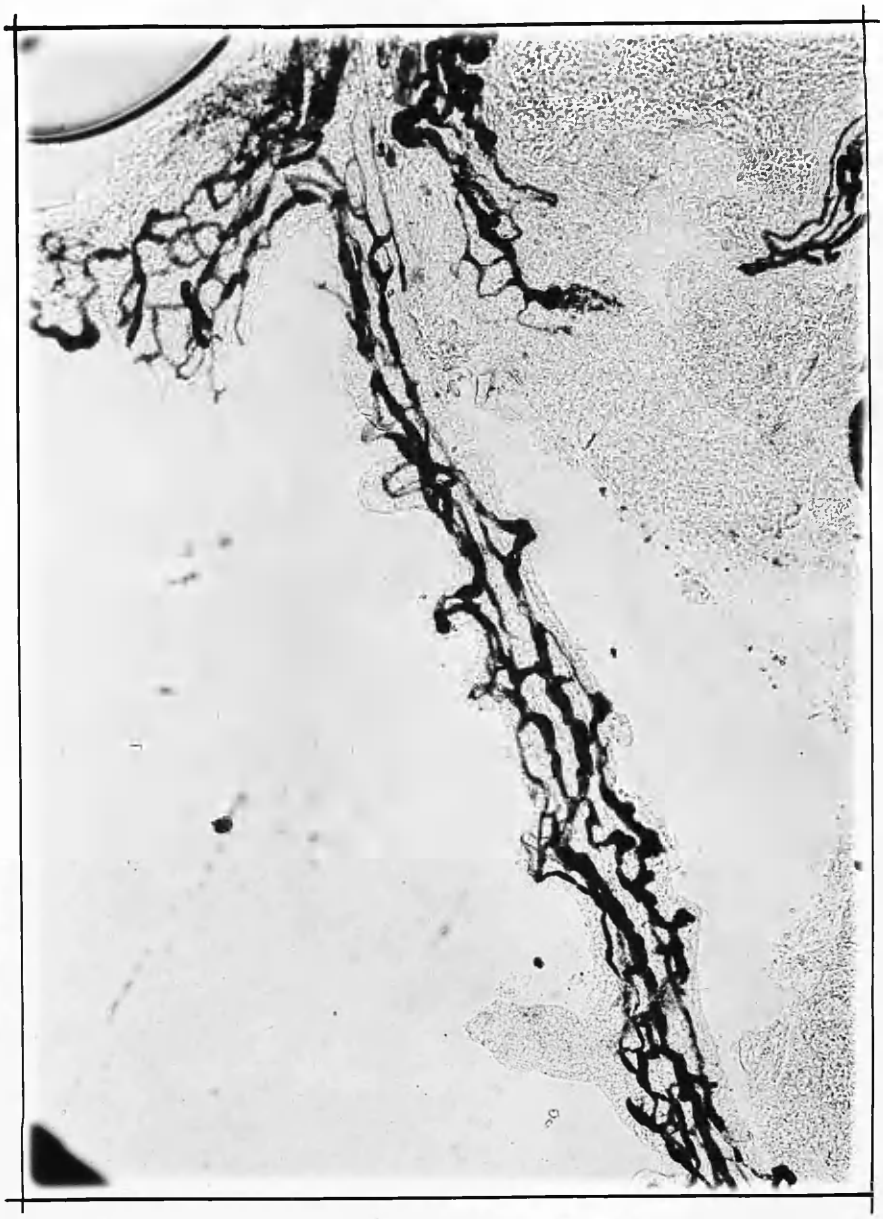

Figure No. 59. X 280.

anastomosing vessels. It is clear that the vascular channels are being derived from the parent vascular anastomoses.

Figure 60 shows two of these early growing ends in higher magnification. One contains only a single vascular arch but beneath it a second vessel is already moving towards it. The other growing end has already acquired a simple anastomotic system.

In Figure 61, the vascular development has increased and at least two anastomosing vessels are seen in addition to the parent vascular arch.

In Figure 62, the entrance of the anastomosing network into the syncytial projection is complete. The anastomosing network is readily seen, and four separate vessels can be seen entering the projection. It is apparent from the photograph that this system of vessels has been derived from the parent anastomoses. The syncytial projection does not remain a simple rounded structure. It begins to elongate and as it grows the

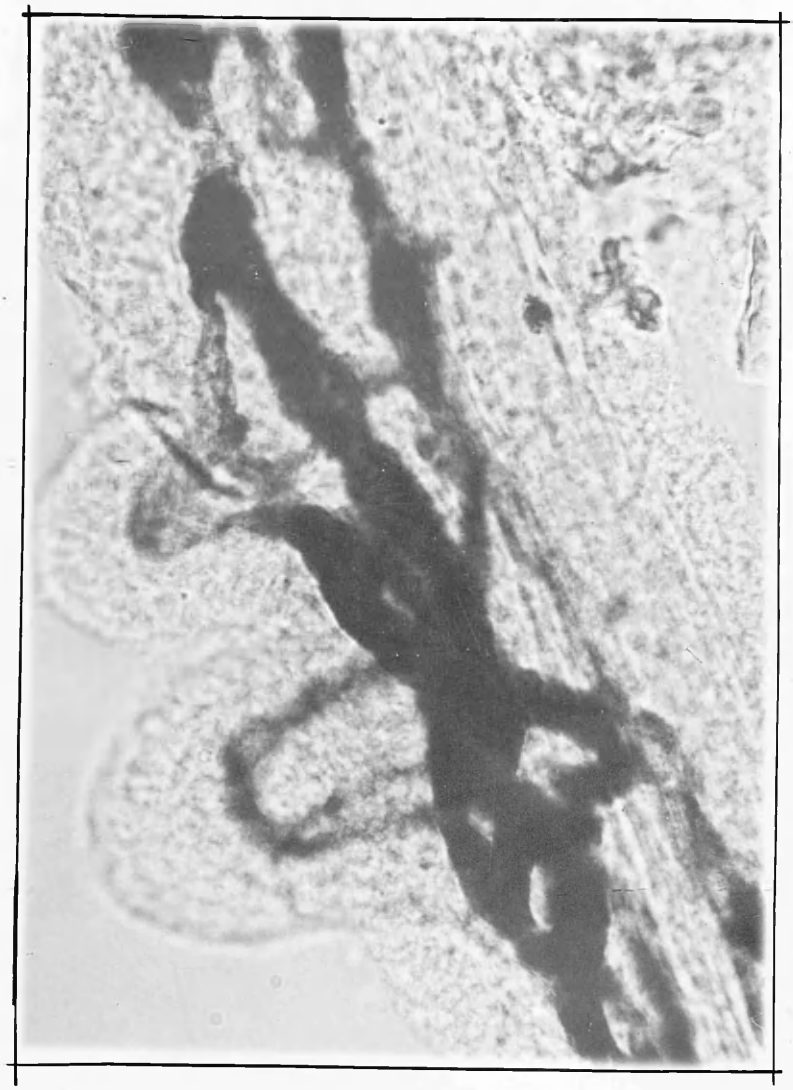

Figure No. 60. X 700.

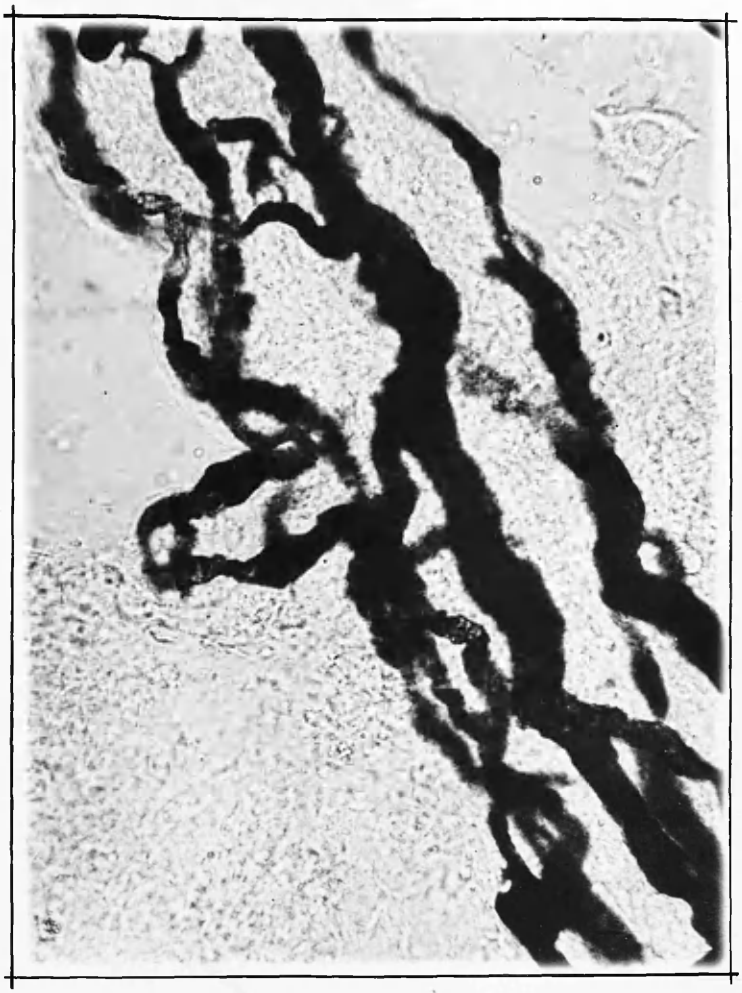

Figure No. 61. X 400.

Figure No. 62. X 700.

anastomoses within grows with it. The growth must be uniform because the covering syncytium never appears empty - the available space within is always fully occupied by vessels. At this stage the daughter growing end is fully independent and will develop further, quite independently of the mother growing end. The elongation of the small growing end and the growth of the anastomoses within are illustrated by Figure 63. At least three stages of growth are seen in this illustration, and the vascular network is clearly seen in each example. The daughter growing end may remain as a single structure but much more commonly division takes place at the tip, forming two or more rounded projections. Into these the vascular channels follow, and this has the effect of dividing the daughter growing end into two separate growing ends. It is understood that they are still in vascular connection with each other. This development is illustrated by Figures 64, 65 and 66.
The vascular connections which attach the small

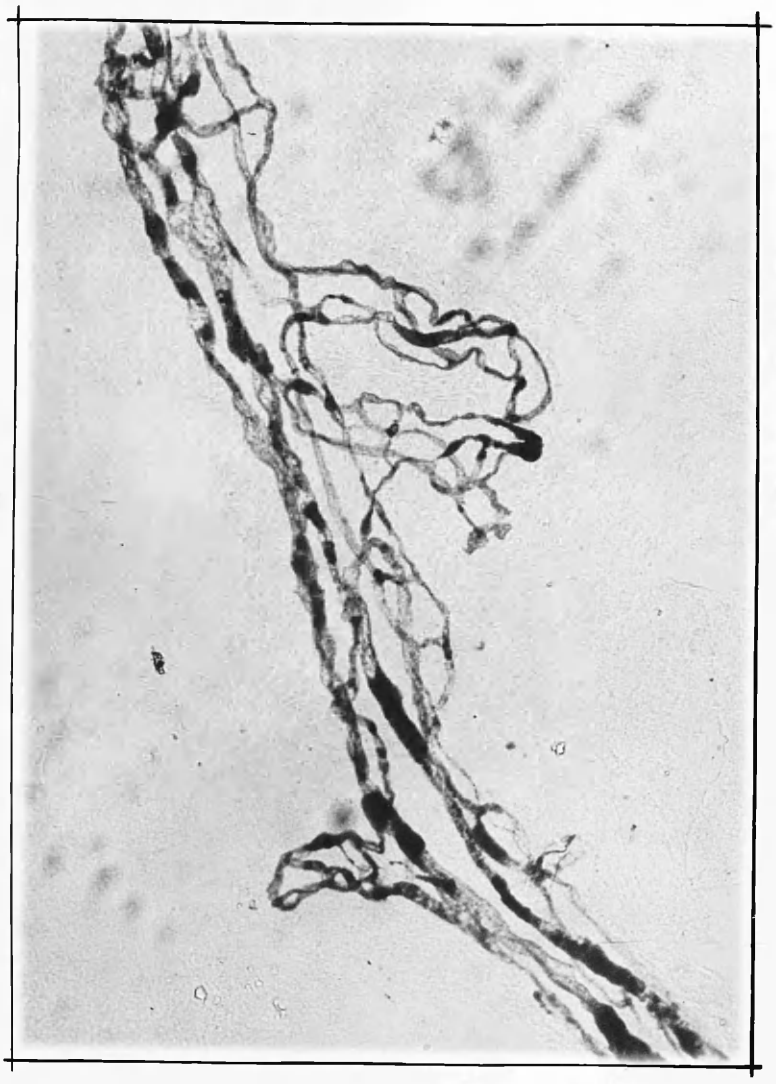

Figure No. 63. X 280.

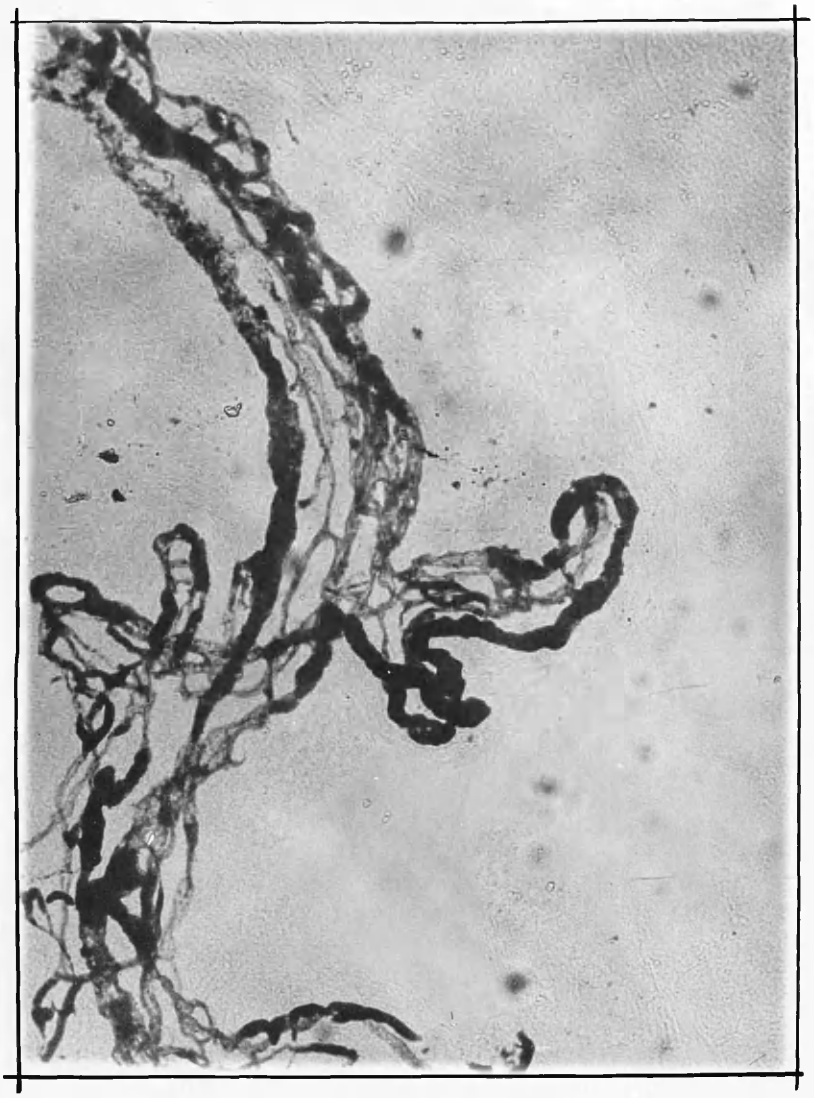

Figure No. 64. X 400.

