Fig. 2.—Portion of the periphery of the regenerate tissue in OVS 8 (Pl. 17, fig. 3) showing the peripheral epithelial band dividing to form the epithelial lining of the incipient periovarian cavity. ×380.

Fig. 3.—Portion of the periphery of the regenerate tissue in OVS 8 (Pl. 17, fig. 3) showing rete-like connections between it and the tubules in the fat body. ×275.

We are indebted to Mr. F. J. Pittock for the photomicrographs reproduced in these plates.

The Giant Cells in the Placenta of the Rabbit.

By G. S. Sansom, D.Sc., Honorary Research Assistant in the Department of Embryology, University College, London.

(Communicated by Prof. J. P. Hill, F.R.S.—Received February 12, 1927.)

[Plates 19–27.]

Material and Methods.

The material on which this paper is based was collected partly by Prof. J. P. Hill and partly by myself. The uterine swellings with their contained embryos were fixed entire, either in Bouin's picro-formol-acetic mixture or in corrosive-sublimate-formol-acetic. The former gave good general fixation and penetrated well, even into the larger specimens. Tissues fixed in it were considerably easier to cut than those preserved in corrosive formol. In order to preserve the fœtal membranes as far as possible intact, it was desirable not to open the uterine swellings, except in the latest stages, where it was, of course, necessary; hence a considerable time was required for the penetration with paraffin.

It is very doubtful if a vacuum embedding bath is desirable for objects of this nature. Membranes may be ruptured unless the change in pressure is very gradual, hence I found it preferable to reduce the possibility of air bubbles forming in the interior of the uterus by employing air-free fixing solutions, followed by air-free alcohols of increasing strength. Clearing was carried out in cedar-wood oil and the tissues transferred direct to paraffin. Little trouble was experienced with air in the interior of the uteri, and this method of employing air-free solutions is well worth the slight extra trouble. If tissues are transferred from aqueous solutions into alcohol the air contained in the water is liberated in the tissues and cannot later be easily removed, since the stronger the alcohol the less air it is capable of dissolving.

I wish to express my indebtedness to Prof. J. P. Hill for his kind assistance and advice. I also wish to thank Mr. Pittock of the Institute of Anatomy for his valuable advice on photographic matters.

The photomicrographs which accompany this paper are untouched photographs, as I considered it more desirable to retain their evidential value than to improve their appearance pictorially.

General.

It is not proposed in this paper to describe the placentation of the rabbit. The already voluminous literature dealing with this subject has covered the ground very completely, and although the various authors are not in entire agreement, there are comparatively few points on which the more recent workers disagree. The very valuable detailed paper of Schoenfeld gives a remarkably clear account of the attachment of the blastocyst to the uterine wall and of the formation of the placenta. This paper was published in 1903, the same year that Chipman's long account appeared in the Laboratory Reports of the Royal College of Physicians of Edinburgh. Chipman appears to have had a very complete series of rabbit embryos fixed and cut *in utero*, but his photomicrographs are very difficult to interpret and afford little evidence in support of his statements. One of the main points on which he differs from Maximow and Schoenfeld is the formation of syncytiotrophoblast. He denies that any plasmodial change in the trophoblast occurs until the tenth day and states that the latter, before and during attachment to the uterine epithelium, is purely cellular in character. This statement it is impossible to accept, since in all well preserved specimens of 8 to 8½ days, the trophoblast is definitely differentiated into a cellular layer and a syncytial layer, even where fusion with the uterine epithelium has not yet taken place and where the latter is still a continuous, cellular, epithelial layer. (Plate 19, figs. 1 and 2.) Moreover, after fusion with the uterine epithelium has occurred, the nuclei of the maternal symplasma are clearly distinguishable from the more deeply staining nuclei of the syncytiotrophoblast. (Plate 20, fig. 3.)

Chipman states that Maximow, having postulated the formation of two syncytial layers, one maternal and one fœtal, finds a difficulty in disposing of the maternal syncytium, and considers his explanation artificial; but when one is confronted by a stage comparable to that illustrated in figs. 1, 2 and 3, where two syncytia, having rather different staining reactions, are undeniably present, there is very considerable difficulty in deriving them both from the uterine epithelium; moreover the uterine epithelium is intact in some places

where the other syncytial layer is present (figs. 1 and 2). Therefore, if this syncytium is maternal in origin, it can only have been formed by the union with the cytotrophoblast of cells detached from the uterine epithelium, or at all events cells which have migrated from their sites of origin in the maternal tissues and passed out through the uterine epithelium or uterine glands. This alternative explanation is highly improbable, but, as a matter of fact, certain cells do appear to be budded-off from the maternal tissues, though apparently not in sufficient numbers to account for the amount of syncytiotrophoblast present. Moreover, there is very strong evidence that the syncytiotrophoblast is the direct product of the cytotrophoblast, for intermediate stages are fairly numerous. The significance of these budded-off cells, many of which appear to be degenerating (Plate 20, fig. 4), is not at present known, and apparently other writers have not described them. It is probable they are simply effete uterine epithelial cells in process of elimination.

First appearance of the Giant Cells.

In many rodents there appear in the uterine tissues during pregnancy conspicuous elements known as giant cells. These cells, which reach an enormous size, sometimes as much as 0·3 mm. in length, are usually mononucleate, but a certain number are multinucleate. They are present in great numbers in the walls of pregnant uteri of the rat, water-vole and rabbit, but are rarely found in the placental labyrinth. In the rat and water-vole they occur around the entire obplacental region of the uterine wall, but are most numerous in the region of the periplacental furrow which surrounds the placental disk. In the rabbit their distribution is less constant, some parts of the antimesometrial uterine wall being crowded with them and other parts almost devoid of them.

There is a great discrepancy in the works of previous writers as regards the first appearance of the giant cells. This is no doubt due partly to the fact that some of them based their conclusions on insufficient material of the requisite stages and partly to the difficulty of determining the precise origin of the structures themselves. Schoenfeld states that they appear on the seventh day when the disappearance or rupture of the zona allows the blastocyst to become attached to the uterine wall. The attachment, according to him, is actually conditioned by the penetration into the uterine wall of trophoblastic cells, or rather of the trophoblastic syncytial masses, which give origin to giant cells. If the giant cells are of fœtal origin it ought to be possible to determine the precise time of their first appearance, *e.g.*, in this case their appearance coincides with the attachment of the blastocyst; but where an author tries

to derive them from maternal tissues there is difficulty in deciding when they arise. Chipman states that they appear on the sixth day, and shows a photomicrograph of a portion of the obplacental area in which numerous very large giant cells are present. Now this stage is prior to the attachment of the blastocyst to the uterine epithelium, hence these cells would appear to have been formed *in situ*, and, to judge by their size, I should say they must have been present at a considerably earlier date.

I have examined two series of sections through the uterine swellings at $6\frac{3}{4}$ days' gestation and found no trace of giant cells. In these series the blastocyst is present, and lies free in the uterine lumen and enclosed in its still intact zona. If, as Chipman maintains, fully formed giant cells are present in the obplacental uterine wall at six days' gestation, they must be of maternal origin, for the blastocyst is isolated from the uterine wall by its zona, and in the case Chipman cites the blastocyst was not even present. What then is the explanation of the presence of these cells if one does not accord them a maternal origin ? The most probable explanation, if one excepts the possibility of the stage in question being much older than Chipman thought, is that these giant cells had persisted from a previous pregnancy and that the uterus was *post-partum* instead of 6-days' gestation.

From my own observations I am led to believe that the majority of the giant cells in the uterus of the rabbit are of fœtal origin, and that only in the later stages are any formed from the maternal tissues.

At $6\frac{1}{2}$-days' gestation the blastocyst lies free in the uterine cavity and is still invested in its zona, which, however, shows signs of disappearing. The blastocyst is orientated in its definitive position, with the embryonal area adjacent to the placental ridges of the uterine mucosa. As Schoenfeld has described, there are present, at various places on the antimesometrial hemisphere, localised trophoblastic multinucleate thickenings, which represent the predetermined areas for attachment to the uterine epithelium. The latter consists of a very definite layer of columnar cells with ovoid nuclei. The vascularity of the mucosa is very marked, particularly in the periplacental region, where the folds appear as if gorged with blood. The endothelial cells lining the superficial capillaries tend to stain very deeply, and, in some places, the endothelial cells seem to pass between the uterine epithelial cells so as to reach the surface of the mucosa. (Plate 20, fig. 5.)

During the course of the 7th day the wall of the blastocyst, freed from its zona, comes into contact with the uterine epithelium, and the multinucleate trophoblastic thickenings fuse with the latter, thus attaching the blastocyst

around its antimesometrial hemisphere. The embryonal area is still free from, though in close apposition to, the placental ridges of the mucosa. Towards the close of the 7th day the uterine epithelium in the obplacental region shows marked changes. The epithelial nuclei multiply and the cytoplasm undergoes great hypertrophy. Cell outlines disappear and the numerous nuclei become crowded together in the middle region of the cytoplasm which exhibits a differentiation into two zones: (i) a deeper, dark staining, finely granular zone in continuity with the epithelium of the uterine glands, and (ii) a superficial, pale-staining zone having a finely reticular or foam-like structure.

