

## **Uterus and embryo : I. Rabbit : II. Man / by Charles-Sedgwick Minot.**

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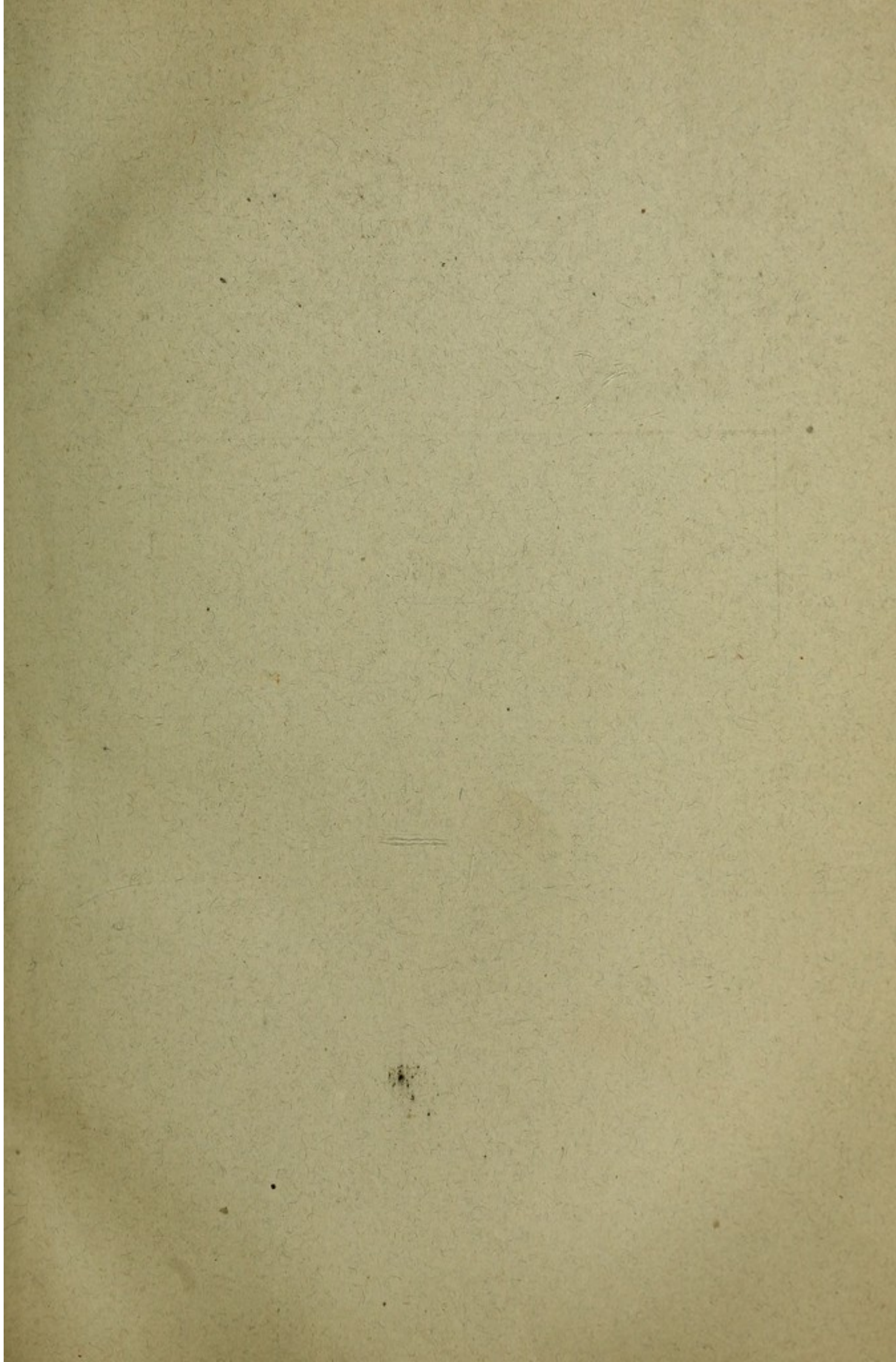
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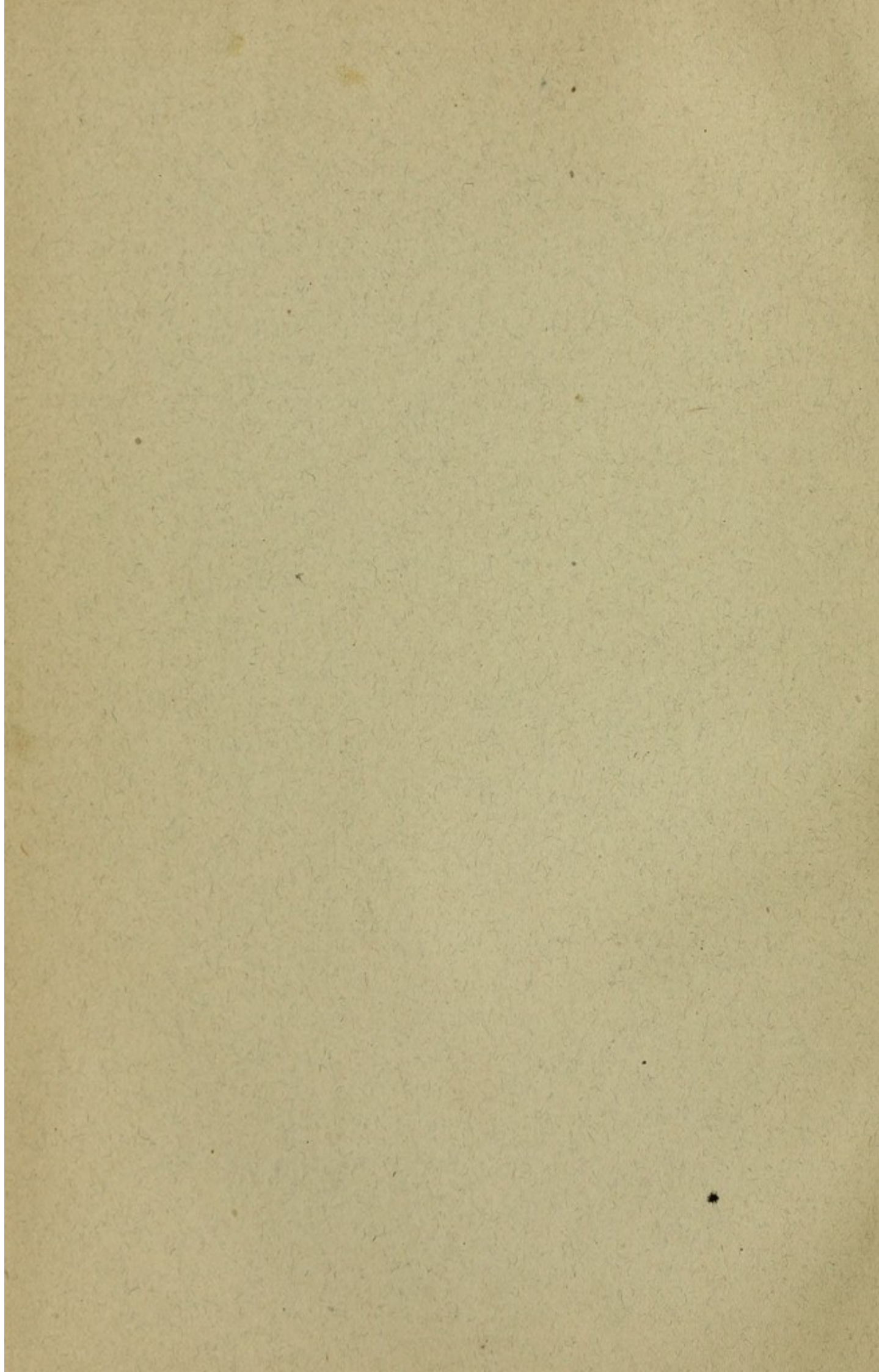
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# UTERUS AND EMBRYO:

296

I. RABBIT; II. MAN.

BY

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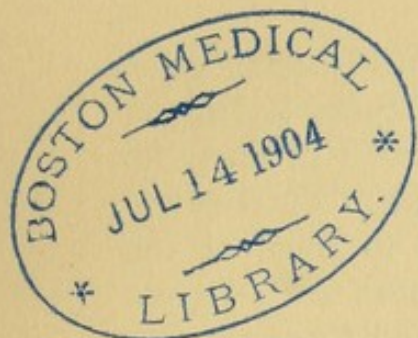
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UTERUS AND EMBRYO:—I. RABBIT; II. MAN.

CHARLES—SEDGWICK MINOT,

HARVARD MEDICAL SCHOOL, BOSTON, MASS.

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THIS paper arose not as the result of a special investigation, but as the outcome of general studies undertaken in connection with the preparation of a *Treatise on Human Embryology*. For



such a work, knowledge of the foetal envelopes seemed especially important. I was thus led to examine them, and found in so doing that the structure of the parts differed in many respects from what had been assumed. The rabbit's uterus was examined in the hope of obtaining light as to some of the changes in the human uterus, but the differences are so great that little help was gotten; but on the other hand I was brought to a conception of the changes in the rabbit's uterus so fundamentally different from the views of previous writers that I was induced to carry my observations far enough to make sure of the essential alterations. The following communication is therefore in no sense monographic, but only supplementary to the work of others. My own work has been accomplished by the aid of a grant from the American Association for the Advancement of Science, without which it could not have been carried out. The recipient of such aid naturally wishes to publish what he has accomplished, since such a publication is the most fitting acknowledgment of the assistance enjoyed. I feel my obligations to the Association the more deeply because the grant is the first made from its Research Fund. May I express the hope that that fund will be largely increased, and the Association enabled to make numerous grants to other workers, for in so doing it will do more for the promotion of science than, I believe, by any other means whatsoever.

### I. RABBIT.

The observations here recorded were made upon pregnant uteri of the rabbit at various intervals from the sixth to the fifteenth day of gestation, both inclusive. The uteri were cut out carefully, stretched very slightly, and the ends of each uterus tied to an iron rod; the specimens were then hardened in Kleinenberg's picrosulphuric acid, according to the directions given in Foster and Balfour's *Embryology*, 2d ed. pp. 425, 426. Although this reagent worked fairly well, and preserved the histological elements of the uterus and of the older embryos satisfactorily, it failed to preserve the blastodermic vesicles in uteri of six and seven days; and in the older specimens, after hardening, the extra-embryonic foetal membranes were somewhat rumped. Owing to the great difficulty of obtaining doe-rabbits

in Boston, and their consequent high price, I have been unable to experiment with other methods of hardening. The specimens after hardening were for the most part stained *in toto* with alum cochineal and eosine, imbedded in paraffine and cut into serial sections with an automatic microtome, made by Herr G. Baltzar of Leipzig.

§ 1. **Uterus at six days and three hours.** — The position of the ova is recognizable externally, being marked by a very slight protuberance on the free side of the tubular uterus. Transverse sections show that there is a considerable dilatation of the uterine cavity, corresponding to the swelling; the walls are considerably thinned out by stretching. The glands are much altered, otherwise there is no striking change in the uterine structure. The shape of the glands varies, but everywhere their cavities are very much expanded, and the epithelial linings of adjacent glands are separated only by very thin connective tissue partitions; on the side of the mesentery the glands are distinctly tubular, and grouped on folds of the mucosa; the relations of these folds are described in the next section. On the opposite side of the uterus, that is, away from the mesentery, the glands are short, with wide cavities, constituting a series of irregular ampullæ with wide mouths. The epithelium is thickened everywhere; it stains deeply, and has enlarged nuclei; it has many intercellular vertical fissures, and therefore a good many of the cells are separated from their neighbors; adjacent cells project unequally, rendering the surface of the epithelium irregular. The change in the epithelium is greatest opposite and least near the mesentery, but is everywhere similar in kind, though varying in degree.

I am unfortunately unable to state anything in regard to the relations of the ovum, owing to the failure of its attempted preservation in my specimens.

§ 2. **Uterus of seven days and three hours.** — The placental swellings are well marked as smooth, rounded bulbs only a little larger in diameter than the unaltered uterus between the swellings, and not projecting at all on the mesenterial side of the uterus. Transverse sections show at once the changes which have taken place. As is well known, the rabbit's uterus has six longitudinal folds, symmetrically disposed; the line of insertion of the mesentery (mesometrium or broad ligament) corresponds

to the space between two folds, which alone participate in the formation of the placenta; accordingly we may designate them as the *placental folds*. In the region of the swellings the placental folds are already hypertrophied, and form a marked contrast to the opposite side, where the folds have completely disappeared, and their glands have become shorter and somewhat contorted; the two lateral folds are intermediate in appearance. In the placental folds there is a great increase in the connective tissue, which consists solely of anastomosing cells, forming a loose meshwork of very granular protoplasm, of which only a small amount is accumulated around each nucleus. Described in other words, the cells are small, granular, with long processes continuous with those of adjacent cells. The glands extend only a short and nearly uniform distance down from the surface of the folds; the glands themselves are somewhat dilated; their epithelium stains deeply; its free surface is quite irregular; the nuclei are greatly increased in number, and lie crowded throughout the whole thickness of the layer; the nuclei are round or oval in outline, with a well-marked reticulum densest superficially. In many places the nuclei are grouped, three, four, or five together, and sometimes one can distinguish a distinct outline around the group. These appearances I interpret as evidence that the nucleus of each cell proliferates, rendering the cell multinucleate. The blood-vessels are likewise hypertrophied in the placental folds, and to a less extent in the adjacent folds, but not at all in the folds opposite the placenta. In the placental folds there are larger blood-vessels running for the most part longitudinally, and all situated in the zone next the muscularis; between this zone and the glandular layer, the blood-vessels are, on the contrary, all of small calibre, most of them taking a more or less radial course, and lying approximately in the plane of the transverse sections. All the blood-vessels of the mucosa have, so far as I have observed, the character of capillaries, for they consist of merely an endothelium without adventitial or muscular envelope, although some of them are many times the diameter of ordinary capillaries. The blood-vessels of the placenta of the Guinea pig are stated by Creighton, 77a, p. 544, to have the same character. There is a single layer of connective tissue cells condensed around the vessels, and representing the commencement of the perivascu-

lar decidual cells, though the cells themselves scarcely differ yet from the ordinary connective tissue cells between the vessels.