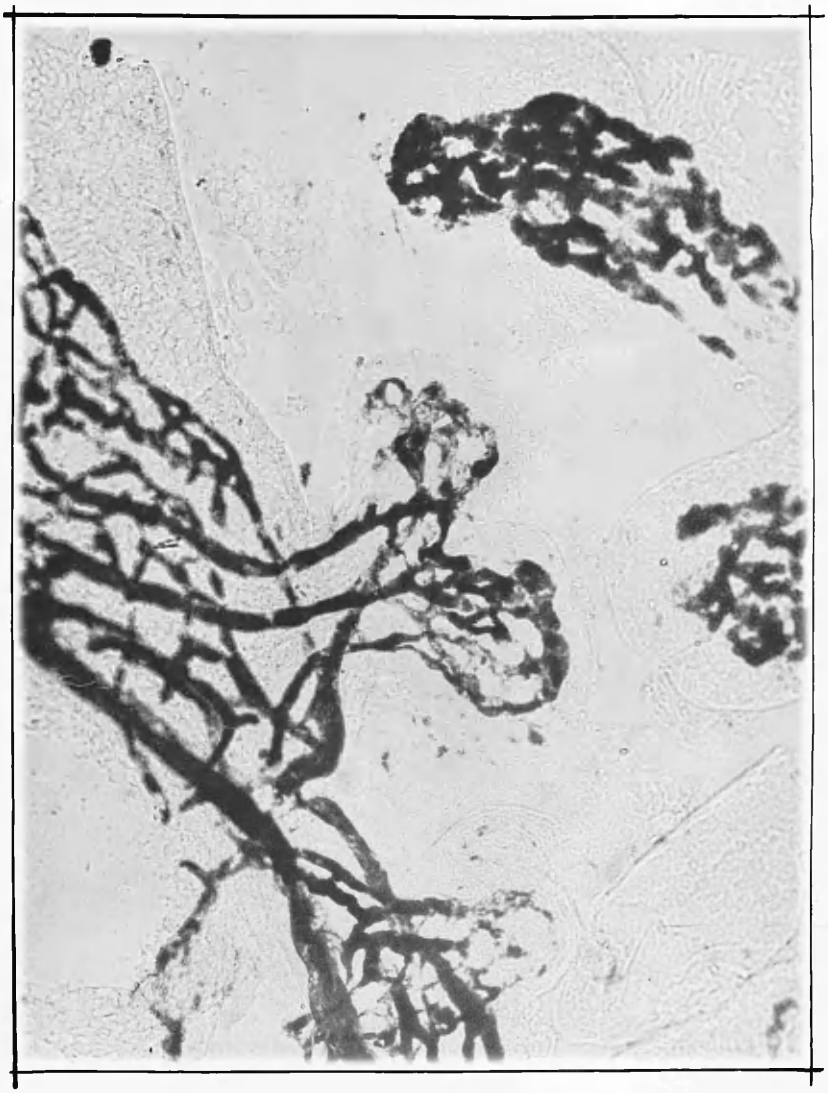

Figure No. 65. X 400.

Figure No. 66. X 280.

growing end to its parent vessels are apparent in Figures 65 and 66. There is, quite clearly, a vascular connection by four separate vessels. In some of these growing ends the peripheral vessels appear to be of greater diameter than the vessels in the centre. In others, the reverse is true, and it would appear that the appearance depends on the volume of injected dye within them. If the dye is in considerable amount the vessel diameter appears greater and, of course, the reverse is also true.

The daughter growing end continues to lengthen and increase in bulk. As it grows it produces its own daughter growing ends. There in turn grow and produce other growing ends. Thus it is apparent that the "fringe" region throughout pregnancy will gradually increase in volume. Towards term growth slackens and the tip of the growing end begins to show the characteristics of the mature capillary. This growth of the growing end has been considered already in detail in the previous section.

It is apparent that the villi of the "fringe" are really the daughter growing ends of the parent growing end. The anastomoses within the villus is the vascular anastomosis associated with the tip of the growing end.

Figure 67 is the tip of a growing end at term and it has the familiar structure of the mature capillary and villus.

It should not be assumed that the vascular anastomosis present at the tip of the growing end is only seen in its adult form in the last few weeks of pregnancy. In quite early pregnancy villi and their capillaries may assume the adult form and the inference is that not all growing ends have the same growth rate.

These points are illustrated by Figures 68 and 69.

Figure 68 shows the "fringe" area at twenty eight weeks and it will be apparent that the tips of the growing ends are not dissimilar from the mature "fringe" derived from a placenta at full term. Figure 69

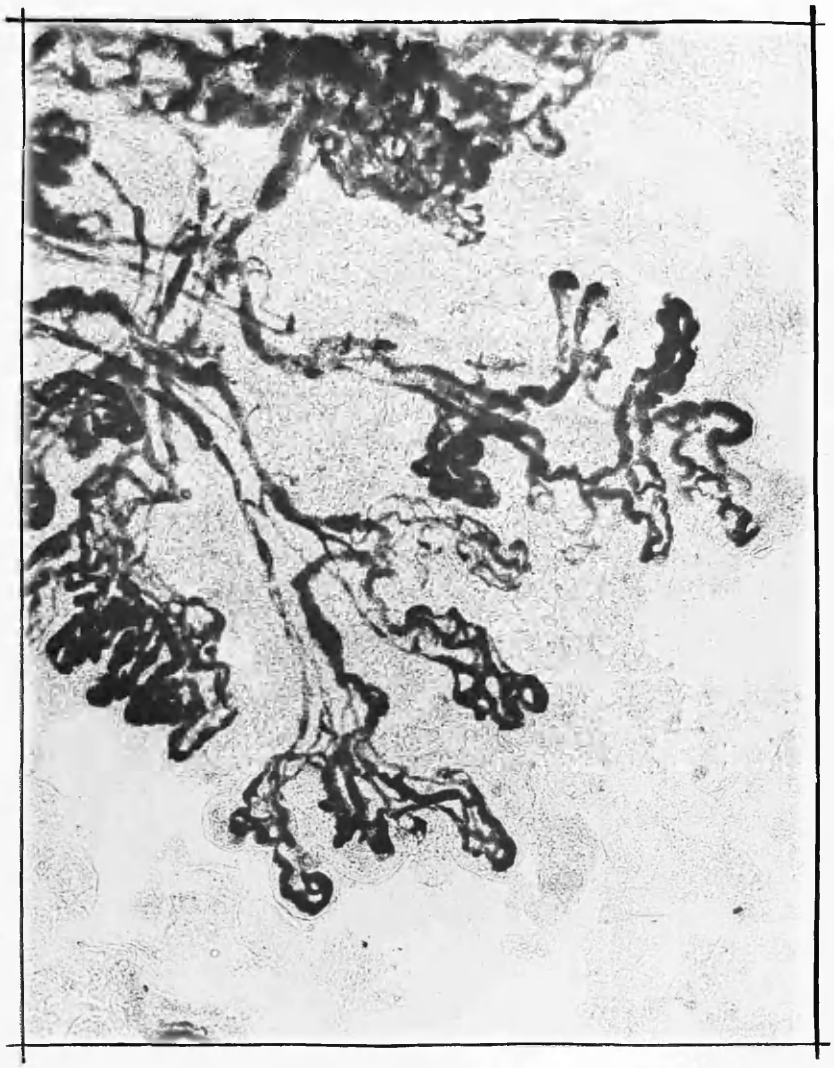

Figure No. 67. X 280.

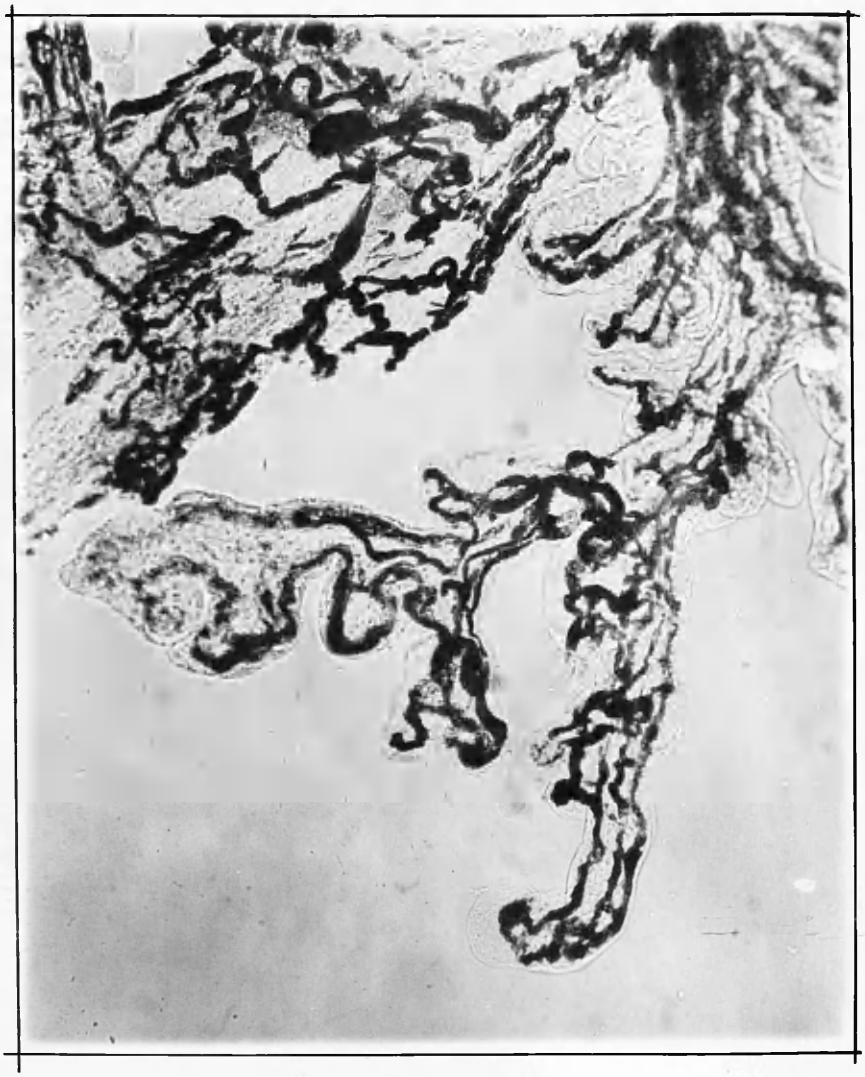

Figure No. 68. X 400.

Figure No. 69. X 400.

illustrates in contrast the "fringe" region also at twenty eight weeks, showing more primitive growing ends.

In contrast Figure 70, shows the "fringe" from a twelve weeks placenta. It is obvious that a much more primitive growing end is present. This is a short squat structure with a tremendous anastomosing system, pushing out daughter growing ends in several directions at once.

As growth continues the less distal segments of the growing ends assume the characteristics of vascular trunks. They become longer, their diameter increases and they bear at their distal regions the capillary "fringe" within their growing ends.

The macroscopic structure of the cotyledon has been described already in this study. The "fringe" area is more difficult to demonstrate except in fairly high magnification. The characteristics of the smaller vascular trunks are demonstrated in Figure 71. The repeated divisions of these small trunks in the

Figure No. 70. X 280.

Figure No. 71. X 80.

"fringe" region is apparent. At their extremities are borne the growing ends with their capillary structures.

Figure 72 demonstrates the smallest vascular trunks. At the extremities of these small trunks are borne the masses of growing ends which are seen in the photograph as spherical masses of tissue.

Figures 71 and 72 were photographed from specimens produced by a combination of techniques. In an attempt to combine the digestion technique with ordinary histological methods, the "fringe" region after digestion was stained with carbol fuchsin, cleared with zylol and then mounted in ordinary mounting medium. The larger trunks are seen with great clarity but unfortunately the growing ends are clumped together and, appearing as balls of tissue, fail to reveal their fine structure. However the method holds much promise and should in future yield better preparations.

It would be rational to assume that the arterio-venous anastomoses seen in the growing

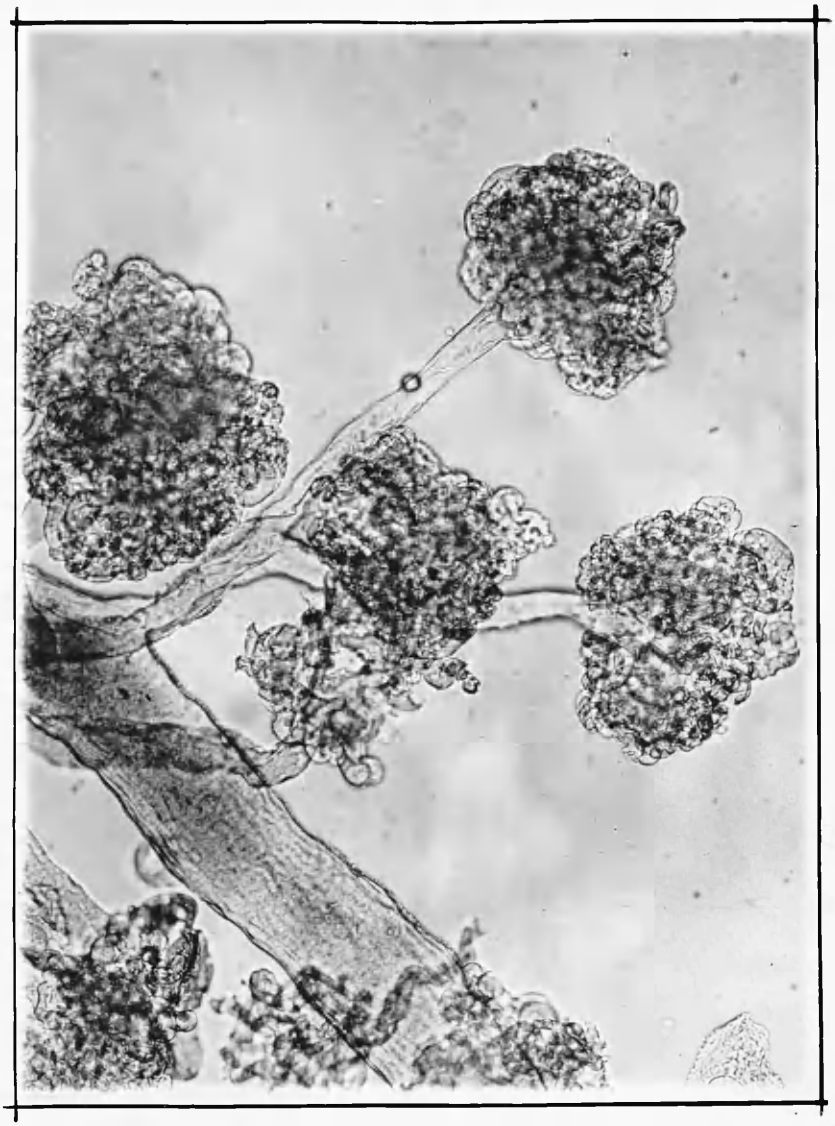

Figure No. 72. X 200.

ends would continue to be present when these have become vascular trunks. This does not seem to be the case. The vascular trunks, containing artery and vein, running side by side, appear to be quite independent of each other. The preparations of "fringe" made to demonstrate this point fail to show any obvious connection between artery and vein. The anastomoses appear to disappear with maturation. This aspect of development is illustrated by Figure 73. In order to confirm this point it is clear that further investigation of specimens from this level, is desirable.

COMMENT.