The epithelial nuclei are situated in the inner zone of more deeply staining cytoplasm and define its outer limits. The more deeply situated portions of the uterine glands remain unchanged, but the superficial parts undergo changes comparable to those in the uterine epithelium. The trophoblastic wall of the blastocyst has in places fused with the above-mentioned outer cytoplasmic zone, and its nuclei appear embedded in it (Plate 21, figs. 6 and 7). At certain places, where the multinucleate trophoblastic masses are present, the uterine epithelium is destroyed and these multinucleate bodies may be seen passing into the corium (Plate 22, figs. 8 and 9), where they increase in size and form the giant cells of the obplacental region. These giant cells are active phagocytic bodies of irregular shape, their cytoplasm being often drawn out into long pseudopodial like processes. Their nuclei are large and contain dark chromatin granules. Where they have passed through the uterine epithelium and reached the sub-epithelial capillaries the walls of the latter are destroyed and the red blood corpuscles engulfed.

At about this time connection is also established with the two periplacental ridges through the agency of well-marked trophoblastic multinucleate swellings. The maternal tissues at these periplacental sites of attachment seem particularly active, the folds being exceedingly vascular. One often finds at this stage a band of deeply staining spindle-shaped cells, clothing the wall of the blastocyst where it bridges over the furrow, between the periplacental attachment and adjacent obplacental attachment. These spindle-shaped cells are quite distinct from the trophoblast cells of the vesicle wall with which they are in contact. It is probable that they are degenerating uterine epithelial cells, but red blood corpuscles are present amongst them and it is possible that endothelial cells of the superficial capillaries, which have been opened up, are also present. The significance of this is not clear to me, but it is noteworthy that it occurs in the region where the giant cells of the late placenta take their origin, and where the trophoblast is especially active (Plate 22, fig. 10).

During the 8th day, when the attachment of the blastocyst to the placental ridges takes place, there is a progressive destruction of the uterine epithelium and uterine glands of the obplacental region, under the influence of the trophoblast. The uterine epithelial symplasma becomes broken up into masses of vacuolated cytoplasm containing deeply staining pycnotic nuclei. The invading trophoblast cells are clearly recognisable, but although many of them have increased in size they are not remarkably large, incomparably smaller than those figured by Chipman at 6-days' gestation. There is a considerable thinning of the uterine wall at this time, especially around the antimesometrial pole. This is due partly to the destruction of the uterine epithelium and glands and partly to stretching by the expansion of the fluid-filled blastocyst. In the placental region most important changes are taking place. The syncytiotrophoblast is formed and invades the uterine symplasma, in the manner so clearly described and figured by Maximow and Schoenfeld and referred to above (Maximow's figs. 1 and 2 and Schoenfeld's fig. 10).

By the middle of the 9th day the uterine epithelium at the antimesometrial pole has almost disappeared, together with the uterine glands. The epithelial nuclei are recognisable as masses of darkly staining pycnotic nuclei overlying the connective tissue of the mucosa. The latter is in many places so thin that these degenerating nuclei are almost in contact with the layer of circular muscle. The trophoblastic giant cells are more clearly recognisable now, owing to their increase in size, but they are not very numerous around the antimesometrial wall. That part of the trophoblast just outside the periplacental furrow is proliferating rapidly, the multinucleate masses thus formed passing into the maternal symplasma and becoming giant cells. It is this part of the vesicle wall which provides the bulk of the giant cells present in the later stages. Maximow drew attention to the proliferation of the trophoblast in the periplacental region, and stated that its cells became giant cells which invaded the maternal tissues, and his fig. 12 is a true representation of the condition which obtains ; yet other workers appear to have ignored this evidence in favour of the trophoblastic origin of these structures.

Although the destruction of the uterine epithelium is initiated by the penetration therein of the multinucleate trophoblastic masses, it apparently continues independently of their presence, or rather the extent of the destruction does not seem to be proportional to the number of giant cells present in the tissues. By the end of the 9th day for instance, the uterine and glandular epithelia over some parts of the antimesometrial wall have disappeared, the uterine wall there consisting of the two muscle coats, a very thin connective

tissue layer and a membrane composed of a single layer of cubical cells derived from the more deeply situated portions of the uterine glands which have escaped destruction. This layer is in fact the regenerated uterine epithelium, which, from now on, persists throughout gestation, in spite of the fact that numerous giant cells come into contact with it and pass through it into the underlying tissues. Comparatively few giant cells are to be found in the antimesometrial uterine wall at this period, but they occur in large numbers in the masses of detritus in the uterine cavity. In the periplacental region, on the other hand, many of the uterine glands persist unchanged throughout gestation and yet the trophoblast is here proliferating very rapidly.

The explanation of this is to be found in the migratory nature of the giant cells, and also in the varying susceptibility of the tissues in different regions to the attack of these cells. The absence of large numbers of giant cells from the antimesometrial uterine wall is probably largely due to the very rapid destruction and sloughing-off of the superficial layers. The tissues into which they have penetrated have liquefied and come away from the uterine wall, carrying the giant cells with them. By the 10th day, indeed, the antimesometrial wall has reached its thinnest condition. The muscle layers are immune against destruction, and although, during the latter half of pregnancy, giant cells are found embedded in both longitudinal and circular muscle coats they do not appear to have any destructive action on them.

From the 10th day until the 25th the giant cells are conspicuous objects in the obplacental uterine wall. They attain their maximum size and number at about the 17th day when they occupy more than half the thickness of the wall (Plate 23, fig. 12). A certain number of them have arisen *in situ* by subdivision of the earlier invading cells (figs. 13 and 14), but there is comparatively little indication of giant cell division at this time (17 days) and the majority have certainly migrated to their present positions from the thickened layer of trophoblast in the region of the periplacental ridges. This layer of trophoblast I propose to speak of, henceforth, as the "trophoblastic fringe," but it should be noted that it consists not only of trophoblast but also of an underlying layer of entoderm.

The entoderm of the bilaminar omphalopleure, it may be mentioned, persists after the more or less complete disappearance of the trophoblast, as a thin membrane forming the antimesometrial wall of the yolk sac cavity. It is distinguishable up to about the 14th day; at about that time it breaks down, with the result that the yolk sac splanchnopleure comes into apposition with the uterine wall (Plate 24, fig. 15). In the earlier stages of development,

the antimesometrial hemisphere of the blastocyst is formed by the bilaminar omphalopleure, which near the placental margin is in continuity on the one hand with the chorion læve, passing to join the placental margin, and on the other with the yolk sac splanchnopleure. The trophoblast over the greater part of the bilaminar omphalopleure fuses with the uterine wall and disappears as a continuous layer. Close to the junction with the chorion læve and yolk sac splanchnopleure, however, the trophoblast persists as a thickened layer of actively proliferating cells—the trophoblastic fringe.

The trophoblastic fringe is sometimes found with its distal edge free in the uterine cavity, as in fig. 16, but usually that edge fuses with the uterine wall and remains attached thereto until about the 17th day (Plate 25, fig. 17). Its cells reach a large size and are budded off, either singly or more often as compact groups or "cell islands" into the uterine cavity. They become attached to the regenerated uterine epithelium, pass through it and come to rest in the underlying tissues. A considerable number of these cells pass directly into the mucosa where it is in contact with the trophoblastic fringe. These cell islands (fig. 18) are composed of large cells with distinct cell outlines and one or two deeply staining nuclei rich in chromatin. Their cytoplasm which stains deeply with eosin has a finely granular or reticular structure. They are very conspicuous objects in the uterine cavity at 12-days' gestation, but later their place is taken by other structures, of a quite different appearance, which are also products of the fœtal trophoblast in the periplacental region, but which arise by a process of budding from the chorion læve.

Reference to Plate 26, figs. 19 and 20, will explain the relationship of the fœtal membranes in this region at 17-days' gestation. The membrane covered by the layer of tall columnar entoderm cells thrown into folds and villi, occupied by fœtal capillaries, is the yolk sac splanchnopleure. At the junction of this membrane with the chorion its entoderm is reflected back as a thin layer of fusiform cells in contact with the trophoblast; it has, in fact, little changed since its first appearance. Around the antimesometrial hemisphere it is no longer present as a continuous membrane. The trophoblastic fringe is still clearly recognisable, being composed of cubical cells proximally and of large ovoid or spherical cells distally. The distal cells are identical in character with those of the cell islands to which they have given birth; they are, however, less actively proliferative at this time (17 days) and some of the cells show degenerative changes. The proximal continuation of this trophoblastic layer forms the trophoblast of the chorion læve. It is that part of the original trophoblastic wall of the vesicle which has neither taken part in the formation of the placental

labyrinth nor fused with the uterine wall. A portion of it occurs in the interplacental furrow.