We find at this stage all the regions of the placental swellings, to be found in later stages, already definitely marked out.

These regions are as follows:—

1, PLACENTAL: subdivided into

*A, glandular zone.*

*B, sub-glandular vascular zone with (a), sub-glandular zone with small vessels (b), outer zone with large vessels.*

2, PERI-PLACENTAL.

3, OB-PLACENTAL.

Each of these regions comprises two folds of the mucosa, viz.: the *placental*, the two folds next the mesentery;<sup>1</sup> the *peri-placental*, the two lateral folds; and the *ob-placental* region, the two folds opposite the mesentery. The three zones of the placental area persist and become much more marked in later stages, owing to the great divergence of the processes of histological differentiation in each zone. Of the two vascular zones, the *sub-glandular* is characterized later by its very large multinucleate cells, while the *outer zone* is characterized by its crowded uninucleate decidual cells. All the regions and their subdivisions will be perhaps better understood by the descriptions and figures of the nine days' uterus. (See below.)

In my specimens, although the uterus seemed to be very well preserved, the blastodermic vesicles were completely shrivelled up; hence I could make no observations as to the relations of the embryo to the uterine wall.

§ 3. **Uterus of eight days and three hours.**—It is unnecessary to describe the appearances at this age in detail, as they have been described already with admirable clearness and exactitude by Masquelin and Swaen, 114, 25-30. I have therefore only to confirm their account and refer to certain points on which my observations extend or differ from theirs; it is also necessary to describe the extra-placental structures, which are left out of consideration by Masquelin and Swaen.

<sup>1</sup> Although this use of the term mesentery is etymologically indefensible, it seems permissible, and not likely to lead to misunderstanding any more than the etymologically indefensible terms cell, endothelium, terminology, etc., etc.

The connective tissue is but little altered from the condition at seven days ; it has the same adenoid character ; the cells are elongated in directions more or less parallel to one another, and the appearance of the protoplasmic reticulum therefore varies according as the section passes at right angles or parallel with the long axes of the cells ; in the former case the meshes are smaller, in the latter larger and longer. The perivascular cells have grown ; Masquelin and Swaen trace their origin to a metamorphosis of the connective tissue cells, in doing which I entirely agree with them ; these authors likewise describe fibrillæ in the connective tissue, but in my preparation I can find none, nor from what we know of the structure of the mammalian uterus is it probable that any are present ; in regard to this point I think that Masquelin and Swaen's account needs rectification.

The placental blood-vessels have increased in size, and, I think, in number ; their epithelium, particularly in the larger vessels, is decidedly thickened.

The uterine epithelium has entered upon its complex degenerative metamorphosis — most of the changes have been seen and correctly described by Masquelin and Swaen for the placental area. They conclude that the changes lead to a new formation of blood corpuscles out of the substance of the epithelium. My own observations oblige me to regard the changes as phases of a hyaline degeneration with hyperplasia of the degenerating elements, and having nothing to do, therefore, with blood formation. In all parts of the uterine dilatations the epithelium is considerably thickened (Plate XXVI., Fig. 1). The thickening is due to the enlargement and fusion of the epithelial cells, and this enlargement of the cells is due to the proliferation of the nuclei and to the growth of the protoplasm, which begins later and continues longer (as later stages show) than the multiplication of the nuclei. That the nuclei multiply within each cell can be distinctly seen in my specimens of this age ; the same fact has been observed by Masquelin and Swaen. The growth of the protoplasm is more properly described as an enlargement, due to degenerative metamorphosis. As to the nature of this metamorphosis I am unable to speak with much precision. The substance presents a very granular appearance, and possesses a slightly greater affinity for coloring-matters

than the unaltered protoplasm. Examination with an apochromatic oil immersion shows in some parts of the degenerated epithelium a distinct network, the threads of which are rather coarse and hyaline in appearance. In default of chemical and further microscopic examination we may accept the hypothesis that the degeneration consists in direct change of the protoplasmic reticulum into hyaline substance, accompanied by thickening of the reticular threads. The degeneration of the epithelium has progressed much further over the non-placental area than elsewhere, and much less over the placental area: the peri-placental regions are in an intermediate stage.

It is also important to note that the deep portions of the glands are nowhere degenerated. The glandular layer may be divided accordingly into an upper degenerated zone and a lower not degenerated zone.

In the placental area there is no stretching of the tissues, and accordingly the glands retain their tubular character. The nuclei fill up most of the epithelial layer; there are three, four, or even five, in each cell in the upper part of the gland; the cells of the fundi are but slightly altered from their usual appearance. The embryo is attached to the maternal placental surface only by the ectoderm, without any participation of the other germ layers, direct or indirect, so far as I can observe. That portion of the ectoderm which is soldered to the uterus is very much thickened, in marked contrast to all other parts of the layer. As shown in Fig. 1., Pl. XXVI., the placental ectoderm runs over the surface only of the placenta, and stretches straight across the mouths of the glands, shutting them completely; it does not dip down into the glands at all, and possesses no villi whatsoever. On the surface, between the glandular orifices, the uterine epithelium, already degenerated, is clearly distinguishable.

In the other regions the stretching of the walls stretches the glands also, and of course proportionately to the extent of the strain; hence, in the non-placental area the glands become slits running parallel to the surface, and in the peri-placental part become wide cavities. The upper zone of the peri-placental glandular layer has its epithelium changed into a very thick layer, and beginning to undergo resorption, as evidenced by the presence of cavities. As we follow round towards the non-pla-

central area, the evidences of resorption are greater, and over the area itself a large part of the upper glandular zone has disappeared altogether. Similar relations are found in the uterus of nine days, from which the drawings have been taken. For the sake of greater clearness, and to avoid repetition, we pass at once to the next stage. The fact that I have found the uterus at eight days so much nearer in its stage of development to that of nine than to that of seven days, may be attributed to accidental variations.

§ 4. **Uterus at nine days and three hours.**— Fig. 2, Pl. XXVI., represents a transverse section through a swelling. The attenuation of the walls everywhere, except in the placenta, is very marked, and affects both the outer and inner muscular layers, *lm*, *cm*, and the mucosa, *muc*. In the placental region, *Pl*, on the contrary, the walls are thickened; the placenta itself is formed chiefly by the hypertrophy of the connective tissue of the two longitudinal folds nearest the mesentery, *mes*: the superficial glandular layer, *gl*, owing to its deeper staining, is readily distinguished even by the naked eye; each lobe of the placenta is imperfectly subdivided into two lobules; the embryo, in the specimen figured, appears in transverse section over the right-hand lobe, directly above the furrow separating its lobules; the actual disposition is shown in Cut 1; in Fig. 2 the embryonic structures are purposely omitted on account of the small scale; to the consideration of the foetal membranes the next section (§ 5) is devoted.