The microscopic changes in the structure of the "fringe" from the early weeks of pregnancy until full term indicates the basis of placental growth. The definitive cotyledon would appear to develop from the primary growing end produced after embedding. It is presumed that the number of such growing ends produced initially would give the placenta its permanent endowment of cotyledons. The earliest fringe, at six weeks,

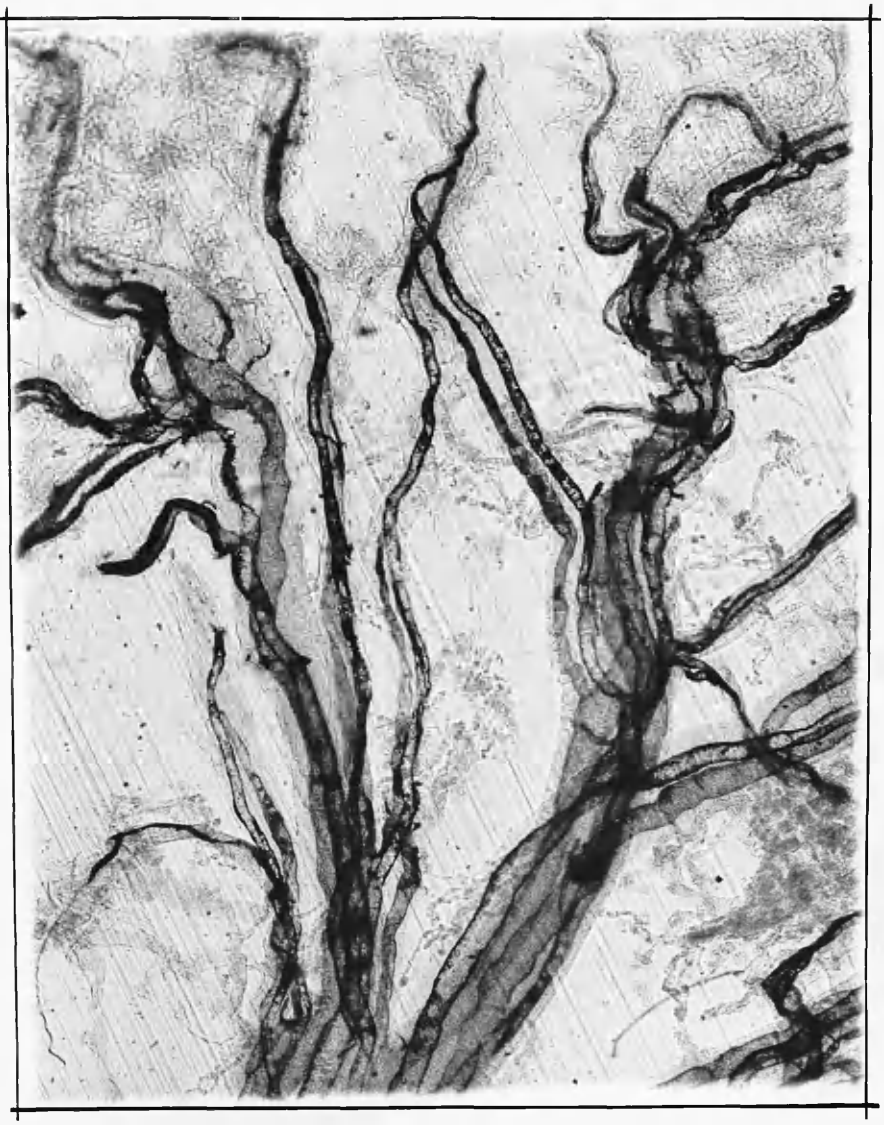

Figure No. 73. X 80.

studied in this investigation was composed of short squat growing ends packed full of vessels. There is no reason to doubt that the primary growing ends or mature villi developed initially were any different in structure.

The growing end when traced through pregnancy has been seen to fulfil three functions. Firstly it increases in length and thickness and will eventually form a vascular trunk. Secondly it produces, by divisions at its bulbous end, a multiplication of the growing ends. These, in turn, continue to grow as growing ends and will again produce, by division, a further multiplication of the growing ends. This process continues throughout pregnancy and appears only to halt with the onset of labour. Thirdly, each growing end also produces daughter growing ends by means of rounded syncytial projections from its lateral free surfaces. These can be produced at any level and are very numerous. The daughter growing ends become larger and constitute growing ends in their own right. With growth they will divide at their tips, into other growing ends.

This production of growing ends both by division, and their production de novo by the parent growing ends, continues throughout pregnancy. The number of growing ends which could be produced by full term is obviously of astronomical proportions. It explains the great increase in the volume of the cotyledon and placenta as a whole.

This method of growth explains adequately the comparative absence of "fringe" in the larger vascular trunks, since each growing end is growing outwards and producing daughter growing ends which do the same thing. Thus the fringe must always be peripherally situated in the cotyledon.

PART THREE.

A STUDY OF PLACENTAL GROWTH IN ERYTHROBLASTOSIS FOETALIS.

INTRODUCTION.

The growth of the placenta and the structures which produce this growth, have been described at some length. It is apparent that growth continues in the placenta until full term, and ceases only with the onset of labour and its expulsion from the uterus. The stimulation for this growth would appear to be under some general bodily control since most placentae at full term, within broad limits, have comparable sizes and weights. There are exceptions of course, and these have been indicated. The placental structures producing this growth, the cotyledons, have a close resemblance to each other. They grow at much the same rate and in the same fashion, and produce in each placenta a final appearance which is closely comparable. The impression gained is that of an orderly restrained growth under some general bodily control at all times. It would appear that this orderly restrained growth can be modified by disease. The small placenta in severe pre-eclampsia and the excessively large placenta in

erythroblastosis foetalis are examples of how this growth process can be modified.

It is the intention in this section to describe the placenta in erythroblastosis foetalis and present a picture of its excessive growth. The structures responsible for its growth will also be described in some detail both macroscopically and microscopically.

Erythroblastosis is a disease of newborn infants caused by a peculiar incompatibility of the foetal and maternal blood. It has been known since antiquity and its pathological manifestations adequately described for many years.[44] It is only since 1939 when Levine made the crucial observation that certain mothers may be immunised by the blood of their infants, that the pathogenesis of this condition has been recognised. The incompatibility arises from the fact that in certain pregnancies the foetus possesses a factor - the Rhesus Factor - which the mother does not. This factor acts as an antigen and forms antibodies in the mother's tissues which can pass back again into the foetus,

through the placenta, where they destroy foetal red cells and produce an anaemia, often of severe degree - neonatal icterus gravis - or so severely damage the foetus that death occurs. Such dead foetuses are grossly oedematous, and produce the well known condition of hydrops foetalis. In a large proportion of cases, the newborn infant may have only a mild or moderate anaemia which readily responds to treatment. Such variations in the pathogenicity of the condition have been related to the variations in formation and foetal absorption of the antibody.

FOREWORD.

The morphology of the placenta in erythroblastosis has not been described previously. Placental studies have been confined to macroscopic and histological descriptions of affected placenta. It has been noted for many years that placentae in icterus gravis and hydrops foetalis are often larger than the normal. Both Ballantyne[2] and Schridde,[66] among others, noted many years ago that placentae from severely affected foetuses were enlarged and

oedematous. The placenta from such a foetus has been described by Hellman and Hertig[39] as having a foetal placental ratio of 3:1 or less. It would perhaps be more correct to speak of them as being "bulkier", since this is the impression that affected placentae give in naked-eye view. In contrast some placentae, in this condition, appeared relatively unaffected and could not be distinguished grossly from normal. The degree of enlargement has been related to the severity of the condition. The greatest change being found in those cases where the child was stillborn and hydrops foetalis was present. The foetal surface of the placenta in erythroblastosis has not shown any characteristic changes except where the placenta has been excessively large. In such cases the foetal vessels in the chorion have been noted to be larger than usual and of greater diameter. If foetal blood destruction was severe the chorion was stained with bile pigment. The maternal surface of the placenta, in contrast, has shown characteristic changes. The degree

of change being most marked in severe erythroblastosis when the child was grossly jaundiced or anaemic at birth or hydrops foetalis was present. The maternal surface, in such cases, has been described as bulky or oedematous. The lobes were prominent, swollen and when floated out in water, the fringes of the lobes presented a characteristic friable and feathery appearance. The colour of the lobes has been described as white or yellowish white and has imparted to the maternal surface a characteristic appearance. The colour changes and size of the lobes being most prominent in the severer degrees of the condition.

The histological appearance of affected placentae have been described by a number of writers. Novak[86] described the villi as being enlarged with partial persistence of Langhans layer. The stroma was either oedematous or hyperplastic and the capillaries within the villi relatively diminished in number. There were also many areas of intra-capillary

erythropoiesis.[53] In contrast, Potter while agreeing that the villi were larger than normal, described the capillaries as being frequently increased in number within villi and possessing a characteristic peripheral distribution. The persistence of Langhans layer appeared to be variable and was frequently not seen.

The route by which foetal antigen reached the maternal blood has been ascribed to breaks in the syncytium allowing foetal blood to escape.[43] These areas, as described by Kline, were characterised by necrosis and clotting of foetal blood producing inter-villous thrombi. Potter[52] however has examined such inter-villous thrombi and found in most cases that the red cells of both mother and foetus were the same blood groups. She concluded that the presence of such thrombi could not be used as proof that foetal red cells escape, at such areas, into the maternal circulation.

THE MODE OF INVESTIGATION.

This will be described under three headings.

1. The Rationale of Investigation.
2. The Materials.
3. The Methods.

1. The Rationale of Investigation.

This study of placental changes in erythroblastosis foetalis was based on the possibility of placental dissection after digestion with trypsin. Placental dissection implied that individual cotyledons could be selected and removed for further study. The length and weight of selected cotyledons were obtained and their structural characteristics compared with normal cotyledons at or near term. In addition the capillary or "fringe" region was studied in injected and non-injected specimens and the structures present compared with those of normal placental fringes. It was possible therefore to present a complete picture of the placenta in erythroblastosis

foetalis.

2. The Materials.

Twenty four placentae were investigated in this study. They were all derived from proven cases of severe erythroblastosis and were divided into two groups. In the first group fourteen placentae were employed to demonstrate the gross anatomical characteristics of this condition. The second group of ten placentae were used to demonstrate the microscopic structure.

In the first group nine placentae were derived from pregnancies where the child had survived although jaundiced or anaemic whilst five placentae were derived from pregnancies with stillborn foetuses showing hydrops foetalis. The second group of ten placentae were equally divided between pregnancies resulting in living children and hydrops foetalis.

Each of the twenty four placentae were derived from pregnancies where erythroblastosis had been recognised in the ante-natal period with the presence of antibodies. The Coomb's

Test was noted to be positive in all of the surviving children. In the stillborn children the presence of hydrops foetalis was confirmed histologically. By observing these precautions the rejection rate of placentae was high, but they ensured that only true examples of erythroblastosis would be studied.

In all cases placentae were studied as soon after delivery as possible. Where delay was anticipated the placentae were placed in deep freeze until required. This precaution prevented the possibility of artefact by decomposition.

3. The Methods.

The methods of investigation were similar to those employed in Part Two for investigating the growth of the placenta.

The macroscopic structure was investigated by digesting with trypsin the fourteen placentae already described. After digestion, each placenta was dissected into its constituent cotyledons, dried between layers of absorbent lint to remove excess fluid and then weighed.

Thereafter the numbers of large and medium cotyledons were counted in each placenta. Selected large and medium cotyledons were carefully removed, measured, weighed and when necessary dissected more carefully into their divisions of vascular trunks. In this fashion the macroscopic characteristics of each placenta could be ascertained and the findings compared with normal placentae at or near term.

The microscopic structure was investigated with both non-injected and injected placentae. When injection was employed the dye was introduced into the umbilical vein. It has been explained already that a more complete filling of capillary vessels is obtained by introducing dye into the umbilical vein alone.

THE RESULTS OF THE INVESTIGATION.

These will be considered under two headings.

1. The Macroscopic Structure of the Placenta.
2. The Microscopic Structure of the Placenta.

1. The Macroscopic Structure.

The results of this part of the

investigation are shown in full in Table "J" and for convenience will be reproduced in sections when the results are discussed.

The external appearances of the placenta in erythroblastosis have been described, and the findings in this investigation agree with those observations. The swollen appearance of the placental lobes is most marked in severe erythroblastosis. The white or yellowish discolouration of their surfaces appear to be most apparent in those cases where the foetus is still born and hydrops foetalis is present. The nature of the white or yellowish-white areas over the lobes becomes apparent after digestion of the placenta. The effect of digestion, as explained already, is to separate not only related cotyledons from each other, but also individual vascular trunks. Thus, after digestion a great many vascular branches are seen to be present and by their concentration and abundance impart to their parent cotyledon, at its periphery, the characteristic pallid appearance. When floated

TABLE 'J'

Condition	Diameter	Placental Weight gms.	Number of Cotyledons. L. : M.	Weight of Cotyledons. L. (gms) : M.	Length of Cotyledons. L. (cm) : M.	Weight/ Count Ratio	Condition of Foetus	Coomb's Test.	Blood Trans-fusion.
Interus gravis	15	105	12 : 38	3.62 : 1.54	8.0 : 10.0	2.1	Alive	Pos.	+
"	16	100	9 : 24	7.34 : 3.04	7.0 : 5.0	3.0	Alive	Pos.	+
"	19	225	5 : 67	7.15 : 2.88	3.0 : 3.0	3.0	Alive	Pos.	+
"	15	130	7 : 31	6.74 : 4.96	4.0 : 3.0	3.4	Alive	Pos.	+
"	14.5	225	12 : 32	8.49 : 3.08	6.5 : 5.0	5.0	Alive	Pos.	+
"	21	160	13 : 19	8.09 : 5.21	7.0 : 5.0	5.0	Alive	Pos.	+
"	15	100	8 : 14	8.0 : 2.5	8.0 : 6.5	4.5	Alive	Pos.	+
"	15	275	7 : 43	10.04 : 2.64	5.0 : 3.0	5.5	Alive	Pos.	+
"	16	215	7 : 36	4.12 : 3.07	4.0 : 3.0	5.0	Alive	Pos.	+
	Av16.2	Av. 170.5	Av.No. 42.4	Av.7.06 : 3.21	Av5.83 : 4.83	Av4.05			
Hydrops Foetalis	14	90	4 : 19	6.89 : 5.72	7.0 : 5.0	4.0	Stillborn	-	-
"	16	160	11 : 28	8.53 : 3.20	12.0 : 9.0	4.1	Stillborn	-	-
"	11	100	11 : 8	4.24 : 2.66	9.0 : 7.0	5.2	Stillborn	-	-
"	16	265	13 : 20	30.02 : 6.98	9.0 : 7.0	8.0	Stillborn	-	-
"	18	400	16 : 15	19.81 : 5.963	8.0 : 5.0	12.9	Stillborn	-	-
"	Av15	Av. 203	Av. No. 29	Av13.89 : 4.92	Av.9.0 : 6.6	Av6.84			
Total Averages	15.8	182.1	37.7	10.2 : 3.8	6.2 : 5.4	5.00			

out in water the density of the fringe is readily apparent. It is in much greater abundance than the fringe of a normal placenta. Since the fringe is composed of the smaller vessels and their related capillaries, it follows that many more capillary vessels must be present in the erythroblastosis placenta. This will be referred to again when the microscopic structure is discussed.

The structure of the placenta, as demonstrated in Part One, has revealed that the lobe of a placenta is composed of an aggregation of cotyledons. These vary in number and size. The larger cotyledons, since they determine the size and bulk of a lobe, are the most important. This finding implies that the size of the large cotyledons are directly related to placental size and bulk. In Table "I" this observation has been made use of to compare the average values of a normal series of placentae with the average values of a comparable series of erythroblastosis placentae.

TABLE "I"

AVERAGE VALUES FOR NORMAL PLACENTAE
COMPARED WITH ERYTHROBLASTOSIS PLACENTAE.

Type of Placenta.	Placental Diameter Average. (cm.)	Placental Weight Average. (gm.)	Number of Cotyledons Average Large and Medium.	Length of Cotyledon Average. (cm.)	Weight of Cotyledon Average (gm.)	Weight/Count Ratio Average.
Normal 34th - 40th week.	15.9	165.3	50.8	Large 5.4 Medium 4.1	Large 6.5 Medium 2.18	3.4
Erythro-blastosis Foetalis.	15.8	182.1	37.7	Large 6.2 Medium 5.4	Large 10.2 Medium 3.8	5.0

Table "I"

Type of Placenta.	1. Placental Diameter. (Average) cms.	2. Placental Weight. (Average) gms.	3. Number of Cotyledons. Average (L and M)
Normal			
34th-40th week	15.9	165.3	50.8
Erythroblastosis Foetalis (Icterus Gravis and Hydrops foetalis)	15.8	182.1	37.7

The average values for normal placentae have been obtained from the results shown in Part Two when the growth of the placenta was considered. The average values for erythroblastosis placentae have been obtained from the series of results shown in Table "J".