As the placental ridges increase in size, the circum- or periplacental furrow deepens and the chorion læve creeps up the margins of the placental disk thus forming the inner wall of the circumplacental furrow. It consists of two layers, (*a*) trophoblast and (*b*) mesoderm. The trophoblast has the form of a single layer of densely crowded cubical cells, many of them in a state of very active mitosis. The cytoplasm stains intensely with eosin, the nuclei are exceedingly rich in chromatin and mostly spherical. From this layer there are budded-off into the uterine cavity great numbers of multinucleate spheres, which have a characteristic form (Plate 27, fig. 21). They consist of spherical masses of cytoplasm crowded with densely staining nuclei, similar to those of the chorion læve. The nuclei are arranged either peripherally, close to the surface of the cytoplasm, or are aggregated into spherical masses, occupying in some cases the central region of the cytoplasm, in others placed excentrically. The cytoplasm of these multinucleate spheres is at first similar to that of the parent cells, but it soon becomes coarsely reticular and in that part where the nuclei are aggregated it stains very faintly.

These bodies occur in great numbers in the uterine cavity, between the yolk sac splanchnopleure and the regenerated uterine epithelium, and also in the interplacental furrow, where a similarly modified portion of the trophoblast is to be found. Unlike the giant cells these multinucleate spheres are not active; they lie free in the uterine cavity amongst the detritus formed by the degenerating uterine epithelium and may be seen in all stages of decay. A very considerable destruction of maternal tissues, uterine epithelium and connective tissue takes place in the circumplacental furrow at this time, and there is little doubt that this destruction is brought about by the trophoblast of the chorion læve, possibly with the object of reducing the area of attachment of the placental disk to the uterine wall preparatory to parturition. Although there is no doubt that the majority of these multinucleate spheres are budded-off from the chorion læve, it is probable that some of them contain nuclei derived from the degenerating uterine epithelium.

We find therefore a marked change in the seat and character of trophoblastic activity in the periplacental region after about the 15th day. The trophoblastic fringe, from the time of its appearance as a definite localised thickening of the vesicle wall at nine days until the 14th day, exhibits proliferative activity. Its cells enlarge, become detached, penetrate the uterine epithelium and pass into the corium of the mucosa, where they grow to an enormous size

and may be found in large numbers in the muscle layers. After the 15th day, however, there is a reduction in the activity of this layer, and by the 17th day it has apparently ceased to proliferate. The trophoblast of the chorion læve, on the other hand, is almost inactive until the 14th day and reaches its maximum activity about the 21st day. The multinucleate spheres, to which it gives origin, do not possess the power to penetrate the uterine epithelium, hence they are never found in the mucosa. Their nuclei become structureless, intensely black-staining bodies, which soon break up into smaller fragments and ultimately disappear. The outer cytoplasmic walls sometimes persist after the disappearance of their contents.

The Origin of Giant Cells from Maternal Tissues.

According to Duval, Minot and Chipman, the giant cells of the rabbit are all products of maternal tissues. Duval derives them from the connective tissue cells; Minot and Chipman from uterine epithelial cells; Schoenfeld, on the other hand, considers that they are purely trophoblastic in origin, and my own observations leave me with little doubt that his view is correct, in so far as it applies to the large giant cells of the peri- and obplacental regions; but Schoenfeld was not concerned with the later stages of pregnancy, and it is during the latter half of gestation that cells, having the character of giant cells, appear in the deeper tissues of the placental ridges.

The careful observations of Maximow led him to believe that a certain number of giant cells were formed from the periendothelial elements (the "perithel" layer of Maximow), or from the endothelial cells themselves, and there is very strong evidence in support of this view.

If one examines the deeper placental region at 12 days one finds the endothelial cells of the maternal capillaries in a state of very active proliferation (fig. 22). The cells, which are large and ovoid, with conspicuous nuclei, form in-bulgings into the lumina of the capillaries. Many of the nuclei are to be seen in stages of mitosis. It is difficult to believe that these cells are trophoblast cells which have destroyed and replaced the endothelium of the capillaries, for they are found in vessels close to the mesometrium, far from the deepest limit of the placental labyrinth. The fact that they are dividing mitotically also militates against the view that they are trophoblastic. It is equally difficult to believe that they are glycogen cells, to which they bear no resemblance. It seems extremely probable that they are greatly hypertrophied endothelial cells, such as occur in the placenta of the rat and water-vole. According to Maximow, a certain number of these cells become detached from the endothelium and are

carried in the blood stream to other parts of the uterine wall. He regards this as the normal procedure, but I think it is more probably accidental. Some of these hypertrophied cells form bridges across the lumina of the capillaries and it is quite possible that they might break away from their attachment to the adjoining cells and come to lie free in the blood stream.

This endothelial proliferation increases as gestation proceeds, but owing to the increase in size of the placenta it becomes more and more confined to the region close to the mesometrium. Meanwhile, the enormous giant cells of the obplacenta gradually disappear. Many of them fragment, forming a number of smaller uni- or multi-nucleate cells, which are quite inconspicuous and apparently inactive. A certain number of the large cells, especially those situated in the circular muscle coat, seem to undergo absorption without fragmentation; the cell body becomes very thin and attentuated and is difficult to distinguish from the muscle fibres between which it is compressed.

By the 25th day of gestation there are no large obplacental giant cells remaining, but some of the capillaries in this region are surrounded by many small giant cells, identical in appearance with those around the deep placental capillaries. In most cases the endothelial walls of these vessels are intact, and but little hypertrophied, the giant cells forming a sheath around them, but in others the vessel walls appear to be formed in part by these cells.

The question arises as to the origin of these small obplacental giant cells. There are three possibilities :—

(i) They may be the daughter cells of the original obplacental giant cells and therefore of fœtal origin.

(ii) They may be maternal endothelial cells which have migrated in the blood stream, as Maximow suggests, or through the muscle layers, to the obplacenta from their seat of origin in the mesometrial region.

(iii) They may be formed from the obplacental endothelial cells, or connective cells.

We may consider these three possibilities in order.

(i) In the obplacenta at 21 days' gestation there are present a number of very large giant cells, some of which exhibit signs of impending division by amitosis. By the 25th day no large cells remain, but some groups of smaller cells are recognisable which are obviously the products of larger cells, and they are identical in appearance with the cells aggregated around the capillaries (fig. 24). It is certain, therefore, that some at least of these small giant cells are trophoblastic elements.

(ii) If the maternal endothelial cells migrate to the obplacenta *via* the lumen of the capillaries, one would expect to find very many of them free in the blood stream, but, as a matter of fact, the number of free-swimming cells is exceedingly small. Very rarely a free cell may be found, but, as already mentioned, this is probably accidental, since the hypertrophied endothelial cells project into the lumina of the capillaries and their area of attachment to the vessel walls becomes greatly reduced compared with their bulk. A serious objection to their transportation in this manner is the risk of their causing a stoppage of the blood stream in the smaller vessels, and the possibility of their being carried to other regions than the uterine wall. As to whether they migrate through the muscle layers or not is another matter, and one which is very difficult to determine, but I have seen no indications of their migratory character.

(iii) If these elements are formed *in situ* by proliferation of the endothelial cells of the obplacental capillaries, one would expect to find these latter in a state of active proliferation and hypertrophy, as is observable in the mesometrial region, but here the capillary walls are in most cases intact and of normal appearance, the giant cells forming sheaths around them. I can find no evidence of their origin from connective tissue cells.

It seems highly probable, therefore, that these small obplacental giant cells are all remnants of the great trophoblastic elements, and that their accumulation around the capillaries has some other significance. It should be clearly understood that although many of the endothelial cells of the deep placental capillaries undergo great hypertrophy and exhibit proliferative activity, they never attain to the dimensions of the obplacental trophoblastic giant cells. Compared with the latter, they are inconspicuous. Their greatest length is about 0·1 mm., whereas the trophoblastic giant cells sometimes reach a length of 0·4 mm.

These endothelial giant cells are confined to the immediate neighbourhood of the capillaries. They attain their maximum size by the 21st day, after that fragmentation of the nuclei sets in and about the 25th day many of them are to be seen undergoing degeneration.

Summary.

In the pregnant uterus of the rabbit, two kinds of giant cells are found. The larger and most conspicuous variety is derived from the fœtal trophoblast, cells from which become detached from the blastocyst, about the 7th day of gestation and penetrate into the obplacental mucosa. These cells grow rapidly and attain an enormous size, sometimes as much as 0·4 mm. in length. They persist until about the 22nd day, when fragmentation sets in and they become.

broken up into comparatively small bodies. Large numbers of these cells are also formed from that portion of the trophoblast of the proximal zone of the bilaminar omphalopleure, which projects free into the uterine cavity after the attachment of the blastocyst to the placental folds on the 8th day and the disappearance of the remainder of the omphalopleure. The cells proliferated off from this "trophoblastic fringe," pass into the uterine cavity, penetrate the regenerated uterine epithelium of the antimesometrial uterine wall and enter the underlying tissues. The proliferation of this "trophoblastic fringe" persists until the 16th day of gestation.