The connective tissue of the placenta is already far advanced in its metamorphosis, which progresses as described by Masquelin and Swaen. It consists of a rich cellular network, Fig. 3, *conn*, of which the cell bodies are much larger than in previous stages; these bodies are for the most part elongated, with very irregular surfaces, and are, therefore, perhaps best characterized as roughly spindle-shaped; their long axes are more or less parallel with the blood-vessels; the nuclei are round, oval, or elliptical, granular, but with a clearer cortical layer, as is usually the case in young connective tissue cells: compare Rollett's Figs. 4 and 5 in Stricker's *Handbuch der Lehre von den Geweben*, I., pp. 63 and 65. The processes of the cells are numerous and very fine, forming a meshwork, between the cells, of such delicacy that it can be followed out only with high powers

(400–500 diams.). The observation of the threads of this network has led certain investigators to assume the presence of connective tissue fibrillæ. Scattered about in the connective tissue are a not inconsiderable number of leucocytes, *l, l, l*, easily recognized by their size and shape, their granular appearance, deep staining and characteristic nuclei. Around the blood-vessels is the perivascular layer of decidual cells, *per v*, which have already been amply described by Masquelin and Swaen, Ercolani, Godet, Creighton, and others. Ercolani's descriptions, of which the most important to us is that of the rabbit at fifteen days,<sup>1</sup> **89**, p. 278, is far from sufficient. Godet's paper I know only from an unsatisfactory abstract. Creighton's account of the perivascular layer in the Guinea pig, **77a**, 544, is also good, and he agrees with the Belgian authors in tracing the origin of the cells to the metamorphosis of the connective tissue. Ercolani opposed this view and maintained that the uterine mucosa is completely destroyed, leaving the whole placental tissue of the mother to arise as a new formation. My preparations render it impossible to agree with Ercolani, since they show all the phases of the metamorphosis. It is only necessary to follow, in Fig. 3, the three series of cells numbered 1, 2, 3, 4, each, and to find in all parts of the placenta the same appearances; to see the perivascular layer at six and seven days, before it is much differentiated; and finally to see the perivascular accretions at later stages, to render inevitable the conviction that the perivascular layer is modified connective tissue. Neither at this stage nor at any earlier or later one have I been able to detect any evidence whatsoever of the resorption of the connective tissue affirmed by Ercolani, **89**. Masquelin and Swaen describe multinucleate cells, but I fail to find them until later stages.

The blood-vessels have their endothelial lining considerably thickened, each cell for itself, and to its individual degree, Fig. 3, *Endo*; they are stained by alum-cochineal and eosine more deeply than the adjacent decidual cells, from which they are sharply distinguished. I am unable to recognize any cells which might be interpreted as intermediate stages between the endothelial and decidual cells, as we should anticipate, were Erco-

<sup>1</sup> The specimen described by Ercolani I consider to have been probably really only about thirteen days.



lani's suggestion correct that the decidual cells arise from the blood-vessels. The contents of the blood-vessels are blood corpuscles and coagulum; the blood corpuscles resemble the ordinary red globules of the rabbit, a point deserving notice in view of the change occurring later. There are occasional leucocytes, but they are nowhere numerous.

The two layers of the vascular zone are now distinguishable not only by the size of the vessels (not well illustrated in the section drawn as Fig. 2), but also by the much greater development of the perivascular cells in the outer zone; in the subglandular zone the cells are now not far from their maximum development, forming a coat one or two cells thick around the vessels; on the outer zone, on the contrary, the number of layers of cells has still to increase very much; consequently as development progresses, the difference between the subglandular and outer zone becomes more conspicuous.

The epithelium and glands repay careful study at this stage. The degenerative processes are similar in certain essential respects in all parts of the uterine swelling. The likeness concerns five chief points: 1°, the deep portions of the glands show little change in the epithelium; 2°, the upper portions are very far degenerated; 3°, the protoplasm of the degenerated epithelial cells is fused into a continuous thick hyaline mass, the growth of which ultimately obliterates the cavity of the glands; 4°, the nuclei of the degenerated epithelium multiply enormously; 5°, the degenerated tissue is absorbed by progressive vacuolization.

But although these resemblances are dominant, each of the three principal regions, the placental, peri-placental, and ob-placental, presents now a very distinctive appearance, and has its distinctive further history.

In the peri-placental region, with which we begin, because the relations are more obvious there than elsewhere, we find the appearances shown in Fig. 4. The line of demarcation from the placenta, though not definite or sharp, can be approximately determined, but the passage into the ob-placental region is very gradual. The most striking feature of the section is the degenerated and enormously thickened epithelium, *h.ep*, deeply tintured by the eosine, and remarkable for the crowded band of nuclei. Within the area of the degeneration the former

gland cavities are closed; the diameter of the glands has enormously increased, and in some places two adjacent glands have swollen until they have come in contact and fused, the glands then forming a network; in the placental region the conversion of the glands into a network goes very far. The distribution of the nuclei as at *a* and *b* preserves in some parts the original grouping in opposite walls of the gland tube; at other points they lie in irregular patches. Secondary cavities, *vac*, appear at various points; they are irregular in size, shape, and position, and arise by the resorption of the degenerated tissue. There is probably a certain amount of resorption carried on upon the surface against the connective tissue, for that surface becomes jagged and irregular, presenting a corroded appearance, as can be seen at various parts of Fig. 4. The vacuolization is, however, the principal factor of destruction. As to the manner in which the spaces are produced in the heart of the very compact layer, my observations give no satisfactory information. There are no accumulations of leucocytes either in the epithelial layer nor even in the connective tissue (see Fig. 4), in which all the cells are copied with approximately entire accuracy from the preparation. The only material I have ever noticed in the vacuoles is broken-down fragments of the surrounding hyaline tissue (epithelium) itself. The hypothesis may be suggested that the resorption vacuoles are produced by liquefaction, but the suggestion calls for no further discussion since there are no direct observations to test the validity of the hypothesis.

The deep portions of the peri-placental glands, Fig. 4, *gl*, are dilated transversely to an extent which has converted them from tubes into wide vesicles. Towards the ob-placental region the transverse stretching gradually increases. The epithelium differs but little from that of the resting utricular glands; it is composed of cylinder cells with basally placed oval nuclei.