In order to facilitate presentation of the values obtained, Table "I" will be reproduced in sections.

1. THE DIAMETER OF THE PLACENTAE.

It will be seen from Table "I" that an increase of diameter is not a characteristic

of the placenta in erythroblastosis foetalis. This accords with the naked eye view that affected placentae appear to be bulkier on the maternal aspect rather than of greater diameter across the foetal chorion.

2. THE WEIGHT OF THE PLACENTA.

The average placental weight in erythroblastosis is seen to be greater than in the normal. In this series, amounting to a ten per cent increase which is not a very dramatic increase. It should be pointed out that the increase in weight has been obtained by a proliferation of the delicate tissues composing the cotyledons. These tissues normally weigh very little and the increase in weight indicates none the less that proliferation of placental tissue has taken place.

3. THE AVERAGE NUMBER OF COTYLEDONS.

The results shown above are of considerable interest. It is clear that the increase in the bulk of erythroblastosis placentae, is not due to an increase in the

numbers of larger cotyledons. Indeed the average number of cotyledons is less than the normal average. It follows from this that the factor or factors which produce a bigger placenta in erythroblastosis do not influence the total number of cotyledons.

THE AVERAGE LENGTH AND WEIGHT OF THE COTYLEDONS.

Table "I"

Type of Placenta.	4. Length of Cotyledons. Average. (cm).	5. Weight of Cotyledons. Average. (gms).
Normal.	Large 5.4 Medium 4.1	Large 6.50 Medium 2.18
Erythroblastosis Foetalis (Icterus Gravis and Hydrops foetalis)	Large 6.2 Medium 5.4	Large 10.20 Medium 3.8

4. THE AVERAGE LENGTH OF COTYLEDONS.

It will be seen from Table "I" that large and medium cotyledons are longer in erythroblastosis placentae than in normal placentae. The increase in both types of cotyledon are in the order of one centimetre. It should be recalled, that the length of a

cotyledon does not adequately express its bulk. The increased length, does explain in part, the undue prominence of the lobes, since their lengths reflect cotyledon size.

5. THE AVERAGE WEIGHT OF COTYLEDONS.

The average weights of large and medium cotyledons are seen to be greater in erythroblastosis. The increase is most marked in large cotyledons where the average weight has almost doubled that of normal cotyledons. The weight more accurately reflects cotyledon bulk and there can be little doubt that this has increased in erythroblastosis to a considerable degree. Taken in conjunction with the increase in length, an adequate explanation is afforded for the prominent lobes of the placenta in erythroblastosis.

6. THE WEIGHT/COUNT RATIO.

Table "I"

Type of Placenta.	Weight/Count Ratio. Average.
Normal	3.4
Erythroblastosis (Icterus Gravis and Hydrops foetalis)	5.0

The rise of the weight/count ratio during pregnancy, as already explained, reflects increasing placental weight with a fixed number of cotyledons. The ratio is higher in erythroblastosis and confirms that the bulk of such placentae, in terms of their weight, has increased considerably, beyond the ratios expected for normal placentae.

THE ERYTHROBLASTOSIS PLACENTA.

It is now the intention to examine erythroblastosis placentae and for this purpose the results shown in Table "J" will be compared and discussed. The placentae in this Table have been divided somewhat artificially into two groups. In the first group the placentae were associated with living children at birth, whereas in the second group the foetuses were stillborn and showed hydrops foetalis. The division, from the clinical point of view, has been made into severe and less severe forms of erythroblastosis, as judged by foetal survival. To facilitate discussion Table "J" will be reproduced in

sections as each of the values are examined.

1. THE DIAMETER OF THE PLACENTAE.

Table "J"

Condition	Diameter of placentae. Average (cm)
Icterus Gravis	16.2
Hydrops foetalis	15.0

It will be apparent from the Table that a larger placental diameter is not a feature of the more severe form of this condition. Even a placenta, in the hydrops group, which weighed 400 grams. had a diameter of only 18 cm. This is less than that recorded for many normal placentae at or near term.

2. THE WEIGHT OF THE PLACENTA.

Table "J"

Type of Placenta.	Weight of placentae (gms.)	Average (gms.)
Normal	50:60:90:125:130:150:150: 160:200:200:210:250:255:300.	165.3
Icterus Gravis	100:100:105:130:160:215:225: 275.	170.5
Hydrops	90:100:160:265:400.	203

It will be seen from the above results that the average placental weight is greatest in hydrops foetalis. The weight difference between normal and erythroblastosis placentae is very small and hardly significant. It should be noted that the heaviest placenta investigated was from a hydrops foetalis and weighed 400 grams. In contrast a hydrops placenta only weighed 90 grams. which was much below the average weight. This small placenta, in terms of development of cotyledons, showed the typical features of hydrops placentae. It is clear that placental weight alone is not an accurate criterion of the severity of the condition.

3. THE NUMBER OF COTYLEDONS.

Table "J"

Type of Placenta.	Number of Cotyledons. (Average)
Normal	50.8
Icterus Gravis	42.4
Hydrops	29.0

In this series the average numbers of

large and medium cotyledons are least in hydrops placentae. It is apparent that the increase in weight of hydrops placentae has not been secured by an increase in the number of cotyledons.

4. THE LENGTH AND WEIGHT OF COTYLEDONS.

Table "J"

Type of Placenta.	Length of Cotyledon. Average. (cm.)		Weight of Cotyledon. Average (Gms.)
Normal	Large	5.4	6.5
	Medium	4.1	2.18
Icterus Gravis	Large	5.83	7.06
	Medium	4.83	3.21
Hydrops	Large	9.0	13.59
	Medium	6.6	4.92

4. THE LENGTH OF COTYLEDONS.

The average length of cotyledon shows very little difference in icterus gravis from normal values. In contrast hydrops placentae show a marked increase in length. Medium and large cotyledons in this condition are on the average more than two to four centimetres longer in each case. This increase in length explains

in part the prominence of the placental lobes which is such a well marked feature of hydrops placentae. The largest, large cotyledon measured, in hydrops, was 12 cms. long. If a normal large cotyledon at twelve weeks measures 2-3 cms. in length, the increase is most striking and emphasises the excessive placental growth in this condition.

5. THE WEIGHT OF THE COTYLEDON.

Both icterus gravis and hydrops placentae show increases in average weights of both large and medium cotyledons. The increase is the greatest, by far, in hydrops. The heaviest large cotyledon in hydrops, obtained in this series, weighed 30.02 grams. If a normal large cotyledon at twelve weeks weighs only one gram. the excessive growth of erythroblastosis placentae becomes very apparent. As already pointed out, weight is a better estimate of cotyledon bulk than its length. The increase in bulk in this condition is quite tremendous, when compared with the usual 5-6 grams. weight of a normal large cotyledon at term. The

heaviest large cotyledon found, in an incomplete hydrops placenta and not shown in the series, weighed 50 grams!

6. THE WEIGHT/COUNT RATIO.

Table "J"

Type of Placenta.	Weight/Count Ratio.
Normal	3.4
Icterus Gravis	4.05
Hydrops	6.84

The weight/count ratio is seen to be least in normal placentae, greatest in hydrops, and intermediate in erythroblastosis. This ratio expresses very accurately the balance between placental weight and number of cotyledons. The rise in the ratio number expresses the continued and excessive growth of placentae in erythroblastosis which reaches a maximum in hydrops foetalis. It has been shown already that cotyledon counts are not greater in erythroblastosis than in normal placentae.

COMMENT.

The results shown in Tables "I" and "J" have been examined and several comments can be made. It is apparent that if the two divisions of erythroblastosis placentae are compared with comparable normal placentae, significant differences are found. As a whole erythroblastosis placentae weigh more, the average length and weight of cotyledons are greater. The weight/count ratio is significantly higher, but surprisingly the numbers of cotyledons counted, for each placenta, are not any greater in erythroblastosis than in normal placentae. It is clear that as a group erythroblastosis placentae show excessive growth when compared with the normal. However when erythroblastosis placentae are divided into the two groups which produce living and stillborn children, a significant difference between them becomes apparent. The consistently greater placental weights, lengths, and weights of cotyledons are found in hydrops placentae. Although individual erythroblastosis

placentae, which produce living children, have individual values greater than the normal, yet their average values show little difference from normal average values. The solitary exception is the average weights of large and medium cotyledons which are greater than average normal values. This increase undoubtedly reflects the increased bulk of cotyledons. In the introduction to Part Three it was pointed out that many erythroblastosis placentae show little change from the normal appearance. The differences were seen mainly in those placentae where the stillborn child was a hydrops. These results underline the naked-eye appearances and suggest the true explanation for this variation in appearance. The growth of erythroblastosis placentae, where the foetus survives, would appear to occupy an intermediate position between normal and hydrops placentae. Placental growth beyond the normal has certainly occurred in most erythroblastosis placentae but is often not of sufficient degree to be readily apparent.

In hydrops, the excessive growth is usually of such a gross degree as to be readily apparent and, of course, reflects the extreme degree of blood destruction present in the foetus during pregnancy. The excessive growth, in erythroblastosis, of the placenta is illustrated by the following figures.

FIGURE 74.

In this photograph the maternal surface of a hydrops placenta has been dissected after digestion. Individual cotyledons have been dissected free from each other and in the lower part of the placenta have been displayed to demonstrate their excessive size.

FIGURE 75.

The bulk of a normal undissected cotyledon at term, on the left, is compared with the bulk of an undissected hydrops cotyledon. The hydrops cotyledon is not only bigger, but is manifestly denser. This increased density is produced by the tremendous growth of the "fringe" region.

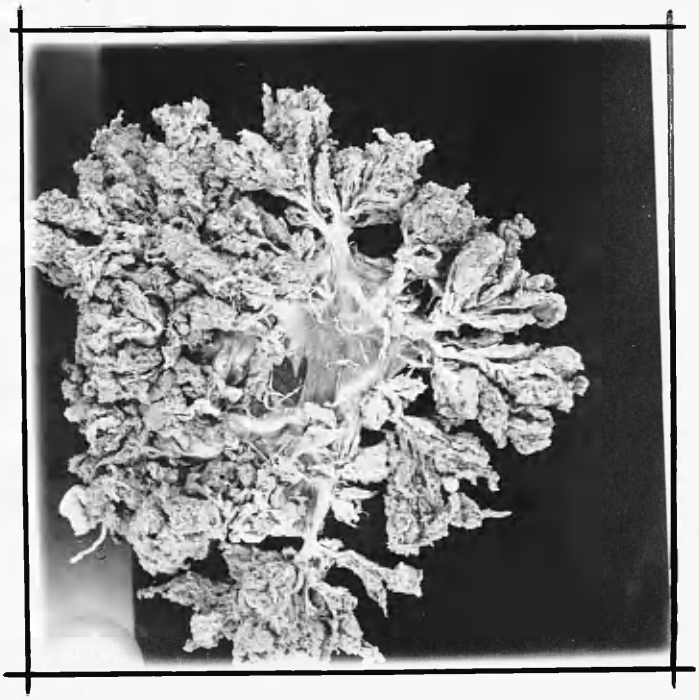

Figure No. 74. Reduced 10 times.

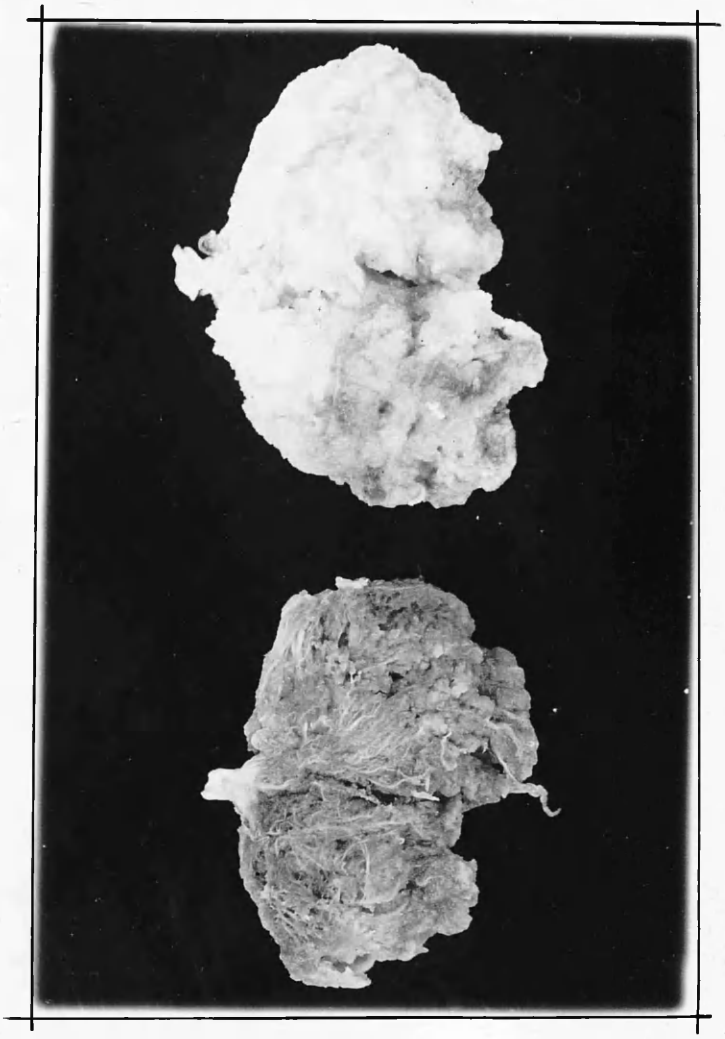

Figure No. 75. Life size.

FIGURE 76.

In this photograph are shown dissected cotyledons of twelve and twenty weeks maturity compared with a dissected cotyledon from an erythroblastosis placenta. The tremendous growth increase is most apparent.

FIGURE 77.

Pairs of cotyledons are seen with maturities of twelve, twenty, twenty four, twenty eight and forty weeks, compared with a pair of cotyledons from a hydrops placenta. In each pair, a cotyledon has been dissected and the other left undisturbed. The increase in size of cotyledons with maturation is apparent. The tremendous enlargement in hydrops is reflected not only in its length but also in the increased density of the fringe.

FIGURE 78.

A large cotyledon from a hydrops placenta has been dissected into its constituent vascular trunks. It will be seen that the form is symmetrical and, apart from its size, comparable to the structure of normal cotyledons.

Figure No. 76. Life size.