The mesometrial giant cells are of maternal origin, being formed by the proliferation of the endothelial lining of the capillaries in the deep placental region. They appear at about the 11th day of gestation and persist until after the 27th day. They never attain a great size and are confined to the mesometrial region. The trophoblast of the chorion læve gives origin to great numbers of multinucleate spheres, which become free in the uterine cavity and in the inter-placental furrow. These bodies are inactive degenerate structures.

REFERENCES TO LITERATURE.

Chipman, Walter, "Observations on the Placenta of the Rabbit, with special reference to the Presence of Glycogen, Fat and Iron." 'Laboratory Reports.' Royal College of Physicians, Edinburgh. Vol. 8 (1903).

Duval, Mathias, "Le Placenta des Rongeurs. Le Placenta de Lapin." 'Journal Anat. et Physiol.' (1889–90).

Maximow, Alexander, "Zur Kenntniss des feineren Baues der Kaninchenplacenta." 'Archiv für mikrosk. Anat.' Vol. 51 (1898).

Maximow, Alexander, "Die ersten Entwicklungsstadien der Kaninchenplacenta." 'Archiv für mikrosk. Anat.' Vol. 57 (1900).

Schoenfeld, H., "Contribution à l'Etude de la Fixation de l'Œuf des Mammifères dans la Cavité utérine, et des premiers Stades de la Placentation." 'Archives de Biol.' Vol. 19 (1903).

DESCRIPTION OF PLATES 19 to 27.

Key to Abbreviations.

Bl. C., Red Blood corpuscle.
Bl. W., Wall of blastocyst.
Bi. Om., Bilaminar Omphalopleure.
Ch. L., Chorion læve.
Cy. Tr., Cytotrophoblast.
E.C., Extra-embryonal cœlom.
End. C., Endothelial cell.
Ent., Entoderm.
F. C., Fœtal capillary.
G. C., Giant cell.
M. C., Maternal capillary.
M. S., Multinucleate sphere.
Syn. Tr., Syncytiotrophoblast.
Tr., Trophoblast.
Tr. Ch. L., Trophoblast of Chorion læve.
Tr. F., Trophoblastic fringe.
Tr. N., Trophoblastic nucleus.
Tr. M., Trophoblastic multinucleate mass.
Ut. C., Uterine cavity.
Ut. Ep., Uterine epithelium.
Ut. Gl., Uterine gland.
Ut. Sym., Uterine symplasma.
Ut. W., Uterine wall.
Ys. C., Yolk sac cavity.
Ys. Sp., Yolk sac splanchnopleure.

PLATE 19.

FIG. 1.—Transverse section through a portion of the placental lobe at about 8 days, showing the attachment of the blastocyst to the uterine epithelium of the placental ridges, and the formation of syncytiotrophoblast from the cytotrophoblast. The uterine epithelium has, in places, become converted into a symplasma, into which the darkly stained nuclei of the syncytiotrophoblast have penetrated. × 190.

FIG. 2.—A section similar to that shown in fig. 1, showing the formation of syncytiotrophoblast from the cytotrophoblast. The greater part of the uterine epithelium is still unchanged. × 200.

PLATE 20.

FIG. 3.—A high-power view of the region shown in fig. 1. The formation of the uterine symplasma by the epithelium of the uterine glands and its invasion by the large trophoblastic nuclei. × 430.

FIG. 4.—Part of the placental ridge at about 8 days, showing the budding-off of cells from the uterine epithelium. × 430.

FIG. 5.—Part of the placental ridge at 8 days, showing the penetration of endothelial cells into the uterine epithelium. × 340.

PLATE 21.

FIG. 6.—Transverse section through a portion of the uterine wall at 8 days, close to the periplacental region, showing the attachment of the blastocyst in the obplacental region. The uterine epithelium has become converted into a symplasma with the nuclei crowded into the central region. The trophoblastic nuclei are penetrating into this symplasma. The thin membrane overlying the symplasma is the entoderm of the yolk sac wall. × 140.

FIG. 7.—A high-power view of this region, showing the maternal symplasma containing a few trophoblastic nuclei. × 300.

PLATE 22.

FIG. 8.—Part of the obplacental uterine wall at 9 days, showing the earliest appearance of the giant cells. The trophoblast multinucleate masses cause local destruction of uterine epithelium symplasma, pass through the gaps so formed and become giant cells. × 180.

FIG. 9.—Part of the obplacental uterine wall at 9 days, showing two newly formed giant cells, lying in the corium just below the masses of pycnotic nuclei formed by the degenerating uterine symplasma. × 190.

FIG. 10.—The attachment of a multinucleate trophoblastic mass to the periplacental ridge at about 7¾ days. The uterine epithelium over the area of contact has disappeared, and the wall of a superficial capillary destroyed. The red blood corpuscles may be seen engulfed by the trophoblast. × 275.

FIG. 11.—Part of the uterine wall in the periplacental region. The actively proliferating band of trophoblast gives origin to the majority of the giant cells. In some places the uterine epithelium has entirely disappeared, in others it is represented by the layer of symplasma with crowded pycnotic nuclei. × 100.

PLATE 23.

FIG. 12.—The uterine wall in the obplacental region at 17 days' gestation. Giant cells are present in great numbers even in the muscle layers. The regenerated uterine epithelium is formed from the basal portions of the uterine glands. × 150.

FIGS. 13 AND 14.—Parts of the antimesometrial uterine wall at 12 days' gestation, showing giant cells in process of division by amitosis. × 170 and 155.

PLATE 24.

FIG. 15.—The antimesometrial uterine wall and the yolk sac splanchnopleure at 21 days' gestation. The original entodermal wall of the blastocyst has disappeared. In the uterine cavity are numerous multinucleate spheres derived from the trophoblast of the chorion læve. × 130.

FIG. 16.—Transverse section through the periplacental region of the uterus at 12 days' gestation. The trophoblast of the bilaminar omphalopleure is in a state of active proliferation and constitutes the "trophoblastic fringe," which gives origin to the majority of the giant cells. × 30.

PLATE 25.

FIG. 17.—Transverse section through the uterine wall in the peri-placental region at 12 days' gestation. The "trophoblastic fringe" is here fused to the uterine wall and the giant cells composing it are invading the maternal tissues. Remnants of the uterine epithelial symplasma are still present. × 190.

FIG. 18.—A cell island in the uterine cavity detached from the trophoblastic fringe. × 170.

PLATE 26.

FIG. 19.—Transverse section through the periplacental region of the uterus at 17 days' gestation showing the arrangement of the fœtal membranes. × 30.

FIG. 20.—A high-power view of the same region as that shown in fig. 19, to show the relationship of the bilaminar omphalopleure (trophoblastic fringe), chorion læve and yolk sac splanchnopleure. The trophoblast of the chorion læve is budding-off multinucleate spheres. × 170.

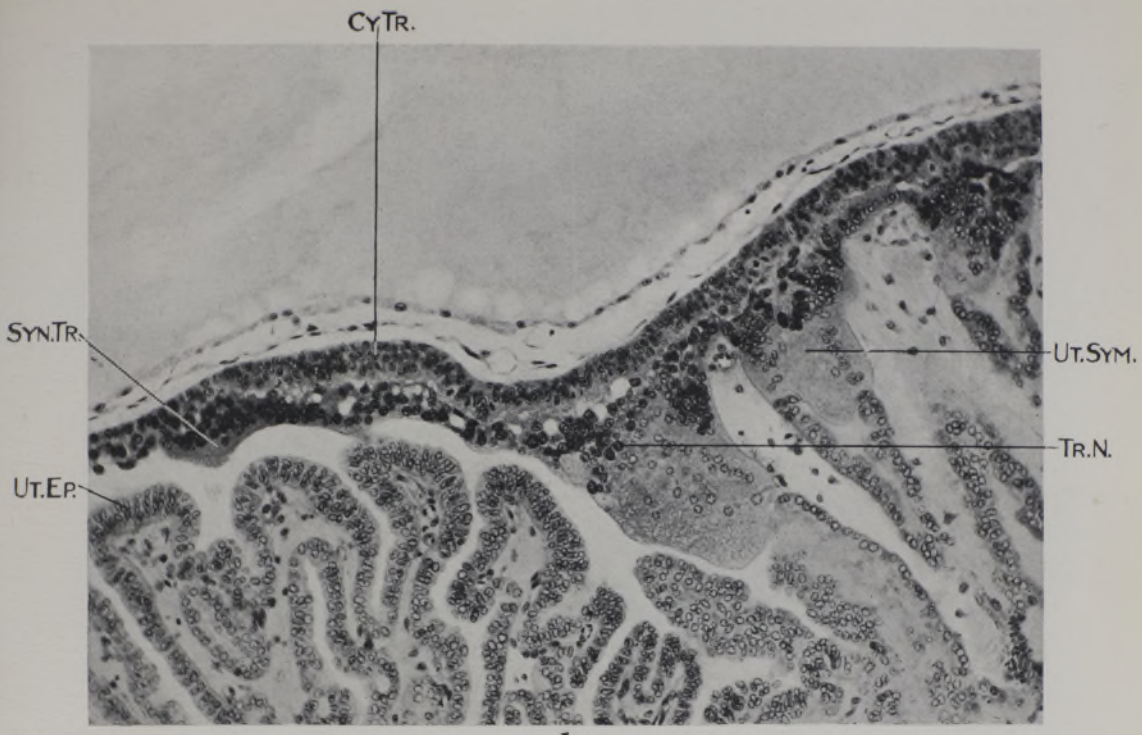
PLATE 27.