In the ob-placental region the mucosa is much thinner than elsewhere. As we proceed from the edge of the peri-placental region towards the pole furthest from the placenta we find that the layer thins out and is more advanced in its degeneration. Near the peri-placental thickening there is a wide superficial layer of degenerated epithelium with the characteristic central band of nuclei, but the prolongations corresponding to the degenerated gland ducts are short; the deep portions of the

glands are oval slits parallel with the muscularis, Fig. 5, *gl.* A little further along, the resorptive vacuolization begins, producing a curious irregular layer, Fig. 5. The degeneration and vacuolization is found still further along to have involved the inner adjacent wall of the gland vesicles, thus producing the appearances shown in the left-hand part of Fig. 5, where there are shallow cups, *gl.*, of epithelium, each entirely separate from its fellows, and all overlaid by the hyaline stratum, *h.ep.* There is usually a dome-like hollow in the degenerated stratum above each cup. Since the processes described vary in rapidity, there is not a uniform, but only a general, progression of stages towards the centre of the ob-placental region. Moreover, the variability is great, and the images from different sections and different parts of the same section are correspondingly multifarious, but the general succession of changes is everywhere the same; hence it would be profitless to expand the descriptions.

The *placental* glands have preserved their tubular character; they are less degenerated than the uterine glands of the non-placental parts; their walls are less thickened and in most parts the glandular cavity is still present. The deep portion of the glands are tubes lined by columnar epithelium. For the rest, I may refer to the satisfactory description of Masquelin and Swaen, **114**, 30-31, except as to one point. As shown in Cut 1, p. 355, the ectoderm of the embryo is firmly soldered to the placental surface over certain areas. The nature of this connection and the accompanying structural changes in the uterus are illustrated in Fig. 7, which has been copied with great care from one of the sections. For the sake of clearness, only the nuclei of the connective tissue have been drawn in; the perivascular cells are represented by their nuclei and outlines, and the nuclei and cells of the foetal ectoderm are given in outline; but there is nothing diagrammatic in the drawing; of course in the figure the distinction between the foetal and maternal tissues is more marked, though not more real than in the section; in fact there is scarcely a cell even on the line of junction of the ectoderm with the uterus about the assignment of which one could have any doubt, so distinct is the texture and the staining of the foetal and maternal tissues. This is a matter of importance, as it renders it possible to ascertain beyond question that there are no villi; nevertheless their presence has been assumed not infrequently. To pass on:

where the ectoderm, Fig. 7, *Ecto*, touches the placenta, the active resorption of the degenerated glands is going on (see the part of Fig. 7, above bracket C); whereas in other parts the glands present the appearance shown in Fig. 7, *A, gz*, and described by Masquelin and Swaen. There is also an intermediate zone shown in Fig. 7, above bracket B, where the transition phases between the two states are found; the zone of transition lies immediately underneath the point where the ectoderm, *Ecto*, joins the uterine epithelium, *h.ep*; here the glands are thickened and hypertrophied; the lumen is obliterated, but the cylindrical shape is irregularly preserved; where the distal end of the ectoderm leaves the placenta, there is again a similar transition: in other words, the resorption is less advanced around the periphery than in the centre of the area of ectodermal attachment. The resorptive process is essentially the same as outside the placenta, — superficial corrosion and internal vacuolization, — but the vacuoles formed are relatively small and consequently more numerous: moreover, the space left by the disappearing epithelium is at once occupied by connective tissue cells, so that there are no cavities. The resorption goes on principally in the superficial layers of the placenta, where it results, as later stages show, in the complete disappearance of the glands immediately underneath the ectoderm; deeper down the glands at the present age are hypertrophied and without lumina, but even in the region of bracket C of Fig. 7 (Pl. XXVII.) most of the glands show very few or no vacuoles.

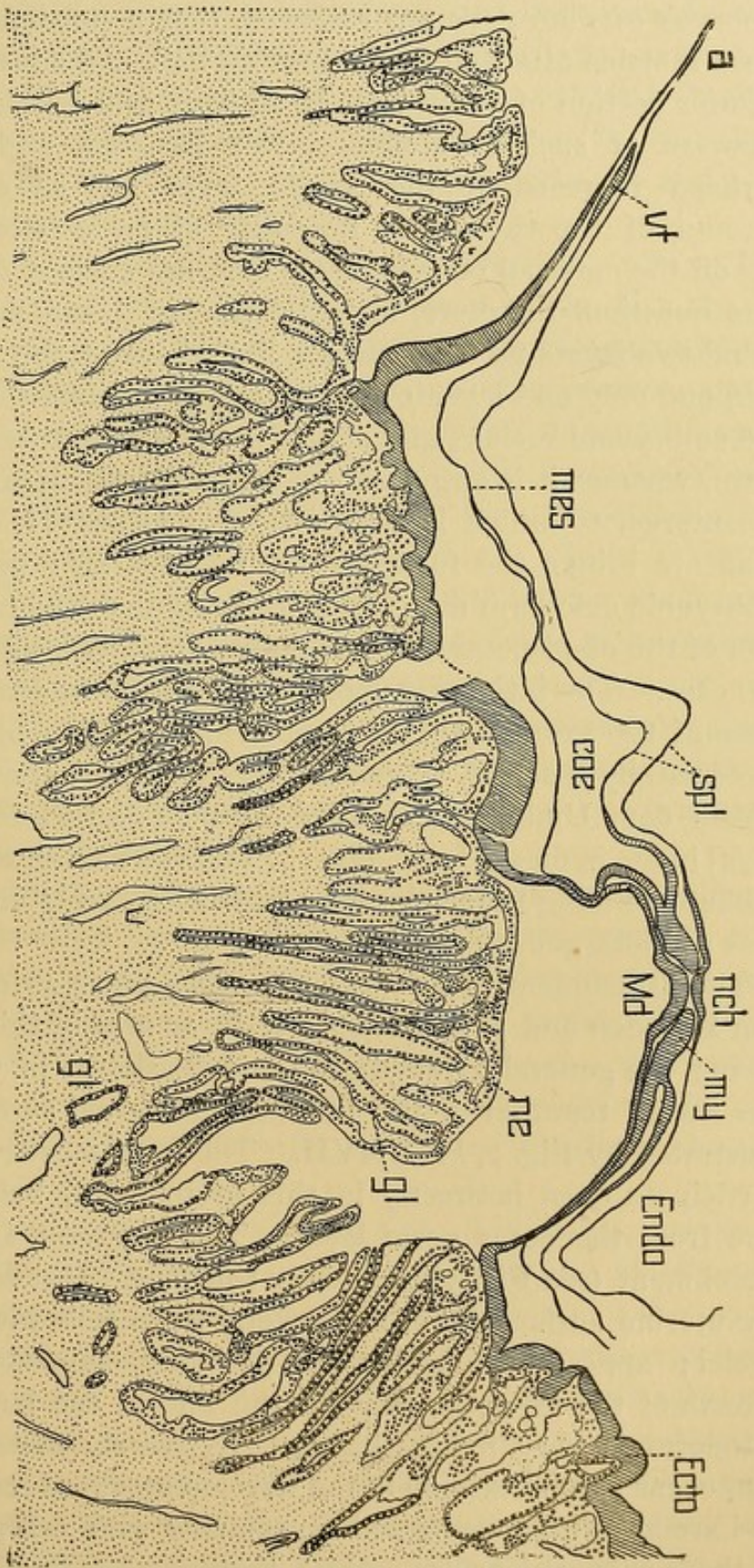
§ 5. **Embryo at nine days and three hours.** — It is not proposed to consider here anything but a few points bearing on the relations of the embryo to the uterine walls.