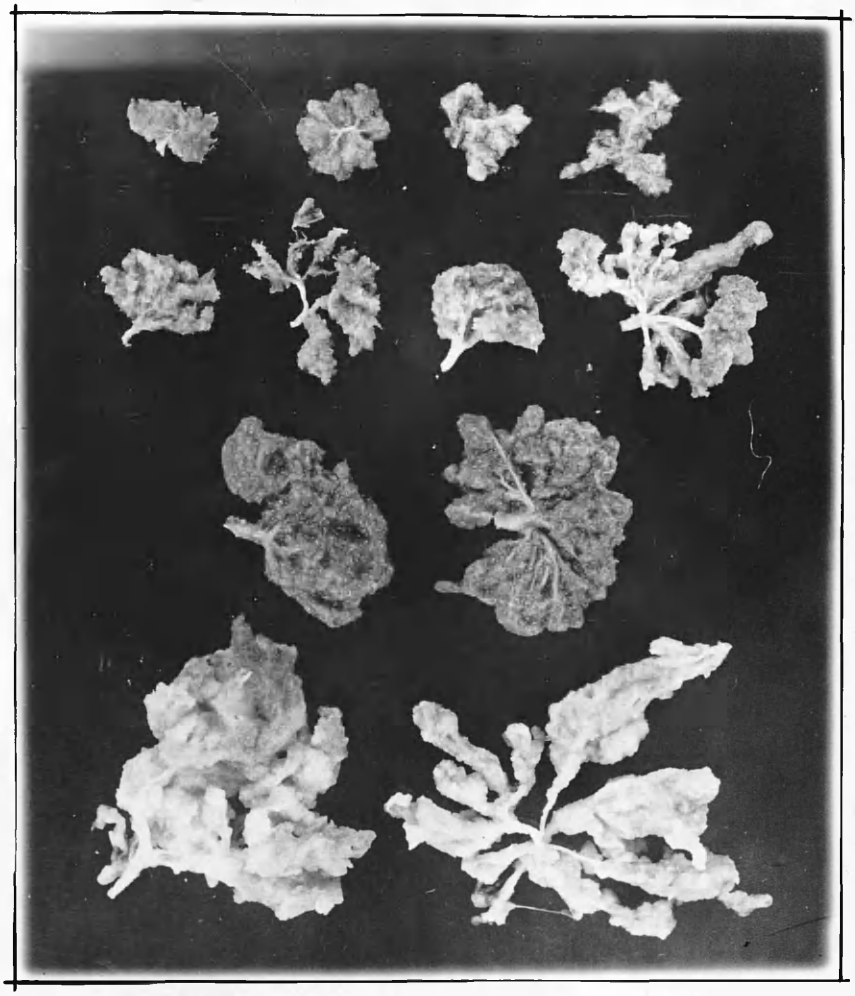

Figure No. 77. Half life size.

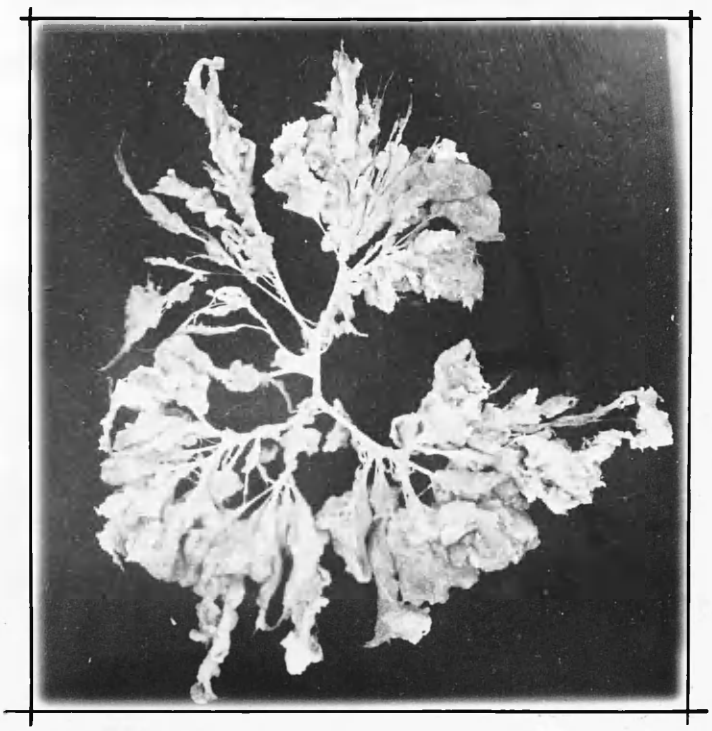

Figure No. 78. Life size.

This symmetry of form implies that stimulation for excessive growth has existed from the beginning of pregnancy and is not a 'latter day' phenomenon. This large cotyledon weighed 50 gms. and was 10 cm. in length.

2. THE MICROSCOPIC STRUCTURE OF THE PLACENTA.

It is evident that in erythroblastosis excessive growth of the placenta takes place. This growth is reflected in the increased length and weight of individual cotyledons. The excessive growth has been noted to be greatest in hydrops placentae. In this section, the structures which produce this growth will be described and compared with the normal growth of the placenta described already, in Part Two. The description will be made by examining the fringe region in both uninjected and injected material. The fringe region, is the area of the cotyledon, in which growth is still taking place most actively. It would be logical therefore to examine this region and comment upon the structures present in this

region. This examination is possible only with microscopic preparations since the ultimate branches are too small and too numerous for ordinary methods of dissection and will be described as follows.

A. NON-INJECTED FRINGE MATERIAL.

B. INJECTED FRINGE MATERIAL.

A. NON-INJECTED FRINGE MATERIAL.

It has been mentioned already that after digestion and dissection the normal fringe region is seen to be composed of a large number of small vessels. This is true also of erythroblastosis but the concentration of vessels is much greater and imparts to the fringe the white appearance so characteristic of this condition.

On examination the structures seen in normal placentae at term are also present but the proportions are different. In addition the density of vessels is much greater and it is not easy to make preparations which show individual growing ends. The varieties of

growing end seen in the fringe are the same as at normal full term but the emphasis is on less mature growing ends. That is, growing ends, which are elongated, with bulbous tips and showing a profusion of daughter growing ends arising from them. The combination of actively growing ends, both parent and daughter, is responsible for the tremendous concentration of vessels present in the fringe and explains its density. In addition, other growing ends are seen of the short bulbous variety, such as are found in much less mature placentae. These can be present in normal mature placentae but are not common and must be searched for carefully. In addition to less mature growing ends, others are seen where growth is obviously taking place much less actively. These resemble the growing ends present in the normal mature fringe. The picture of the fringe in erythroblastosis is that of a much less mature placenta than would be expected from its maturity. It is suggested that the immaturity of the fringe is responsible for its continued

and active growth. The features of the fringe are illustrated by the following figures.

FIGURE 79.

This photograph shows an elongated parent growing end with a characteristic bulbous tip. Along the free margins of the growing end many small daughter growing ends can be seen taking origin.

FIGURE 80.

In contrast, this segment of fringe from a hydrops placenta shows a number of shorter and more robust growing ends. These also show numerous daughter growing ends.

FIGURE 81.

The extent and density of the fringe in hydrops is illustrated by this photograph. The fringe region at twenty weeks maturity is compared with a hydrops fringe.

B. INJECTED FRINGE MATERIAL.

The main impression, on examining injected fringe material, is the tremendous numbers of growing ends which are present. The concentration is so great that, even with

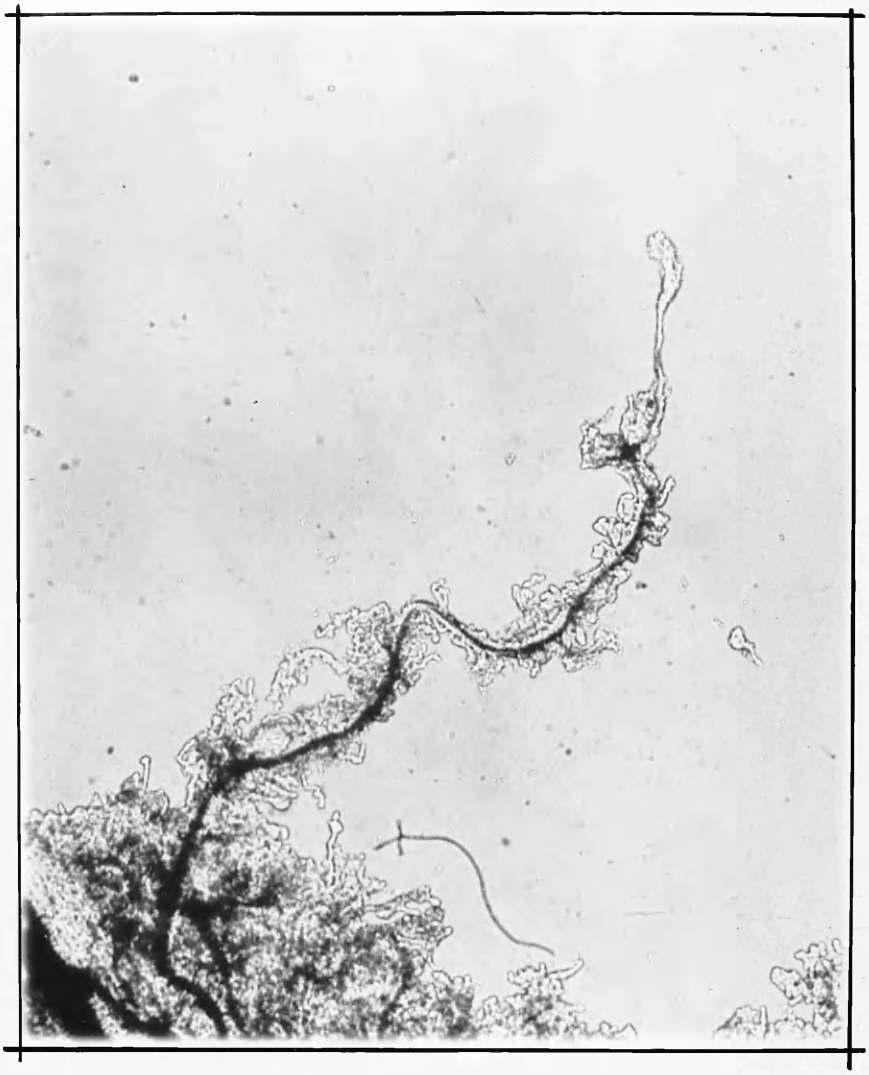

Figure No. 79. X 80.

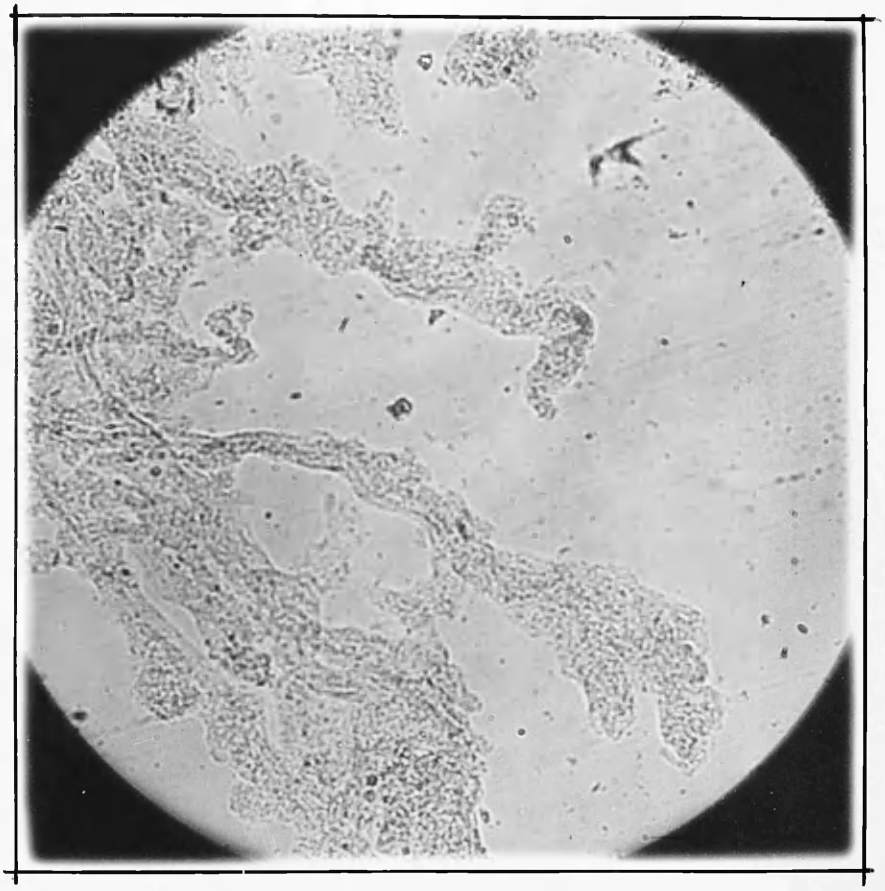

Figure No. 80. X 200.

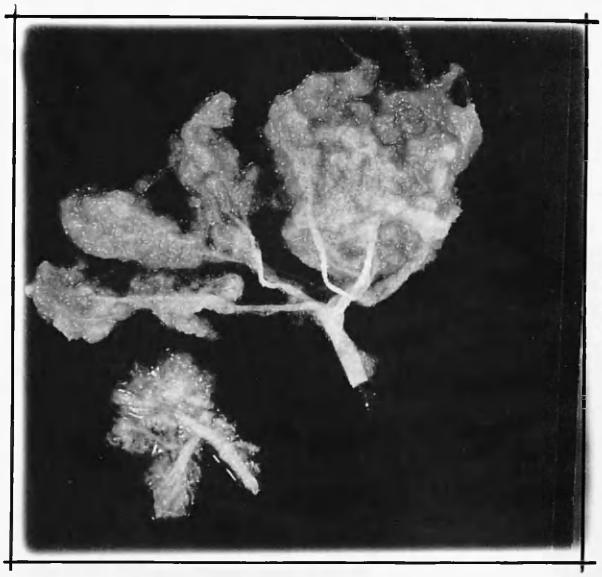

Figure No. 81. Life size.

pressure mounting, it is not easy to secure preparations of single growing ends. In this respect at least, the preparations of capillary vessels are less satisfactory than those obtained from normal mature placentae. The concentration of vessels is illustrated by Figures 82 and 83. In Figure 82 it is not easy to distinguish individual capillary vessels. Figure 83 demonstrates growing ends which are less numerous and whose structure is not unlike the terminal portions of growing ends seen in normal mature placentae.

The most striking feature of the fringe region in erythroblastosis and especially in hydrops, is the large number of primitive growing ends. These short bulbous structures are packed with vessels and resemble very closely similar structures seen in the early weeks of pregnancy. Figure 84 demonstrates such a structure. The concentration of vessels and the widespread system of anastomosing vessels is most apparent. Many of these squat growing ends are already showing division into

Figure No. 82. X 200.

Figure No. 83. X 360.

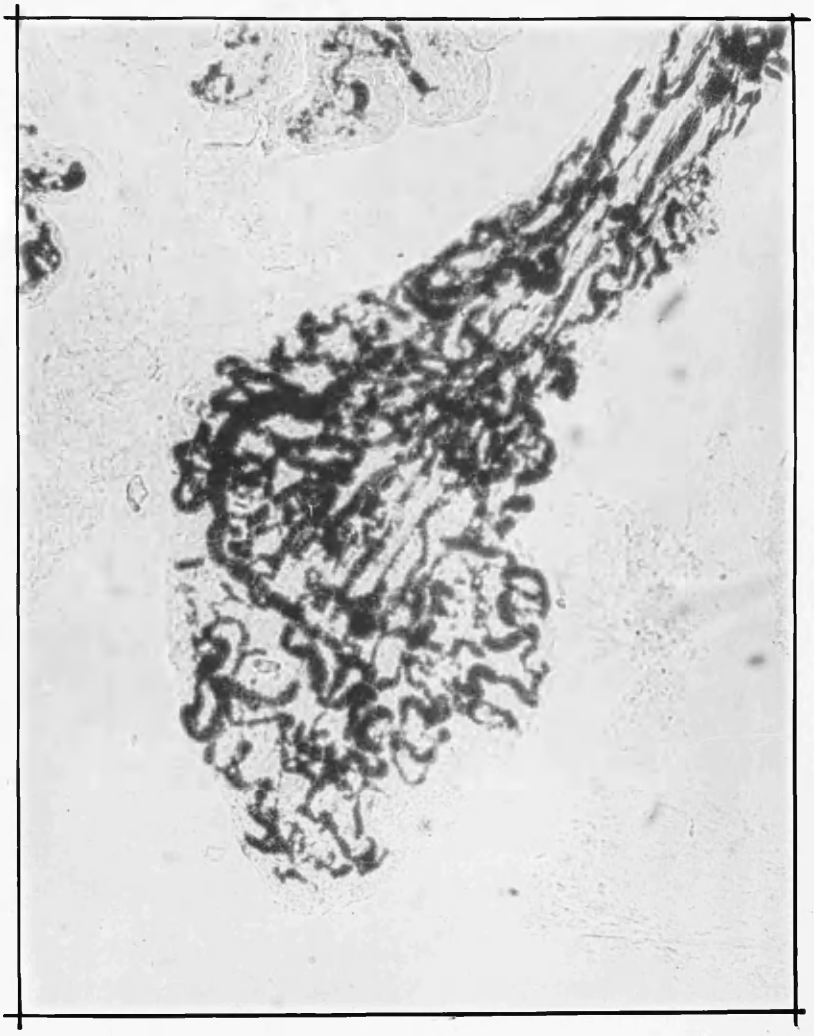

Figure No. 84. X 200.

several daughter growing ends, each containing capillary vessels. Such a development is recorded by Figure 85.