FIG. 21.—A portion of the chorion læve and the multinucleate spheres which are budded-off from it; 21 days' gestation. × 340.

FIG. 22.—A capillary in the deep placental region at 12 days' gestation. The endothelial cells are in active mitosis and greatly hypertrophied. × 155.

FIG. 23.—A capillary in the obplacental region of the uterine wall at 12 days' gestation. Two giant cells are apposed to the endothelial wall, but they are of fœtal trophoblastic origin. × 325.

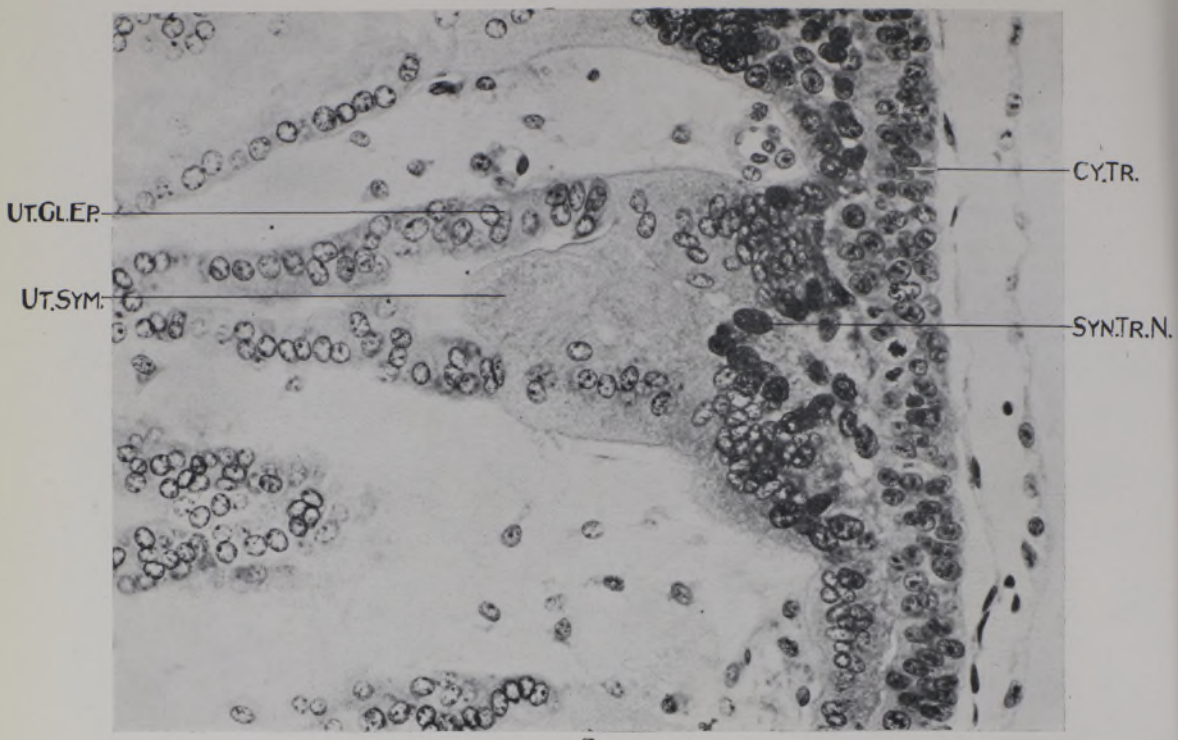
FIG. 24.—A part of the antimesometrial uterine wall at 25 days' gestation. The small giant cells are formed by fragmentation of the large trophoblastic elements. They show a tendency to accumulate around the capillaries. × 95.



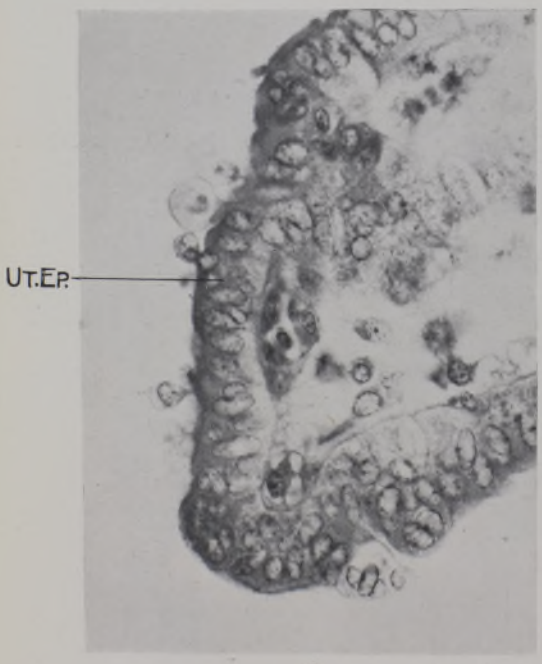
1

2

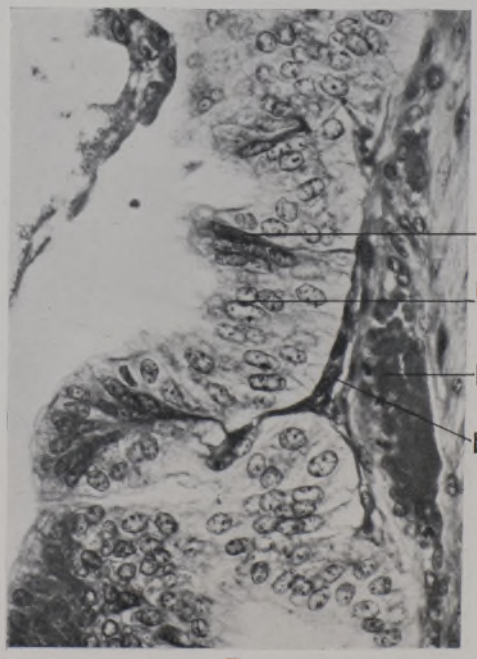
(*Facing p.* 368.)