First, as to the *position of the embryo*: the dorsal surface of the embryo is turned towards the placenta; the embryo may be situated over one or the other lobe of the placenta or across both; its long axis may be either parallel or oblique or at right angles, to the long axis of the uterus. In the specimen represented in Cut 1, both the uterus and embryo appear in transverse section. Similar variability appears in my specimens of uteri of eight days, and of nine days and seventeen hours. The statements of Van Beneden and Julin, 44, and other authors,<sup>1</sup>

<sup>1</sup> Compare Bischoff, *Entwicklungsgesch. d. Kaninchens*, p. 138, and von Baer, *Entwicklungsgesch. II.*, 232.

lead rather to the supposition that the embryo normally lies across the uterus; but this is true in my experience only of the later stages after the embryo is suspended more freely.

Next as to the extra-embryonic portions of the germ layers: my observations compel me to differ as to the composition of the walls of the blastodermic vesicle or yolk sack. Sections through the middle region of the embryo, Cut 1, show an open medullary groove, *Md*, the thickened notochordal band, *nch*, of the entoderm; the mesoderm of the *Stammzone* is undivided; that of the *parietal zone* is split to form the cœlom, *Coe*, which may be followed a considerable distance from the axis of the embryo, when the two leaves of the mesoderm again unite into a single distal plate, *mes*, in which the two layers can be distinguished for a certain distance; the distal edge of the mesoderm is sharply marked; the mesoderm is thickened around its margin. Beyond the margin the ectoderm and entoderm come into contact, *a*; the former is the thicker layer, being composed of cubical cells, while the entoderm consists of very thin broad cells; the two layers continue outwards until, having passed over the periplacental thickening, they reach the region of transition from the peri-placental to the ob-placental area, where the ectoderm changing to a thin flat-celled membrane is intimately conjoined to the degenerated epithelium of the uterus. Where the concrecence takes place, the union of the two layers becomes very intimate, so that it is difficult to satisfy one's self how much farther the ectoderm extends, but apparently it goes completely around, forming a closed vesicle, as is generally stated and as is found later. Apparently the ectoderm is not involved in the resorption of the uterine epithelium, which disappears — but further investigation is required. The entoderm of the other hand is readily followed, and although somewhat crumpled and torn in the ob-placental region of my specimens, there is to my mind very little doubt that it forms a closed sack, corresponding to the entodermic lining of the yolk sack of other mammals. From the observations above recorded it is evident that two germ layers are readily traced for some distance from the embryo, but that beyond a certain line only one layer, the entoderm, is readily followed. Now this fact is carefully represented in van Beneden's and Julin's diagram, 44, Pl. XXIV., but the membrane which stops is there given as entoderm, which, as seen in my



*Cut 1.*—Transverse section of a rabbit embryo, *in situ*, of nine days and three hours. *a*, wall of yolk-sack composed of ectoderm and endoderm only; *vt*, vena terminalis; *mes*, mesoderm; *spl*, splanchnopleure; *coe*, coelom; *nch*, notochord; *MD*, medullary groove; *my*, myotome; *Endo*, endoderm; *Ecto*, ectoderm; *gl*, glands; *v*, blood-vessel; *hc*, hyaline uterine epithelium.

specimens, is continued around. It is probable that when embryos of nine days are removed, that a portion of the ectoderm remains attached to the uterine wall, and consequently the inferior portion of the vesicle is without any ectoderm. Being unaware of such a possibility, van Beneden and Julin have perhaps represented the single layer left as ectoderm on account of the theoretical necessity of an ectodermal covering on the external or apparently external surface of the ovum. The question, therefore, is to be posed: Have not observers found two layers up to a certain limit beyond the *vena terminalis*, and only one layer over the remaining inferior portion of the embryonic vesicle, and *assumed* the single layer to be ectoderm, whereas it is entoderm, and the true ectoderm is left upon the uterus, to which it is indissolubly attached? The view I advocate brings the further question whether a portion of the embryonic ectoderm disappears by being involved in the resorption of the ob-placental uterine epithelium. This I think is not the case. The intimate adherence of the extra-embryonic portions of the germ layers to the uterine walls has been carefully recorded by Bischoff, *Entwickelungs gesch. Kaninchens*, p. 131, "Vom dem Umkreise der Vena terminalis an ist das Ei [of ten days] in die in dieser Lage, etc. . . . und von hier an sind auch alle Eihäute so innig unter einander und durch den Uterus vereinigt, dass es nicht gelingt sie zu lösen."

The attachment of the embryo takes place as described by van Beneden and Julin, p. 402, 403, by an area of thickened ectoderm; the general arrangement is well shown in Cut 1, while the fitting together of the foetal and maternal surface is better illustrated by Fig. 7, Pl. XXVII. The foetal mesoderm does not participate even indirectly in this attachment, but runs along free from the outer germ layer. The ectoderm, as it nears its attachment (see Fig. 7), gradually thickens. Just where it joins the uterine surface there are several large cells with very large nuclei; appearances which are probably connected with the growth of the layer, for beyond the line of the large cells the ectoderm is very much thicker. Extremely distended nuclei also occur very strikingly in the developing supra-renal capsules, and are also there connected presumably with cell proliferation. If these suppositions are correct, there is a modified form of cell division characterized by dilatation of the nuclei and which

deserves special study. Over the area of attachment the uterine epithelium, Fig. 7, *h.ep*, is degenerated as before described, its surface is extremely irregular, but the ectoderm, *Ecto*, is perfectly fitted to every irregularity, but the free surface (towards the mesoderm) is comparatively smooth; the layer consists of two, three, or four strata of cells. Beyond the area of attachment the ectoderm again thins out.

As to how the tissues are held together, my observations afford no explanation. It seems to me possible that the two tissues actually grow together as a grafting unites with a bough; but for aught we know it may be by some other process, perhaps simple agglutination. The thickening of the ectoderm I am inclined to regard as degenerative, and therefore somewhat comparable to the degenerative thickening of the uterine epithelium. I am brought to this view by no conclusive observations, but chiefly by two facts: 1°, that in later stages the ectoderm seems to have disappeared over the greater part of the placenta (see § 7. Uterus of eleven days); 2°, hyperplasia is often the commencement of degeneration, as is familiarly known to pathologists. To this evidence may be added the appearance of the ectoderm at nine days and seventeen hours, which I interpret as indicative of degeneration.

§ 6. **Uterus of nine days and seventeen hours.** — In my specimen there are not many changes from the previous stage last described, but of these changes the following deserve special mention: 1°, the commencing formation of perivascular decidual cells in the peri-placenta; 2°, the reconstitution of the ob-placental epithelium; 3°, the formation of the true chorion; 4°, changes in the extra-embryonic ectoderm; 5°, the contents of the placental blood-vessels.