It has been noted that villi in histological preparations have been described as more numerous, larger and with a greater concentration of capillary vessels than the normal. These alterations are confirmed and explained in the present investigation. The profusion of growing ends explains the greater number of villi, since each villus represents a growing end cut transversely. These growing ends, especially the more primitive varieties are larger and being full of capillary vessels will show more capillary vessels necessarily, on histological section.

COMMENT.

The microscopic growth of the placenta has been demonstrated in erythroblastosis. There can be little doubt that growth is sustained and excessive in this condition. The persistence of primitive growing ends explain why such a sustained growth is possible.

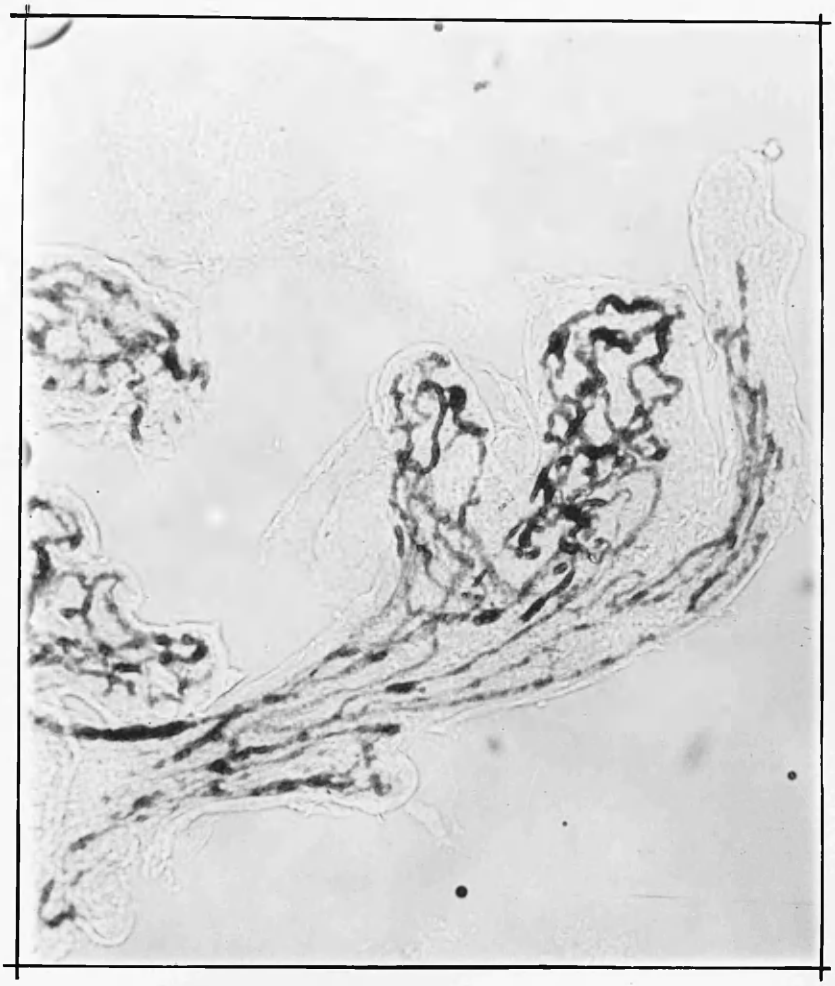

Figure No. 85. X 200.

The symmetrical nature of the cotyledon growth also suggest that the stimulus for this growth has been present from a very early date in pregnancy. The features of this excessive growth will be considered again in Part Four when the growth of the placenta is more fully discussed.

PART FOUR.

DISCUSSION

1. THE ANATOMY OF THE PLACENTA.

2. THE PATTERN OF PLACENTAL GROWTH.

3. THE HAEMODYNAMICS OF THE FOETAL PLACENTAL CIRCULATION.

4. SUMMARY.

1. THE ANATOMY OF THE PLACENTA.

It is intended in this section to discuss the anatomy of the placenta with reference to previous work and the results found in this present study.

In reviewing the literature available on this subject it became apparent that the findings of previous workers fall into certain groups according to the technique employed. For example in the 19th. century when anatomical dissection was the principal technique, most of the observations made had a certain basic similarity. Goodsir[31], Farre[24], Braxton Hicks[41], and Bumm[13] all described the appearance of the cotyledon in much the same way. It was described as "tree-like" in configuration, arising by a vascular stalk from the chorion and inserting its terminal branches into the maternal decidua. The dissections made by Braxton Hicks were excellent and his description of long terminal structures, at the periphery of the

cotyledon, with bulbous ends were exact. These structures can be recognised now as "growing ends" but their significance has escaped attention until now. Braxton Hicks indicated that these structures burrowed into the decidua and fixed the placenta. It is now evident that a certain number of them must end in this way but only because they are the most peripheral and reach the decidua first. Much of the material published by Bumm at the end of the 19th. century had been described previously, and for this reason he was accused of using other workers' findings. This appears unfair because he undoubtedly spent many years, dissecting, in a painstaking way, fresh or preserved placentae. He described the peripheral regions of cotyledons ending by insertion of terminal branches into decidual ridges or elevations. Bumm's conception of the cotyledon was simple, easy to understand, and was accepted for many years. In 1935, Spanner's[70] classic study of the placenta,

introduced a completely new idea of cotyledonary structure and since that time, opinion has swung in favour of Spanner. His illustrations of placental anatomy have been accepted in most parts of the world.

Dissection of a fresh or preserved placenta is extremely difficult and time-consuming and for these reasons, subsequent workers have sought for easier techniques. In 1923, Fraser[82] filled foetal placental arteries with radio-opaque material and took x-ray photographs. These showed that the arteries, on the chorion, were arranged like the spokes of a wheel. In 1924, Davis, Kellog and Amolsch[20] made several observations using the same technique. They reported the presence of an arterio-venous anastomosis within each cotyledon, but could find no evidence of arterial anastomoses apart from the transverse branch between the umbilical arteries at their insertion into the cord. In 1929, Borg and Schordania,[65] independently, using a similar technique of radio-opaque

materials, reported on the arrangement of the foetal arteries on the chorion. They described the arrangement as being in two varieties, and for these Schordania coined the names 'dispersed' and 'magistral'. It is now apparent that Fraser had described the 'dispersed' variety of placenta.

The disadvantages of radio-graphic techniques lie mainly in the subsequent picture which is quite flat. The relationship between arteries on the chorion and within the placenta is only fully appreciated if seen in three dimensions. It was for this reason that Spanner employed a 'filler-corrosion' technique which produces a cast of the placental vessels in three dimensions and permits the relationship of vessels to each other, to be exactly defined. The corrosion technique, as already stated, has many innate disadvantages, but in Spanner's hands many beautiful preparations were obtained which have never been surpassed by subsequent work. He showed that the arteries on the

chorion lie in one plane which is a most unusual occurrence, and quite unlike the three-dimensional arrangement seen elsewhere in the body.

A full account of the larger arterial vessels of the placenta was given by Bacsich and Smout in 1938, using a corrosion technique. These workers confirmed Schordania's division of the placental arteries into dispersed and magistral forms in most placentae but added that some placentae were a mixture of these varieties. They were impressed by the transverse communicating branch between the umbilical arteries and considered that it maintained an equality of arterial pressure in both halves of the placenta. This was the only communication between arteries which they were able to find. Subsequently in 1951, Romney and Reid, also using corrosion specimens, demonstrated an anastomosis between arteries at the periphery of the placenta. In this present study the observations of Bacsich and Smout have been confirmed.

Since the actual foetal vessels are preserved in the digested placenta, it is clear that anastomoses between arteries do not occur ordinarily. The transverse communicative branch was described by Hyrtl[83] in the 19th. century, but a specimen of dissected placenta from the Hunterian Museum at Glasgow University shows this branch and it is clear that John Hunter was aware of its existence a century before Hyrtl.

It has been mentioned that Bumm compared the cotyledon to a tree or bush in its general shape. This comparison was not confirmed by Spanner. He described the cotyledon arising by a vascular trunk from the chorion and thereafter passing down to the decidua where it or its first divisions were inserted into the decidua. Thereafter the trunks emerged, in a curved fashion, and passing upwards entered the placenta again. This is the 'chandelier' arrangement of Spanner. The branches of the chandelier were the long capillary vessels which were borne by the

emergent portion of the vascular trunk. It must be said that the chandelier arrangement has provoked a great deal of argument. Subsequent work has confirmed, and rejected, this downward and upward course of the vascular trunk. Both Stieve[72] and Romney and Reid[64] could not find any evidence of the chandelier arrangement, but Wilkin[78] said that it was present. The present study will be seen to occupy a position between these extreme views and both views are, in a sense, correct. When a cotyledon is dissected it becomes clear that the most peripheral branches, not the main trunks, are inserted into the decidua. In the less mature placenta the decidual insertions of the peripheral vessels can be seen to curve back into the placenta. The less peripheral vessels display the same curved course, as described by Spanner, but do not of course reach decidua. In the mature placenta the emergent portions of the vessels appear to disappear and the insertion ends blindly in

the decidua. This has been related by the author to the development of an obliterative endarteritis within these peripheral vessels which produces a disappearance of the most distal or emergent position. The endarteritis would appear to explain the difference of opinion which exists. It is clear that 'filler' in the corrosion technique could not enter these obliterated vessels, and the decidual vascular insertion would be removed in the subsequent corrosion. The final corrosion cast would fail to show the chandelier arrangement as a rule, but less mature placentae would demonstrate it in their casts. In the mature placenta, if decidua is still present over the lobes of the maternal surface the decidual vascular insertions can be seen as white lines through the decidua. These inserted vessels generally become surrounded by fibrin and calcium to form the discrete white areas which are such a feature on the maternal surface of mature and postmature placentae.

In the present work it has been noted also that the 'dispersed' and 'magistral' arrangement extends also into the cotyledon. In the 'dispersed' placenta the cotyledon at the primary division of its main vascular trunk usually divides into two or three divisions. The 'magistral' placenta, on the other hand, shows a division of its cotyledon into as many as six secondary divisions. In other placentae the division is much less clear cut between the two varieties.

A series of occlusive structures were described by Spanner[70] in the veins of the principal vascular trunks of the cotyledons. He likened these to sphincters and postulated that they behaved like 'sluice-gates' with the specific function of impeding venous return and thus raising the venous pressure. This, he argued, would have the effect of ensuring an efficient venous return. These occlusive structures produced a 'pearl like' configuration along the casts of the veins.

The arteries, in contrast, showed a smoother cast. He also showed histological preparations of these sphincters. Subsequent workers have failed to find any evidence of these 'sphincters' but Wilkin has stated that they are present, and has been supported by Danesino. Danesino,[18] with the use of both corrosion casts and histological preparations has shown 'sphincter-like' structures in the larger veins of the cotyledons and to a lesser degree in the arteries. He described these structures as endothelial structures projecting into lumina and containing muscular fibres. In his opinion, the 'cushions' had different functions in arteries and veins. The arterial cushions were designed to prevent overfilling of the capillary bed, whilst the venous cushions prevented regurgitation of venous blood and at the same time raised venous pressure. Their action he believed was comparable to the valves, in leg veins, and were also comparable to occlusive structures reported elsewhere in the female genital

system.

Spivack[71] has discussed the anatomical peculiarities of the umbilical cord, and in particular the variable appearances of the vessels along their course. It was pointed out in this article, that grooves or furrows and dilated portions were present on the cord at intervals. These were described first in the 17th. century by Hoboken who regarded the constricted portions as valves. At the constricted areas folds of endothelium with a muscle base projected into the lumen and bore a close resemblance to the 'sphincters' described by Spanner and Danesino. Spivack has not considered these folds to be true valves although considering that they might well have some physiological significance. In this study, on a number of occasions, the larger veins and arteries on the chorion and in cotyledons have been opened longitudinally without finding any evidence of true valves. Folds of the lining are present in some placentae at intervals and these could

presumably produce the appearance of a "string of pearls" along a vascular cast, by simple indentation. It should be pointed out that neither Bacsich and Smout[1] or Romney and Reid[64] found any such indentation of their vascular casts. The prevailing idea today is that the "string of pearls" effect described by Spanner represented unequal contraction of the filler employed and was an artefact. However it may well be that these 'folds' vary in frequency in different placentae. Spivack[71] has pointed out that after delivery folds can be made to appear in the umbilical vessels by stimulation of the cord with handling, or perfusion of fluids containing oxygen. It is possible therefore that the incidence of constrictions in the umbilical and placental vessels could depend on the amount of stimulation experienced by these structures after delivery.

The possibility of arterio-venous anastomoses was discussed by Danesino.[18] He

described them as being present at the base of the cord on the maternal surface, and at the origins of the vascular cotyledonary trunks. He found that 'sphincteric' cushions were present in these anastomotic branches and related their presence to the need for preventing blood being regurgitated along the anastomotic channels. In this study no evidence of such large anastomotic vessels have been found, although small arterial and venous branches arise from the main vascular trunks and become quite intimately attached to the chorionic covering of their parent vessels. Such small vessels always end in cotyledons, and it is presumed that, in a corrosion cast, they could give the impression of anastomotic channels. There is no doubt however, that a widespread arterio-venous anastomoses is present in the sub-capillary and capillary region of each cotyledon. These anastomotic branches have not been observed in the larger arteries and veins. It may be that better specimens, at this

level, will reveal their presence. It does seem unusual that such anastomotic channels should disappear as the larger vessels mature. It is clear that further dissection of the larger vessels is desirable to confirm or deny their presence.

Spiralling of arteries and veins have been described by Danesino[18,19] and Romney,[63] within the larger vascular trunks. They have conjectured that this spiralling could diminish or decelerate blood flow in the capillary region if required, and prevent over filling. A simple spiral of two or more turns has been observed, during dissection, in the larger vessels of the primary vascular trunks but not to the degree envisaged by these two writers and certainly not comparable to the spiralling observed in endometrial arterioles. In the majority of placentae, which the author has dissected, the main vessels in the primary trunks lie side by side and it would appear that spiralling of these vessels is not ordinarily

present.

It is apparent that the cotyledon has a form comparable to a cone, and its shape is produced by the division and redivision of the primary and subsequent vascular trunks. The capillaries are, at all times peripheral, and form a layer over the exterior of the cotyledon which intervenes between maternal blood and the larger branches in its interior. In terms of the maternal blood flow this arrangement implies that maternal blood reaches capillaries first. The physiological advantages of such an arrangement, to the foetus, are obvious. It has also been shown that each cotyledon interdigitates with its neighbours and this must ensure a continuity of placental tissue in length and depth. It is perhaps wrong to speak of a "lake of maternal blood" within the placenta. The anatomy of the cotyledon suggests that the blood will, at all times, be within the cotyledons except perhaps immediately under the maternal chorion. On the basis of

corrosion casts Wilkin described the cotyledon as a drum (tambour) with the fringe of capillaries forming the walls of the drum. He noted that on the maternal surface of the 'drum' gaps were present and these were believed to mark the entrance of the maternal arteries into the cotyledon. It is more likely, however, that these gaps mark the sites of the fixing vessels which did not fill with 'filler', for the reasons indicated already, and would therefore not survive corrosion.