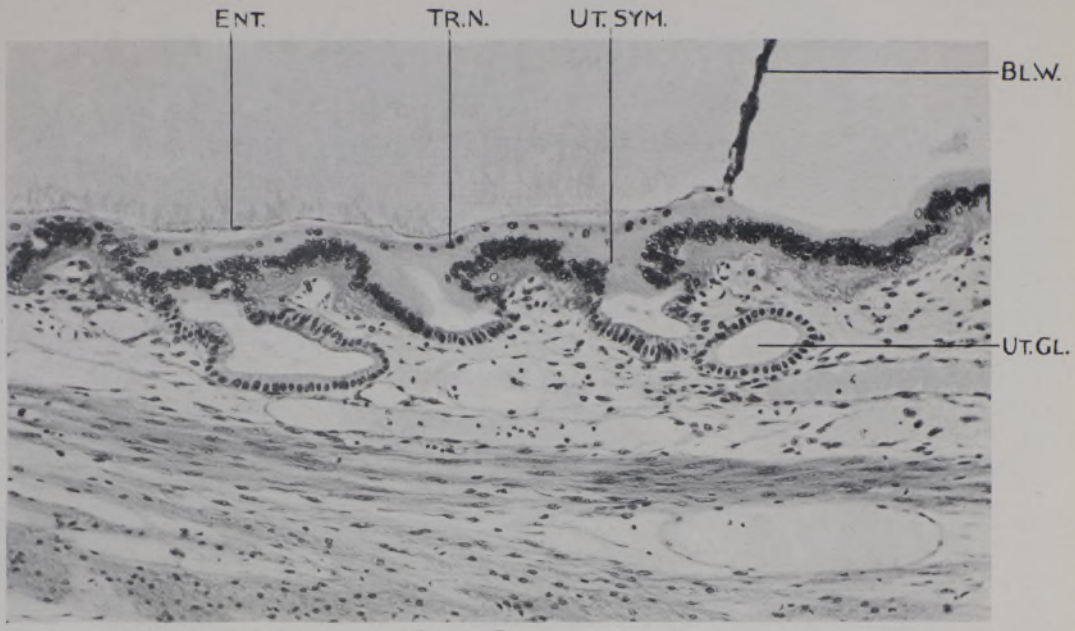
3



4

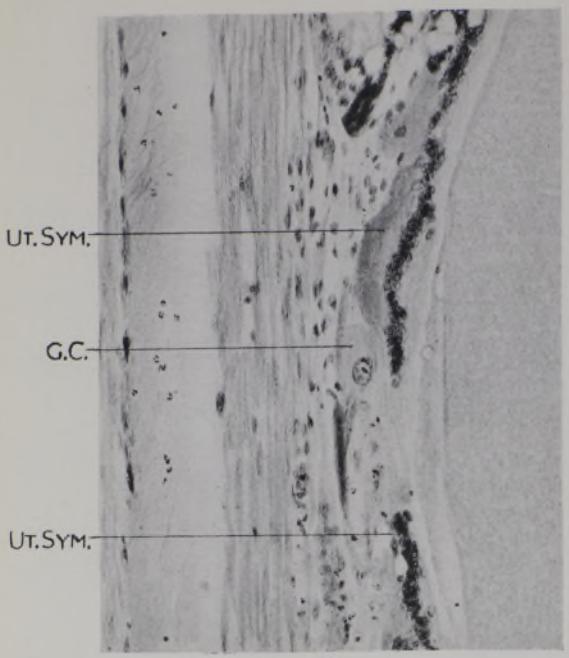


5

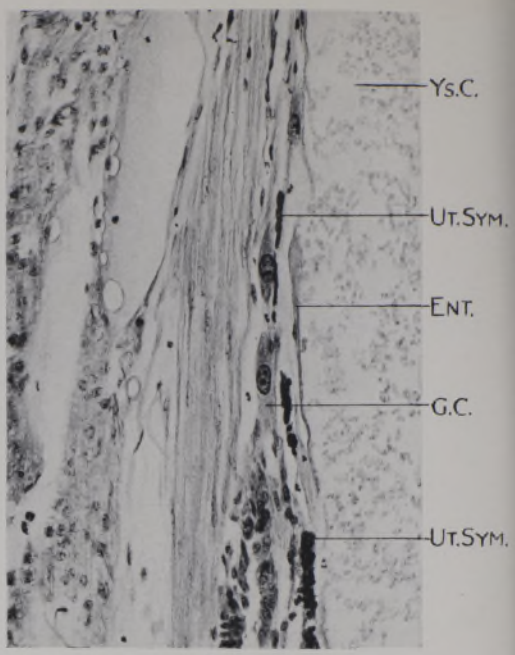


6

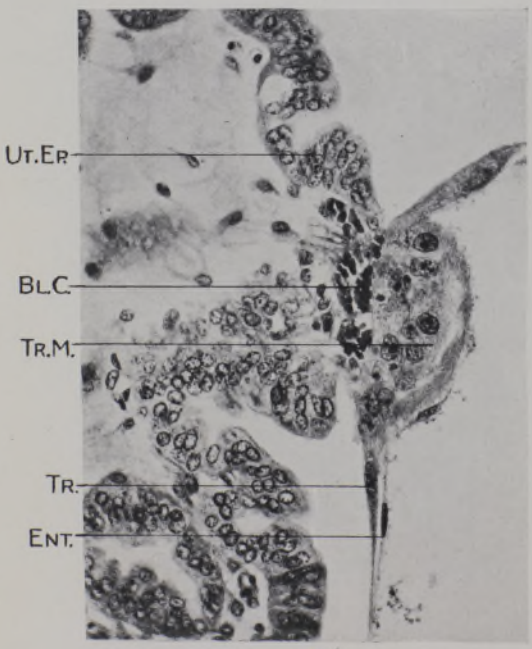
7



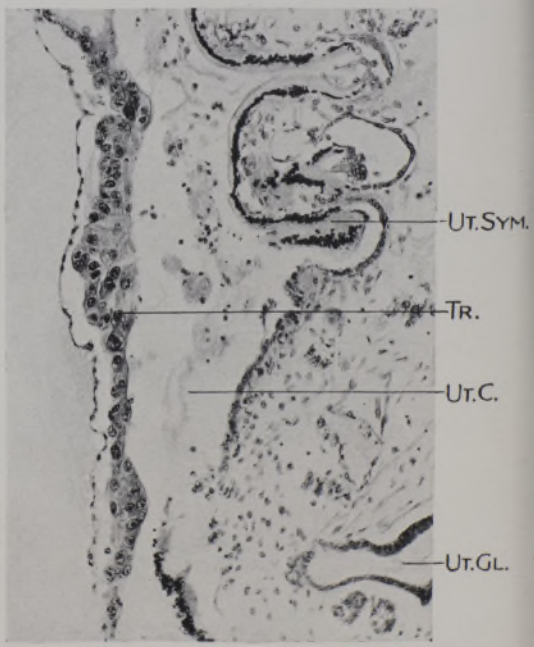
8



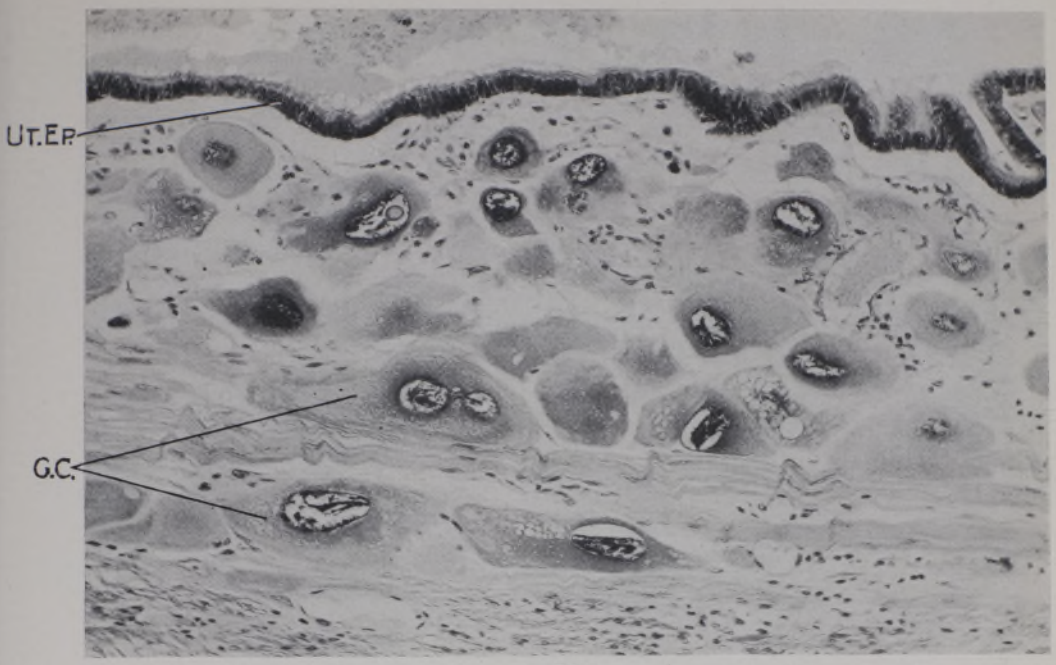
9