1°. The peri-placenta is still only a small bolster at the side of the placenta; its glands are still recognizable and its blood-vessels are more conspicuous; the connective tissue cells are enlarged and have begun to form more or less distinct coats around the blood-vessels. I feel assured that the decidual cells arise here in the same way as those of the outer zone of the placenta; the cells in the two parts appear to me identical in character as soon as they attain their full development, and to differ only in the period during which their development takes place; later on, Fig. 8, Pl. XXVIII., the peri-placenta forms, together with



the outer zone of the placenta, a continuous layer of uninucleate decidual cells, extending over half the uterus.

2°. In the ob-placental region the degenerated portion of the uterine epithelium is almost completely resorbed around the pole opposite the placenta, (compare Figs. 4, 5, and 6). Fig. 6, taken from an older stage, in which the phase existing at nine days and seventeen hours at the pole is found near the peri-placenta, illustrates the manner in which the patches of unaltered epithelium, *gl*, of Fig. 5, grew together by the union of their edges into a continuous sheet of epithelium, Fig. 6, *gl*, forming a series of shallow cups, widely open.

3°. The chorion of mammals, as I have defined it elsewhere, is "the whole of that portion of the extra-embryonic *somatopleure* which is not concerned in the formation of the amnion."<sup>1</sup> The term is not applicable until the mesoderm has united with the ectoderm in the region outside the embryo to form a single membrane: such a union has now taken place; the thickened placental ectoderm is coated by a thin layer of flat cells, epithelial in character and with bulging nuclei. These cells represent the lining of the body cavity, or, as this lining is conveniently called, mesothelium. The mesothelium, and consequently the cœlom, extend a slight distance beyond the edge of the placenta; the mesothelium then bends over onto the yolk sack, of which it becomes the vascular coat, and then runs *towards* the embryo; the vascular coat has a large vessel, *sinus terminalis*, near the end of the cœlomatic space, and the mesoderm stretches a short distance beyond away from the embryo. The ectoderm, on the contrary, extends beyond the end of the mesoderm *away* from the embryo over the rest of the yolk sack. Thus the yolk sack, as is well known, comprises two parts, one near the embryo with walls composed of entoderm covered by mesoderm, and away from or opposite the embryo, with walls composed of entoderm covered by ectoderm; compare the clearly expressed summary of the relations in the rabbit given by Balfour in his *Comparative Embryology*, II., 199, 200.

4°. The ectoderm of the embryo presents the same general arrangement as at nine days. The area of thickened entoderm, however, which is attached to the placenta has changed in appearance; at nine days and three hours each cell outline was

<sup>1</sup> Wood's *Reference Handbook of the Medical Sciences*, II., 143; article, *Chorion*.

distinct, and the protoplasm around each nucleus dense and finely granular; now the cell outlines are hard to follow and the picture is confused by broader lines of hyaline matter, which is colored by the eosine; the nuclei are enlarged, the protoplasm is more coarsely and more irregularly granular, and somewhat vacuolated. The characteristics enumerated concord with the idea that degeneration is going on, — an idea suggested, also, as before stated, by the failure to find this part of the ectoderm in later stages.

5°. The blood-vessels show increased hypertrophy of their epithelium, and the perivascular cells form two or three layers around them; they are especially remarkable for containing a very large number of multinucleate leucocytes and comparatively few red corpuscles. The excessive abundance of white globules continues up to the oldest stage I have examined (sixteenth day). The predominance of nucleated corpuscles causes the contents of the maternal vessels to resemble foetal blood when examined with a low power; with high magnifications the difference is evident. To the foetal blood in the placenta we shall have to recur.

§ 7. **Uterus at eleven days and three hours.** — Very great changes have taken place — so great that they cannot be understood completely until some of the intermediate phases are studied. Want of suitable material has hitherto prevented my doing this. At the present stage — the beginning of the twelfth day — the placenta is distinctly pedunculate, and there is consequently a circular cleft between its sides and the closely adjacent peri-placenta; in the middle of the placenta a deep fissure corresponds, of course, to the space between the two folds of the uterus, out of which the placenta is developed, and therefore runs lengthwise of the uterus. The allantois has acquired considerable size and is attached to the surface of the placenta, from which the ectoderm has disappeared. The glands of the placenta are very far degenerated and altered; in the sub-glandular zone the multinucleate cells have appeared, and in the outer zone the perivascular cells have increased so as to occupy nearly all the space between the vessels. In the peri-placental and ob-placental regions, the modifications are equally noteworthy. Such, in brief, are the more striking changes. Let us consider them with greater detail.

The diagram on Pl. XXIX. will enable the reader to follow the ensuing descriptions. The general explanation of the diagram is given in the next section.

The placenta is shaped somewhat like a mushroom: it has a very thick stalk, with a somewhat broader top. The top is bilobate, there being a deep fissure between the two lobes; this fissure persists at thirteen days (Fig. 8, *f*); its fundus is the subplacenta (Ercolani's cotyledonary organ). The sides of the fissure are, of course, part of the surface of the placenta, morphologically speaking, and bear glands. The three zones of the placenta are well marked. In the outer zone the blood-vessels are very wide, with thickened degenerated epithelium; the perivascular cells occupy the entire space between the vessels in all that part of the zone towards the muscularis and most of the space in the part towards the glands. Next to the sub-glandular zone, therefore, we see the vessels surrounded, each by its separate thick perivascular coat, while the intervening tissue still consists of anastomosing cells, like those which in earlier stages occupied more of the space and which formed the only packing between the vessels at six days. The blood-vessels convert the layer, by their enlargement, into a spongy tissue, which has been described not only in the rabbit, but in other rodents; the vessels themselves have been generally described as glands, but the study of their development renders doubt as to their true character impossible. The vessels are partially empty in my preparations, but they contain very numerous leucocytes, nearly all of which have several nuclei apiece, which are conspicuous from their dark staining: there are a few red globules and here and there a little coagulum. As the corpuscles of the embryo are large nucleated bodies, there is no difficulty in distinguishing the foetal from the maternal blood, even in the upper part of the placenta, where the two circulations are juxtaposed. The middle or sub-glandular zone has undergone greater changes still. In it, as likewise in the glandular zone, the perivascular cells have almost entirely disappeared,<sup>1</sup> but they are, as it were, replaced

<sup>1</sup> This statement is perhaps not correct. There are certain spaces surrounded by epithelial or epithelioid cells to be seen in the upper part of the sub-glandular and in the lower part of the glandular zone; these spaces I have interpreted as parts of the glandular system, but they are perhaps maternal vessels with perivascular cells. The uncertainty as to their character could be probably removed by the examination of the ten days' placenta, which presumably offers the intermediate stages.