It is not possible to discuss in any detail the morphology of the villi and the capillary vessels, because of the lack of intact capillary preparations in previous studies. In the past various workers have made contributions. For example, Spanner described long capillary vessels which floated freely in maternal blood, whilst Romney and Reid described short capillary structures. Stieve described villi as being mutually adherent and sharing blood

vessels. This contention had been resisted by Hamilton and Boyd who[36,37,38] agreed that many villi show syncytial adhesion but doubted whether blood vessels were ever shared. Both Grosser[33] and Browne[81] have shown illustrations of an intact villus and capillaries but, in each case, these appear to have been drawings. In 1953, Finn Bøe[10] demonstrated for the first time intact capillary vessels. The capillary vessel appeared to be a single structure within the villus, but in as much, as the villus was supplied by a four vessel system, he believed that an anastomotic system must be present within each villus. This belief has been sustained by Crawford who has demonstrated within each villus a complicated anastomotic system of capillary vessels. This anastomotic system was supplied by two afferent and two efferent vessels. The arrangement of the capillary vessels has been demonstrated in Part One. It has been shown also that adult villi can be regarded as lobules arising from a parent

vascular trunk and arranged in a three dimensional form. Each villus will have syncytium derived from the parent trunk and appearing, in a histological preparation, to have adhesions of syncytium to neighbours although in reality it is merely the continuation of a common syncytium. In a similar fashion the sharing of blood vessels can be explained as the continuation of a common circulation. In this sense the views of Stieve are essentially correct, although villi are not mutually adherent, and the fringe is "villous", not "labyrinthine" in structure.

It has been shown by Crawford that the familiar villus is really a 'growing end' and as it lengthens its interior becomes filled by a capillary anastomotic system derived from the capillary system of its parent. There is no suggestion of capillaries being created 'de novo'. They are clearly derived from the parent vascular trunk by local growth and extension of capillaries already existing.

2. THE PATTERN OF PLACENTAL GROWTH.

In Part Two, the macroscopic and microscopic growth of the placenta have been studied. The placenta has been shown to increase steadily in diameter and weight throughout pregnancy. In addition the volume of the placenta, as derived theoretically, has been noted to increase many times between twelve weeks and full term.

The continuous growth of the placenta in man is in contrast to the findings in other animals. For example, Barcroft[6] has shown that the placenta of the sheep reaches a maximum in weight long before the end of pregnancy. This is also true for the goat as shown by Elliot, Hall and Hugget.[23] The same result was found by Barcroft, Flexner and others[7] for the rabbit. In contrast the guinea pig placenta appeared to grow

throughout pregnancy as demonstrated by Flexner and Pohl.[26,27] In man it has been suggested that the maximum size of the placenta is reached at the thirty-second week of pregnancy. If the work of Flexner[28] and his colleagues is of significance in assessing placental growth, then the thirty-sixth week should be regarded as the peak of placental activity in man. These workers demonstrated that the maximum uptake of radio-active sodium by the foetus was reached at the thirty-sixth week and thereafter declined rapidly. It is open to question however whether studies of placental permeability by such substances are really an indication of placental senescence. The classification of placentae by the number of tissue layers intervening between maternal and foetal bloods was worked out first by Grosser[33] and confirmed subsequently by Mossman.[48] This classification has been interpreted by many as a physiological rather than an anatomical classification. By

inference, it has been claimed that the placenta, in any species, with the least number of tissue layers is necessarily the most efficient. This inference has been resisted by Barcroft[6] who cautioned against regarding "permeability" and "efficiency" of placentae as synonomous. There is therefore some need for caution in regarding the findings of Flexner as indisputable evidence of placental senescence. Thus diminished placental uptake of radio-active sodium after the thirty sixth week of pregnancy need not indicate necessarily placental senescence. This view is supported strongly by the findings in the present investigation where it has been shown that the placenta grows throughout pregnancy. Indeed in the microscopic picture of growth by "growing ends" there is ample evidence that daughter growing ends are being constantly formed even until the fortieth week.

The classification of placentae on the rigid "tissue layer" system of Grosser[33]

is not really accurate. Each species of animal shows in the development of its placenta the various stages by which it has become modified during its evolution and, as pointed out by Huggett,[42] man is no exception. The nutrition by "local pabulum" in the very early days of the human placenta could be compared to the epithelio-chorial placenta of the pig or the horse. Further, the increasingly deep penetration of the human placenta into the maternal tissues and the breaking down of maternal tissue by local erosion or hystotrophic action is comparable to the syndesmochorial placenta of the sheep and the cow. The comparison can be taken still further when erosion of maternal vessels takes place, the haemotrophic action, and produces an endothelio-chorial placenta as in the dog and cat. The thinning of the human trophoblast in the later development of the placenta, with disappearance of the cyto trophoblast layer, might well indicate that development towards the

haemo-endothelial placenta is under way. This type of placenta is found in the rabbit, and the capillaries of the placenta are immersed in maternal blood without intervening syncytium. The haemo-endothelial placenta of the rabbit is regarded generally as the ultimate stage in placental development. It could be argued therefore that alterations in permeability might reflect tissue layer changes in the placenta, without necessarily indicating senescence. Even so, it is not easy to interpret such a fall in the uptake of sodium in the last weeks of pregnancy as indicating anything other than a reduction in placental activity. This and other evidences of a fall in the vital activities of the placenta has been regarded by some as a "conditioning" or "preparation" for extra-uterine life.

The numbers of cotyledons have been found not to increase during pregnancy, and such an increase is obviously not the pattern by which the placenta grows. Instead the

placenta has been shown, by studying it at different growth periods, to rely for its growth on a fixed number of cotyledons. These cotyledons, for practical purposes, are the large and medium varieties. Since each cotyledon is supplied by an end artery, this implies that one or more cotyledons can be damaged or destroyed by any disease process without involving the remainder. It also implies that any cotyledonary tissue destroyed cannot be replaced. This inability to replace tissue destroyed appears to be the crux of placental growth. It could be pointed out that reliance on a fixed number of cotyledons is hardly efficient. This criticism, however, cannot be sustained when the growth of each cotyledon is considered. It becomes apparent that cotyledons are capable of enlarging their volume many times over during pregnancy. On theoretical grounds the volume of a cotyledon can increase by as much as three hundred times, and the total placental volume by two

hundred times, from the twelfth to the fortieth week. The gross increase in the size of cotyledons has been demonstrated and the pattern of growth by which this increase is brought about, has also been shown. From these studies the reliance of the placenta on a fixed number of cotyledons, can be shown to be based on a sound and flexible pattern. The pattern of growth permits a tremendous expansion, and growth has been shown to continue until full term.

On considering the gross pattern of cotyledon growth, the most striking feature is the manner in which the structure of the cotyledon becomes established early. Even at six weeks the structure of the cotyledon is established. There is a primary vascular trunk, derived from the chorion, with division into secondary and subsequent vascular trunks. The "fringe" is borne at the ends of the smallest divisions and, grossly at least does not look much different from a more adult "fringe". The structure of the

cotyledon at twelve or sixteen weeks does not look any different from the basic structure at forty weeks. There is no feature, apart from size, which would indicate that a cotyledon is mature or immature.

The early establishment of the structure of the cotyledon indicates that in the first few weeks of pregnancy placental growth is taking place very rapidly. This is implicit in the growth pattern, since vascular trunks appear to be derived from mature growing ends. If this is correct, and the average number of cotyledons is 150 - 250 in each placenta, it is concluded that the placenta will produce this number of permanent primary villi in the first few weeks of pregnancy. It is reasonable to surmise that the large and medium cotyledons are produced earlier than the small cotyledons and thereby attain a greater growth. The structure of the cotyledon is of some interest. It has been pointed out in Part One that the main vascular trunks of the cotyledon are within its interior. The fringe

region is always on the periphery and forms, as it were, a thick carpet or layer between maternal blood and the interior of the cotyledon. The vascular trunks are not apparent until the cotyledon has been dissected and the sub-cotyledons separated from each other. The intervention of the fringe between maternal blood and the centre of the cotyledon will ensure that capillary structures meet maternal blood first. This has important physiological implications from the viewpoint of absorption of oxygen and other metabolites from maternal blood. The excretory value of such an arrangement is also apparent. From the point of view of the pattern of growth, the fashion by which the fringe remains peripheral at all times, indicates that growth is not only occurring most actively at the periphery, but also that the cotyledon is growing as a whole. If this were not so one would expect to find areas of fringe at different levels of the cotyledon. The complexity of the cotyledonary structure also indicates that

the cotyledon is a mature product, and not produced from time to time, as required by the placenta. It would not be rational to believe that a complex cotyledon at, for example, twenty weeks had been produced initially only a short period previously. This maturity and complexity of the cotyledon, would appear to be one of the most telling arguments in favour of the view, that the placenta increases in size by the growth of a fixed number of cotyledons.

The direction of growth in the cotyledon is always outwards, towards the maternal uterus. It is only in the smallest vascular trunks at the fringe that a curved course is produced. This curved course produces the "chandelier" arrangement of Spanner. The most peripheral trunks enter the decidua and, at least, in the less mature placenta, re-enter the placenta. The less peripheral trunks show the same curved course downwards and upwards into the cotyledon again. It would appear reasonable to assume that this

curving of the trunks represents the need to secure longer vessels and more capillary structures. It is of course also an indication of the great amount of growth taking place. The uniformity of growth outwards towards the decidua might indicate that some sort of chemotactic effect was being exercised by the maternal tissues. If this were not so there is no reason, anatomically at least, why the growing ends should not proceed to lengthen in a direction other than vertical to the chorion.

The uniformity of growth outwards in definite areas, that is as cotyledons, has advantages. It means that cotyledonary tissue can be concentrated at areas where maternal vessels are sited, and during pregnancy an efficient system of maternal blood supply can be developed to the cotyledons. It is implicit in this argument that maternal tissues will grow at the same rate as foetal tissues. It is also implicit that the placental site on the

uterus will be the same at term as it was at the primary embedding.

The permanency of the placental site is obviously of great importance to the foetus. In such an arrangement the maternal vessels would be in greatest concentration under the placenta and ensure that the metabolic and excretory needs of the foetus were adequately met. As the placenta became larger the same maternal vessels would also increase and deliver an increased quantity of blood. Thus, a continuity of the foetal needs would be ensured and guarantee foetal survival. The alternative view of a placenta acquiring maternal vessels as it increases in size and spreads across the uterus, would be much less attractive physiologically.

A further aspect of placental growth to be considered is the development of the capillary vessels. It has been shown that each growing end contains an elaborate and complicated arrangement of capillary vessels. The primitive growing end seen in the very

early weeks is packed full of vessels all freely anastomosing with each other. The density of the vascular channels makes precise examination rather difficult. The growing end which has lengthened in the course of the next stage of its development is more readily studied. Along the whole length of the growing end is a complex system of anastomosing vessels. In some of these there appears to be two main channels with two subsidiary channels running alongside and all in most intimate and numerous anastomoses with each other. In others the four vessels all appear alike in size, but still in free anastomoses. At the bulbous tip of the growing end the anastomosis is particularly dense with many more channels and not unlike the more primitive growing end. When division takes place at the tip the vascular channels follow into each one produced and recreate the same vascular pattern seen in the parent. This also occurs when the growing end produces its daughter growing ends

laterally. The parent vascular anastomosis enters the small growing end and a similar anastomotic pattern is quickly recreated. The entrance of the vessels into the newly created growing end has been studied. The vessels are not created "de novo" in the daughter growing end. They are derived from the parent anastomosis. It is a subject of some fascination to try to understand why the vessels should accompany this new growing end. In some of the long and slender growing ends penetration of dye is often absent and it is uncertain whether this indicates incomplete penetration or whether vessels have not yet entered them. Incomplete penetration of dye appears the more likely explanation. The structure of the vascular anastomosis is of some interest.

It should be understood that these small vessels are in three dimensions, although photography conveys this rather inadequately. The frequency of the anastomotic channels indicates that the

widest possible distribution and disposal of foetal blood is intended. The method by which this widespread anastomosis may operate has given the writer some thought.

There would appear to be two separate problems to be considered in the circulation of the growing end. Firstly, the circulation within the tip of the growing end, and secondly the circulation within the elongated growing end. It is considered that the four anastomotic channels present in the elongated growing end are basically present in the tip also but rendered less obvious by the large number of anastomotic channels present. If the elongated growing end is considered first it is apparent that the circulation could only be maintained if half the vessels are afferent and half efferent in function. It is not clear however whether these small vessels should all be regarded as arterial or partly arterial and venous in nature. If they are partly arterial

and venous it is not easy to understand how the active pulsations of the arterial afferent supply could be prevented from overfilling and congesting the more passive efferent half. The same problem would appear to exist in the more actively growing tip of the growing end but in an exaggerated fashion due to the greater concentration of vessels present.

It is implicit in the pattern of placental growth which has been presented, that the growing end will in its more proximal lengths eventually become a mature vascular trunk. It is assumed that all the vascular trunks in a cotyledon were primitive growing ends originally. This implies further that if the systems of anastomosing vessels in the growing end were primarily arterial, then the entire venous drainage of the cotyledon must have been derived from arterial vessels originally. Such a conclusion is difficult to accept, since it cannot explain the structural

differences between artery and vein seen at all levels of the cotyledon. The anastomosis seen at the tips of growing ends or villi was regarded by the writer, at first, as simply a device to expose the greatest possible surface area to maternal blood. On further consideration the anastomosis might well play a more vital role and help to explain the circulation of foetal blood in the growing end or villus. If the anastomosis was capable of regulating blood flow by a selective shutting down of its vessels then congestion or stasis of blood would be less likely to occur. Further, the vessels could be partly arterial and partly venous in origin and still function efficiently. The presence of a vascular shunt within the growing end would appear to be, theoretically at least, a desirable physiological mechanism.

It is apparent that further study of this problem would be most desirable. The presence within the cotyledon of numerous

vascular shunts must have important clinical implications, since they could modify in a most selective fashion the volume of foetal blood circulating within the growing ends or villi. The presence of nervous tissue has not been demonstrated convincingly in the placenta, beyond the insertion of the umbilical cord. This infers that the vascular shunt must function by humoral or local stimulation. In turn this implies that disease processes, of whatever nature, could interfere with the shunt mechanism and imperil the continued growth of the foetus. The writer has noted in placentae derived from abortions, that in some areas it is impossible to fill the capillary vessels satisfactorily with dye. The appearances suggest that these vessels have closed down and might indicate the basic reason for certain abortions. However the amount of material examined is not yet large enough to justify a considered opinion and much more

material needs to be studied.

At this point when the origin and growth of the capillary have been described and discussed, it is of interest to consider the physiological advantages of such a method of growth. The growth pattern implies that throughout the life of the placenta fresh capillaries are being formed and the total number, in consequence, steadily rises. The foetus will therefore have an increasing number of capillaries to meet its increasing metabolic needs. Even the smallest capillary structures, so far as one can see, are capable of functioning and there does not appear to be a preliminary stage in development when function is not possible. Thus at all times the entire surface area of capillary vessels is being employed, even although the same capillary vessels are actively growing and producing fresh capillary vessels. This appears to be an admirable arrangement and well suited to the needs of the foetus. Fundamentally,

the pattern of placental growth implies that so long as the foetus is growing normally, placental growth is also necessarily taking place and producing an ever increasing number of capillary vessels to cope with the ever increasing demands of the foetus.

The excessive growth of the cotyledon in erythroblastosis has been considered and compared with normal placental growth. The growth of the cotyledon in erythroblastosis although excessive, is not in any way bizarre. Its growth follows the same pattern as in the normal, but is maintained and produces cotyledons eventually which are longer and heavier than normal. The excessive growth whilst present in erythroblastosis generally has been noted to be greatest, by far, in hydrops foetalis. The ability to produce this growth has been shown to be due to the persistence of more primitive growing ends. These grow most actively and produce many more daughter growing ends. The growth

however is symmetrical and it is reasonable to conclude that the stimulation for their growth has been present since early in pregnancy.