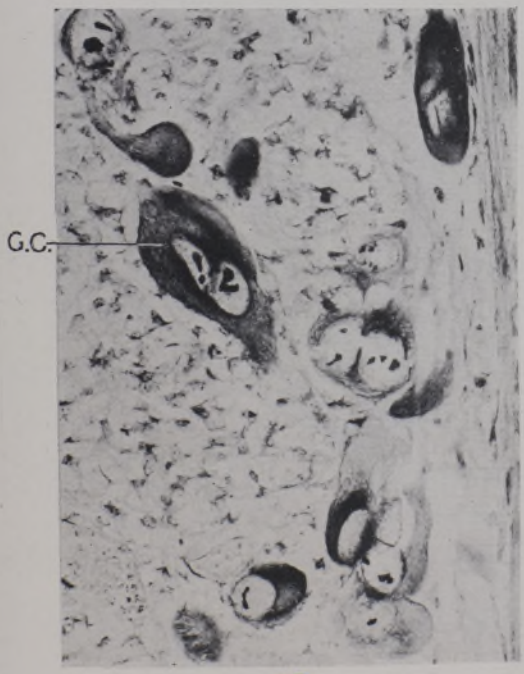
10



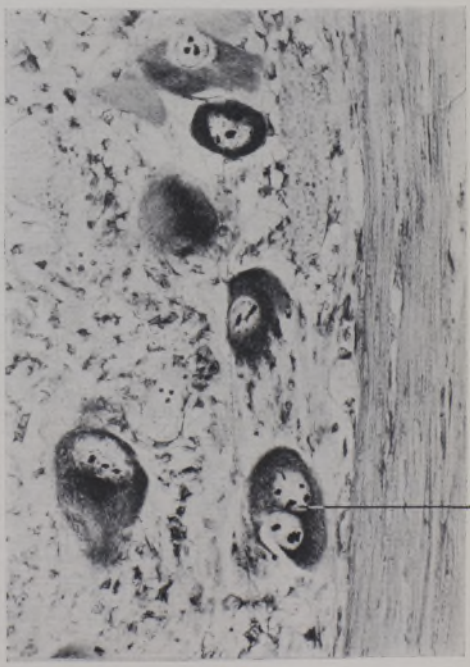
11



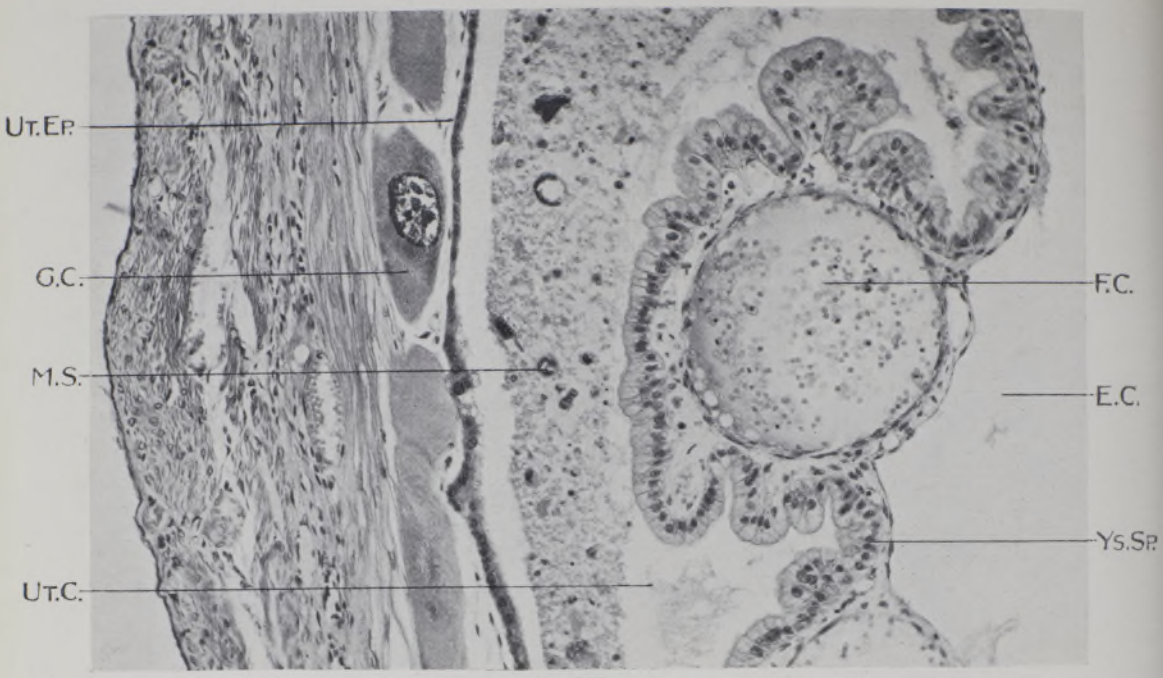
12



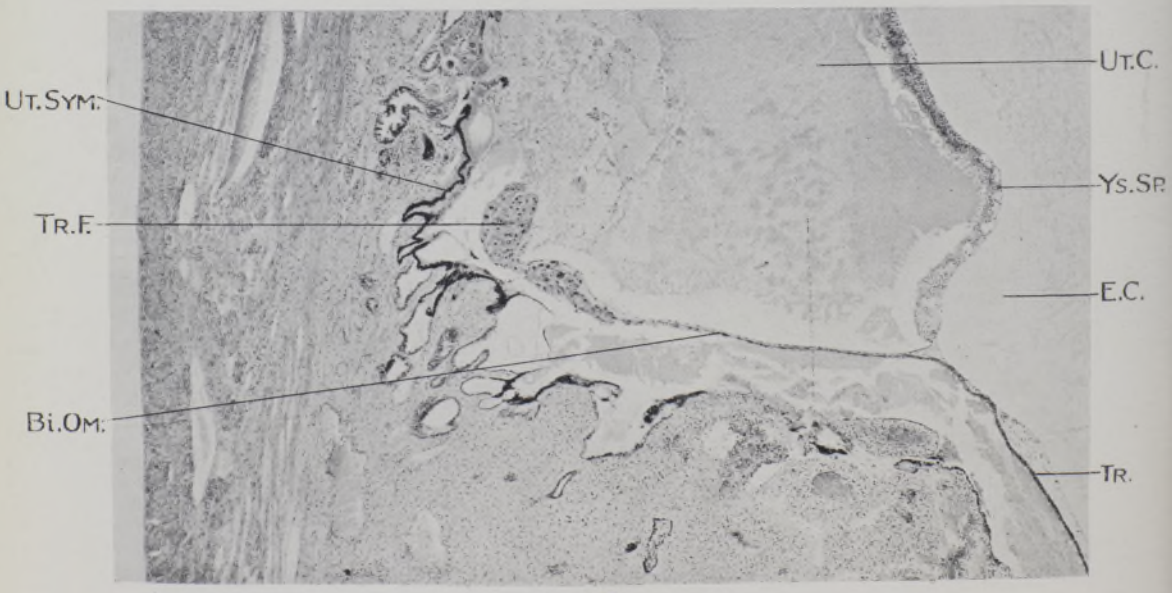
13



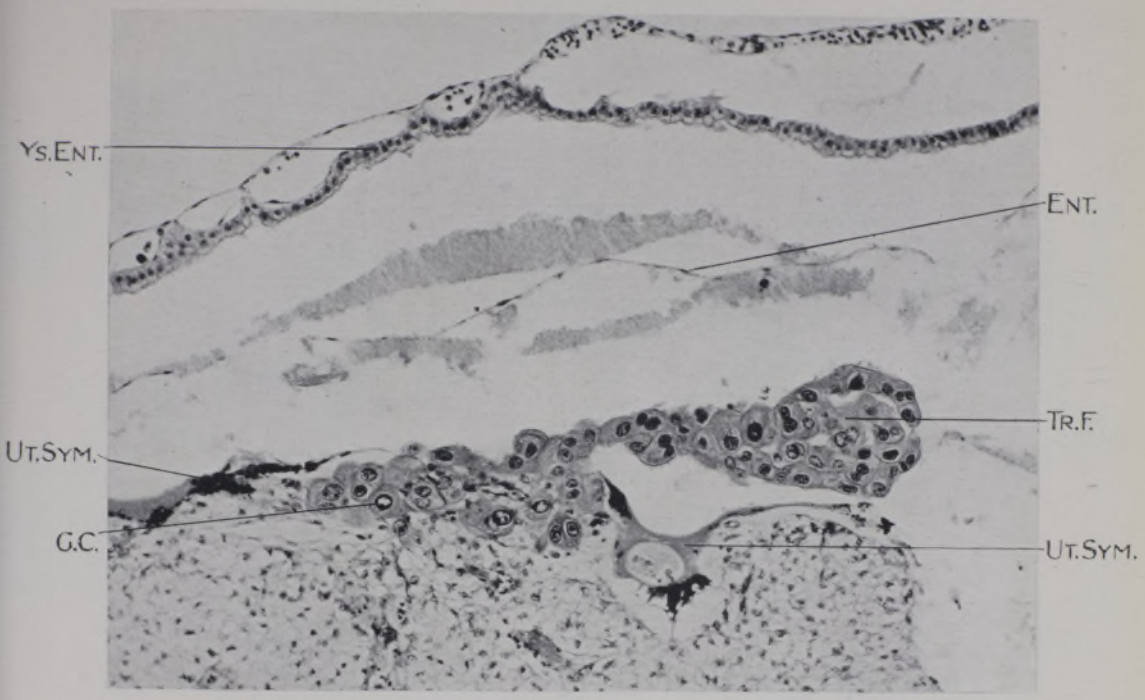
14



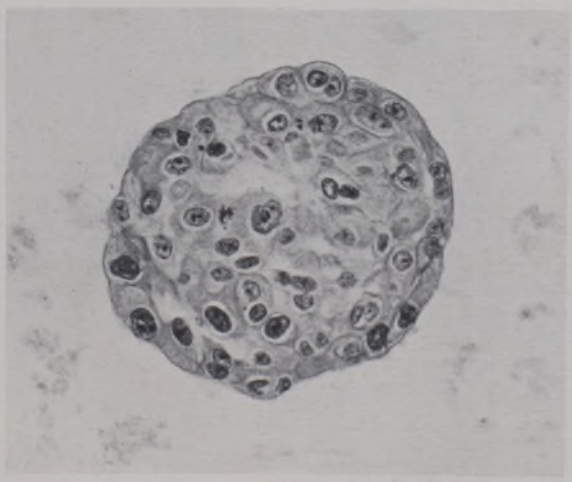
15



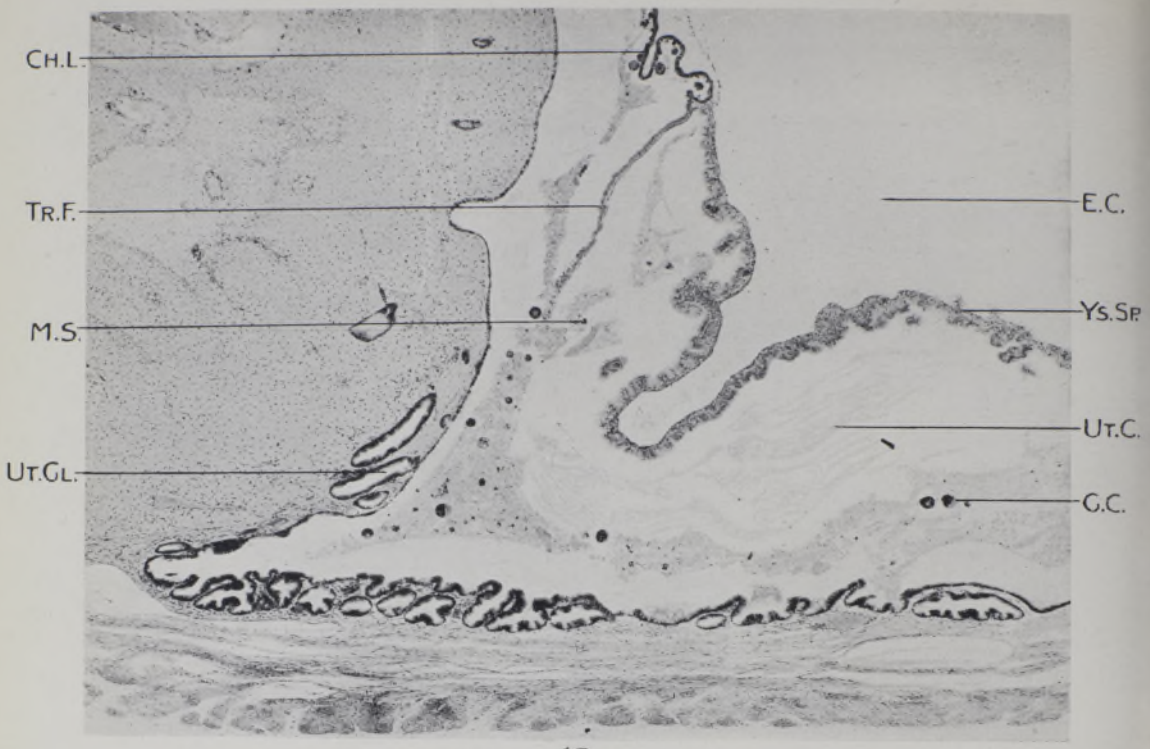
16



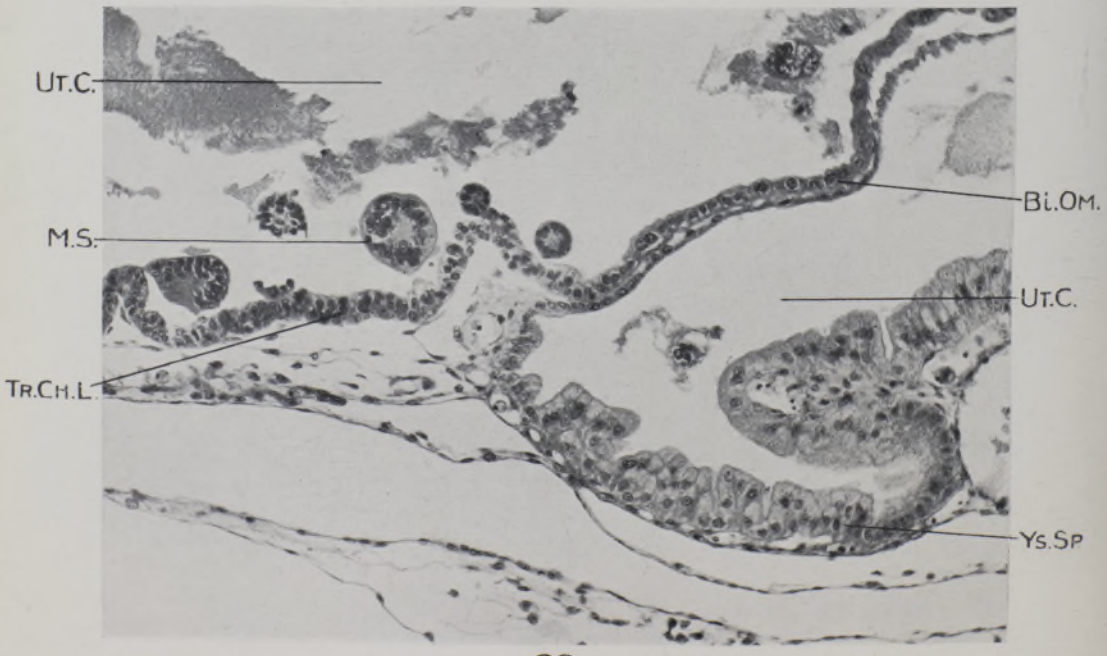
17



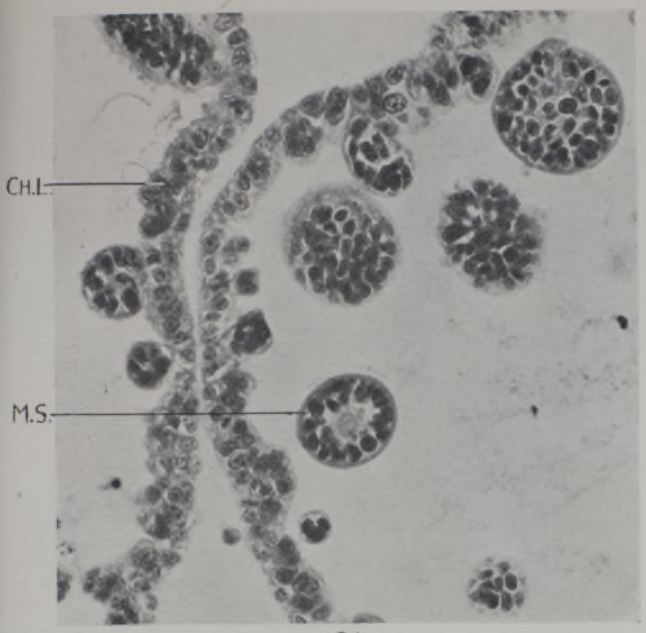
18



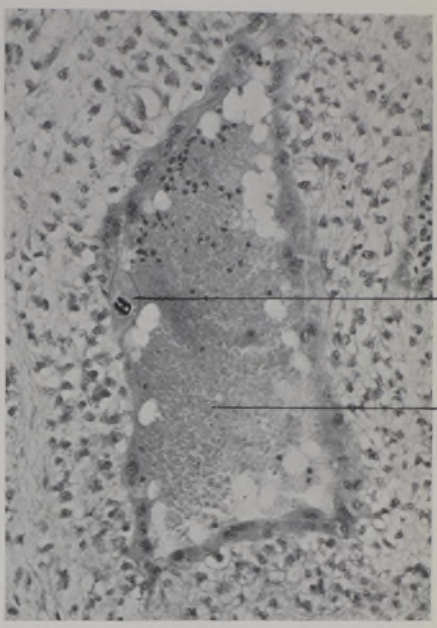
19



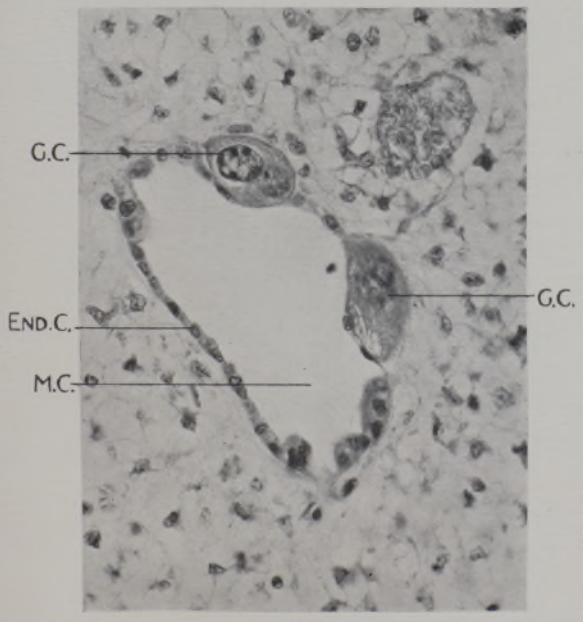
20



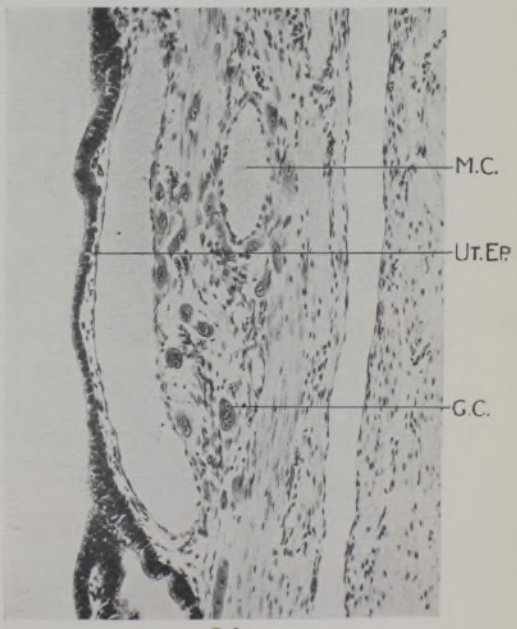
21



22



23



24