The growth factors which produce this excessive growth are presumably the same as in normal placental growth but in greater amount. Whether these factors differ qualitatively is impossible to say. The persistence of primitive growing ends even to maturity suggests that a qualitative difference might exist.

The excessive growth of cotyledons in erythroblastosis and the production of many more capillary structures indicates the tremendous efforts which are being made to secure enough oxygen and other metabolites for the foetus. It would be rational to assume that where foetal blood destruction is greatest, placental hyperplasia and hypertrophy would also be greatest. The tremendous growth in hydrops foetalis certainly bears out this assumption. It

would be tempting to explain placental growth on the basis of foetal oxygen needs, and this may be the most important factor although it is more probable that oxygen does not act directly. A mediation through some other centre is much more likely. A full discussion into placental growth is not yet possible. Many substances, hormonal and otherwise, have been suggested as factors in the production of its growth. There is however no scientific proof of their ability to do so, and the basic reasons for growth must await further fundamental research. This great gap in our knowledge indicates the need for continuing research into this and associated problems.

It is apparent, both in the normal placenta and in erythroblastosis, that the principal task of the placenta appears to be a continuous production of new capillary structures. The expansion of placental volume, estimated theoretically at two hundred times, is a measure of the tremendous

increase of capillary structures. The economy and efficiency of this growth pattern which permits parent growing ends to increase in size and number, whilst at the same time allowing these same structures to function as capillaries, can have few equals in nature. The preoccupation of the placenta with the production of capillaries underlines very effectively, the needs of the foetus. It would be wrong perhaps to stress the oxygen needs of the foetus at the expense of its other metabolic and excretory requirements. Yet foetal oxygen requirements must come high in the list, if not first. The tremendous concentration of growing ends in erythroblastosis, where oxygen requirements are at a maximum, from destruction of red cells, stresses the importance of oxygen for the foetus. Barcroft[4] has emphasised foetal oxygen requirements and his dictum of the foetus living as it were "on Everest while in utero" is worth remembering. He has stressed that the oxygen needs of the

foetus are always tending to be more than the amount of oxygen which can actually be taken up by the placenta, at any stage of pregnancy. The continuous production of capillary vessels throughout pregnancy, underlines the placental effort to overcome this ever present, potential deficit. It has been shown, in this study, that the growth of new capillaries continues until full term although the growing ends do not show the same growth activity seen in earlier weeks of pregnancy. It may well be that this slackening in growth near full term permits oxygen uptake to fall behind the needs of the foetus and converts a potential oxygen deficit, into an actual deficit.

In the past twenty years much attention has been focussed on the relationship between foetal anoxia and foetal survival. A number of writers have emphasised that such a relationship does exist and is most likely to occur in the post-mature labour. The

inference being that foetal anoxia is progressive and the longer that pregnancy lasts the greater the degree of foetal anoxia. This anoxia if not producing unexplained intra-uterine deaths would produce foetal distress in labour. The relationship between foetal anoxia and foetal survival has been pointed out by a number of workers including Eastman (1936)[22]; Seward (1950)[68]; Barcroft (1946)[6]; Guilham, Pontonnier, Brux and Bennet (1952)[34]; and more recently by Walker (1954)[75]; Walker and Turnbull (1953)[76]; and McKay (1957)[45].

It should be stressed that this relationship between anoxia and foetal survival is not, by any means, universally accepted. Post-maturity is not regarded by many as likely to be especially dangerous and Potter (1956) has stated that, in her opinion, post-maturity has not contributed to foetal death. Most recently

Bancroft-Livingston and Neill (1957)[3] have failed to find any correlation between the oxygen level of umbilical venous blood and the occurence of foetal distress. They conclude that the role of hypoxia in prolonged pregnancy and foetal distress has been over-emphasised.

These differences of opinion on such an important matter indicate the need for a fresh examination of the whole subject and especially a complete examination of a series of placentae at or beyond full term in order to determine whether senescent degenerative changes do in fact occur and produce foetal anoxia by diminished oxygen uptake.

3. THE HAEMODYNAMICS OF THE FOETAL PLACENTAL CIRCULATION.

General Considerations.

The foetal placental circulation has been considered, so far, only from its anatomical characteristics. It is clear that the anatomy of the placenta is virtually

the anatomy of its constituent blood vessels. It would be unrealistic to describe the morphology of the placental circulation, without giving some consideration to the fashion by which it functions. Such functional considerations may be termed the haemodynamics of the foetal placental circulation. It is appreciated that the placental circulation is only one aspect of the foetal circulation in general. The general foetal circulation is beyond the scope of this investigation and will not be considered further. It is intended therefore to consider only the foetal placental circulation.

The circulation through the placenta presents many problems, mostly unanswered, which have puzzled and intrigued observers for a very long time. The problems can be stated quite simply. Firstly, what are the mechanisms which allow a small foetal heart, situated at least 60 cm. from the placenta and frequently much more, to

maintain an adequate circulation to the smallest arterial vessels? Secondly, and even more difficult to understand, are the mechanisms concerned with venous return from the placenta to the foetus.

The arterial half of the circulation appears, from a study of its anatomy, to be essentially a simple circulation. The foetal heart, on the basis of experimental evidence, has been regarded by Windle[77] as beating just as fast as it can and without much nervous control. There are no elaborate collateral circulation arrangements between arteries in the placenta and it would appear that foetal survival is dependent on the hypertrophy and hyperplasia of individual cotyledons. A collateral circulation was demonstrated by Romney and Reid[64] in one placenta, at its periphery, but this has not been confirmed in the present study. The only collateral branch commonly present is the transverse branch between the umbilical arteries at the insertion of the

cord into the placenta. This solitary collateral branch which must equalise arterial pressure in each half of the placenta underlines the simplicity of the arterial pattern. The umbilical arteries possess remarkably thick muscular walls, and, as pointed out by Spivack[71] and others, a proportion of the muscle fibres are arranged in a spiral fashion. These arteries, and their placental branches, are capable of marked constriction, especially after delivery. This property would appear to explain the remarkably small lumina often seen in histological preparations of these vessels. It has been suggested by Spivack[71] and Reynolds[61] that this post-partum constriction may be responsible largely, for the presence of endothelial cushions and sphincters reported by Danesino[18,19] and others. Perhaps these structures should not be regarded as commonly present during intra-uterine life. Reynolds[61,62] has pointed out the interesting fact that, during

intra-uterine life the umbilical arteries and branches have rather large lumina. If this were not so the frictional resistance from such small lumina would slow arterial flow and hinder the maintenance of an adequate arterial circulation. He has demonstrated, experimentally in sheep, that as the lumina of cord arteries increase, the pressure within the vessels fall, but the rate of flow increases. This explains, in part, why some foetuses can have very long cords and yet maintain an adequate circulation to the placenta. The diameter of a vessel appears therefore to be more important than its length in this regard. The spiral muscle fibres of the arterial wall ensure also that an adequate propelling force, is constantly present.

The arterial pressure in the cord is remarkably high, estimated by Windle[77] to be about 70 mm. of mercury in the cord and 30-40 mm. of mercury in the capillaries, as estimated by Reynolds.[62] There can be

no doubt about the efficiency of the arterial circulation. Barcroft[5] estimated, in the sheep, that it could rise as high as 500 ml. per minute. Human values would be comparable to this figure.

The demonstration, in this investigation of the extent and complexity of the capillary bed in the placenta has made the foetal circulation even more difficult to understand. For example, it is not easy to understand a capillary pressure of 30 - 40 mm. of mercury being maintained in such a large number of capillaries. The pressure of maternal blood within the intervillous spaces has been estimated by Alvarez and Caldeyro[62] to be not more than 10 mm. of mercury. This disparity, as emphasised by Reynolds[62], between maternal and foetal blood pressures makes the problem of fluid exchange between mother and child not readily understood, if ordinary physiological principles are invoked. Also, it is not easy to understand how

foetal blood can emerge from the large capillary bed of the placenta with any degree of pressure, and yet this does happen. The venous pressure in the cord is not less than 30 - 40 mm. of mercury and how this is achieved, as emphasised by Reynolds,[61] without benefit of gravity, muscular contraction, or an intrathoracic pump, is difficult to understand. It has been suggested by Reynolds,[62] that this high venous pressure may be explained in part, by the sphincter situated in the human ductus venosus. This could impede venous return in a selective fashion, and so maintain a high venous pressure. Boyd,[11] has pointed out that such a sphincter would also have the undesirable effect of raising the portal pressure within the foetus. He also points out that some animals, such as the pig and the horse, do not possess a ductus and yet maintain an efficient circulation.[70] The venous sphincters, envisaged by Spanner and Danesino,[18] would seem to be undesirable

physiologically. Such structures, if present, might raise venous pressure but their frictional resistance would be great. The linear velocity flow of blood in the umbilical vein, as estimated by Reynolds,[61] is at least three-quarters as fast as the arterial flow. This suggests that there is very little obstruction to venous return. The large diameter of the umbilical vein would seem to be of great importance in ensuring a fast venous return. It could be argued that the ductus venosus sphincter might be equally undesirable physiologically. It might also be argued that extensive arterio-venous anastomoses, as envisaged by Danesino,[18] within cotyledons could maintain the rate of venous return. However, the average oxygen saturation of venous cord blood is not less than 90 per cent and this level of saturation does not suggest a quick short flow through the capillary bed. In addition arterio-venous anastomoses have not been demonstrated in

this present study, except at the level of the capillary bed.

There is one more factor which can be considered in any discussion of the venous return, and that is the influence which, uterine contractions have on the foetal blood pressure.[62] Reynolds, has shown experimentally that the painless uterine contractions which occur during pregnancy are followed at once by a corresponding rise in foetal blood pressure, and maintains a constant differential between the pressure of the liquor amnii and foetal blood. It is presumed that increased pressure within the amniotic sac, following contraction, is transmitted by the liquor amnii to the cord. However, although such contractions will raise foetal blood pressure they cannot play a major part in maintaining the foetal circulation, since they do not occur with sufficient frequency even in later pregnancy.

When all the known factors concerning

the foetal placental circulation have been considered, it becomes increasingly clear that the least understood problem is the nature of the venous return. The maintenance of a capillary pressure of 30 - 40 mm. of mercury is not capable of explanation unless the foetal capillaries take a more active part in the circulation of foetal blood than has been envisaged previously. It will be apparent that the foetal placental circulation is a most unusual circulation and perhaps capillary activity is just one aspect of its unusual characteristics.

Although the extent of the capillary bed makes the problem of venous return seemingly more complicated, yet at the same time it may explain why it is possible for capillaries to play a more active role. The numerous growing ends, large and small, with their systems of afferent and efferent vessels in free anastomoses makes it possible for the foetal capillaries to

assume a more active role. If the capillaries, on the other hand, were simply elongated and tortuous vessels without anastomosis venous return would be necessarily slow and sluggish. In the region of the capillary bed foetal blood can pursue many pathways and need never be held up. Also, since these small vessels, even in the parent growing ends, appear capable of absorption and excretion, alternative routes would not deprive the foetus of any of its essential needs from maternal blood. In addition if selective closure or expansion of these anastomotic pathways, at the fringe, were possible, venous return could be even more effectively ensured. Also, selective closure and expansion of vascular pathways would increase or reduce pressure gradients within villi and help to explain the physiological mechanisms concerned. It is clear that if foetal capillary pressure is constantly higher than maternal

intervillous pressure, absorption and excretion are impossible to explain on ordinary physiological principles. Of course, as pointed out by Page[49] substances such as glucose and amino-acid have their own permanent 'carriage-system' across the syncytium and these operate against pressure gradients. Other materials, such as water, would appear to require favourable pressure gradients to ensure absorption. It is possible therefore that a selective shunting of foetal blood within the growing ends could alter pressure gradients as required, in a local fashion, and facilitate absorption and excretion. The stimulation for such a shunting mechanism would require to be humoral or preferably determined by local conditions within the villi.

The conclusions which emerge from this study of the foetal placental circulation suggest that the arterial circulation is essentially simple in nature and designed to deliver the greatest volume of foetal

blood, in the shortest time, to the placenta. The capillary bed by reason of its free anastomotic pathways would appear to play a more active part than has been visualised. This activity would ensure, by selective shunting of blood, not only a rapid venous return but also alteration of pressure gradients within villi and facilitate absorption and excretion. The venous return along the umbilical cord would also appear to be facilitated by the large lumen of the umbilical vein. The presence of sphincters and valves in this circulation would seem undesirable because of their frictional resistance to foetal blood flow.

It is feasible, although there is no experimental confirmation, that the whole capillary bed could function as an 'extra-foetal' heart and so explain the dynamic characteristics of the venous return. A study of viable capillary vessels would be desirable and their response to different pharmacological substances noted. In this

fashion the extent of activity by capillaries could be ascertained and the feasability or otherwise of an 'extra-foetal' heart determined. It is clear that much fundamental work still requires to be done in this region of the foetal placental circulation.

4. SUMMARY.

The anatomy of the placenta has been described on the basis of dissection studies after a preliminary digestion of the placenta, with trypsin. It has been shown that digestion with trypsin removes decidua and fibrin, which normally binds cotyledons together, and has made possible a complete dissection of the placenta. Individual cotyledons have been separated from each other, dissected into their constituent vascular trunks and the basic anatomy of the cotyledon demonstrated. Since the placenta is composed of an aggregation of cotyledons these dissection studies have made the anatomy of the placenta

more readily understood. In addition, by filling capillary vessels with a suitable dye it has been possible to demonstrate complete capillary vessels, and by curtailing the length of digestion to preserve the enveloping syncytium. It has been possible to make observations on the anatomy of the placenta which previously were not feasible because of the lack of a suitable technique. These observations have been compared with previous studies, and discussed in relation to the varied interpretations of placental anatomy made by previous workers.

The anatomy of the placenta has been described in some detail, since an understanding of its structure has made it possible to interpret the manner by which the placenta increases in size. The intimate growth of the placenta has not been demonstrated previously.

In carrying out this investigation into growth full dissection of placentae has permitted the total number of cotyledons

to be counted in a number of placentae at different growth periods. Individual cotyledons, at each of these growth periods, have been measured and weighed. In addition the capillary bed, at similar growth periods, has been examined.

These investigations show that the placenta increases in size by the enlargement of a fixed number of cotyledons and increase is produced both by hypertrophy and hyperplasia. The most actively growing region, in each cotyledon, is the capillary fringe, and an examination of this region has shown that the cotyledon grows by a multiplication of "growing ends". This growth continues throughout pregnancy but appears to slacken near term when the familiar villi and capillaries are seen in greatest number. Such mature villi are really small growing ends which are not growing quite so vigorously and appear as short discrete structures filled with capillary vessels.

In erythroblastosis the growth of the placenta has been shown to be excessive and reaching its maximum in hydrops foetalis. The reason for this continued growth has been shown to be a persistence of primitive growing ends which are usually seen in much less mature placentae. The increased numbers of small vessels and capillaries at the fringe of the cotyledon have been emphasised, and their density has been shown to produce the enlargement and colour changes of lobes on maternal surface of affected placentae.

The structure of capillary vessels has been described and discussed in relation to the abundant anastomoses present along the whole length of each growing end. It has been considered that the placental circulation could only be maintained if the capillary vessels were capable of a selective closure. This implies the presence of numerous vascular shunts throughout the capillary bed and raises

interesting physiological questions of function in the normal and diseased placenta. A most interesting aspect of placental function has been the manner by which the placental circulation is maintained throughout such an extensive capillary bed. The capillary vessels, in the past, have not been considered to play an active part in this circulation but if vascular shunts are present, and operating in a selective or rhythmic fashion then this opinion may need revision. The impulse which drives foetal blood through the placental capillary bed may well reside in the capillary vessels own systole and diastole.

The extent of the problems in placental anatomy and physiology awaiting further elucidation have been indicated, and the need for further basic research stressed.

PART FIVE.

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