by multinucleate cells (compare Fig. 14, Pl. XXVIII., of these cells from an older placenta); their origin appears to be due to the development of clusters of connective tissue cells, which lie scattered about between the blood-vessels; each cluster consists of from three to six cells lying together and connected on the one hand by short processes with one another, and on the other by longer processes with the cells of adjacent clusters. The larger clusters are separated by membranes from one another, and thus every cluster becomes enclosed in a membrane and appears as a multinucleate cell. The development of these cells would doubtless repay more accurate investigation. The multinucleate cells do not yet form a continuous bed under the placenta, but are divided into parts by masses of very loose connective tissue. At the base of the fissure between the two lobes of the placenta the glands have almost entirely disappeared, but we still find a few unresorbed fragments of their degenerated epithelium; these fragments are conspicuous by their very deep staining, both of the hyaline substance and of the nuclei: the neighboring tissues are less colored. The fissure itself is like an inverted J; that is, it is transversely expanded at the base; the floor of the expansion is thrown up into folds and covered by a cylinder epithelium, which I feel some hesitation in designating as the regenerated uterine epithelium, although it resembles the epithelium on the peri-placenta, where the glands are resorbed and the epithelium reconstituted from its degenerated self. On the other hand, as shown in the next section, there is some proof that the foetal ectoderm penetrates, by villous growths, far into the placenta. It seems possible that the fissure is filled by villous excrescence of foetal origin and that the epithelium of the sub-placenta belongs to the villus. This view does not commend itself to me. Neither upon the upper wall of the expansion nor on the sides of the fissure have I recognized any epithelium. The upper part of the fissure is closed by an ingrowth of connective tissue. Hence the lower part is changed into a shut cavity in the centre of the placenta, and into this cavity the folds covered with epithelium project.

So far as I am informed, this curious structure has not been described hitherto, but what appears to be clearly its homologue has been observed by Ercolani, **89**, pp. 290, 291, Tav. IV., Fig. I., O, and specially studied by Creighton, **77b**. Both of these

authors examined late stages when the fissure is completely filled by connective tissue, so that there is no space — a condition found in the rabbit at thirteen days. It will be convenient to designate the structure as the *sub-placenta*. Its occurrence is confined to rodents so far as at present known. Finally, we have to note that at the edge of the placenta, toward the peri-placenta, the sub-glandular layer, which we are now considering, is characterized by the presence of deeply stained fragments of glandular epithelium irregularly scattered through the other tissues and similar in appearance to the remnants of the glands about the sub-placenta. These fragments appear to have been seen by Ercolani, Creighton, Masquelin, Swaen, and others, and variously interpreted, their true nature not being recognized. The disappearance of the glands at the centre and at the periphery of the placenta virtually increases the domain of the sub-glandular layer. The greatest changes have occurred in the glandular layer. Scarcely a trace of the perivascular cells can be found; the space they formerly occupied is taken up by a very loose embryonic tissue; the glands are completely altered; they have lost their special affinity for eosine and cochineal, neither the hyaline substance of which they are composed nor the nuclei they contain being more stained than other tissues (compare Fig. 8); they are irregularly cylindrical in shape, very much contorted, and united with one another at irregular intervals, so as to constitute an actual network: they are very much vacuolated; their deep portions (*fundi*) are somewhat wider than the upper parts; here and there one sees a remnant of the original central lumen. The contorted masses, which I consider glands, are apparently the same as have been seen by Mauthner in the placenta at term, **115**, p. 121. He describes these cords as consisting of the fused epithelium of adjacent foetal villi, and the spaces I have designated as vacuoles he describes as maternal blood-channels; he states explicitly that he has injected them from the maternal vessels, and in other cases found them gorged with maternal blood. These statements are irreconcilable with my own views, detailed in the present article. The uterine epithelium has entirely disappeared both from the top and the sides of the placenta. The top surface is covered by a very thin layer of flat epithelium, Fig. 8, *msth*, which is found, when followed out, to be continuous with the lining of the body cavity of the

embryo; it is therefore mesothelium. Underneath this covering, and above the glands, there is a layer of varying thickness containing some large and a few small blood-vessels with embryonic blood in them, and consisting otherwise only of scattered anastomosing connective tissue cells,<sup>1</sup> which can be followed without the slightest break on the one part until they pass directly into the mesoderm of the superjacent embryo; on the other part, down between the glands, Fig. 8, *mes*; compare, also, later stages, Figs. 10 and 11. Between the glands, also, are blood-vessels containing embryonic blood. On the top surface of the placenta I can find nothing recognizable as even a trace of the foetal ectoderm, which formed a thick and conspicuous covering in the latest previous stage examined (nine days and seventeen hours). At the edge of the top of the placenta, Fig. 8, the relations change: the mesothelium, *msth*, bends up and leaves the placenta, and together with a few subjacent mesodermic cells joins a sheet of cylinder epithelium, *Ecto*, which is shown by its connections to be foetal ectoderm. The ectoderm from the point where the mesothelium, *msth*, bends on to the top of the placenta continues downward, *Ecto*, to clothe the side of the placenta which faces the peri-placenta. Between the placenta and peri-placenta, as shown in Fig. 9, there is a fissure; the ectoderm can be followed to the bottom of this, and from there extends, — not on to the peri-placenta, — but turns abruptly back on to the side of the placenta, up which it stretches a minute distance and thereupon ends abruptly. The disappearance of the ectoderm is discussed in the next section.

The peri-placenta is now characterized by the enormous increase of the perivascular decidual cells and the accompanying expansion of the blood-vessels; by the disappearance of its glands and by the reconstitution, in part, of its superficial epithelium. The peri-placenta appears like the continuation of the outer zone of the placenta, for it directly adjoins it, is of about the same thickness, and is histologically similar. The blood-vessels are wide with hypertrophied endothelium; the perivascular cells are disposed as in the sub-glandular zone of the placenta; that is, in the half towards the uterine muscularis they completely fill the intervascular room, but in the half towards

<sup>1</sup> A layer closely similar to this, and presumably homologous with it, exists in the Guinea pig (Creighton, 77a, p. 558), in the rat (Ercolani), and other rodents.

the interior of the uterus they form a discrete envelope around each vessel, the spaces between the perivascular coats being occupied by simple connective tissue cells. The glands which at nine days, Fig. 4, were so bulky and conspicuous, have almost completely disappeared, being now represented only by remnants of multinucleate hyaline matter scattered superficially, and easily recognized by their distinctive and conspicuous coloration: some of these remnants are still united with the surface. The epithelium is in two forms: on the half of the peri-placental surface towards the placenta it is entirely in the phase of degeneration, while over the other half it is already reconstituted as irregular cylinder epithelium, the cells of which are more or less separated from one another, and somewhat variable in height; this epithelium stops abruptly near the middle of the peri-placenta and is replaced towards the placenta by a hyaline nucleated layer occasionally thickened into a lump, where the nuclei are clustered; the cylinder epithelium is deeply stained by the cochineal; the hyaline epithelium has a marked color from the eosine, and its nuclei are dark with cochineal. The glands are further resorbed under the cylinder epithelium than nearer the placenta.

The ob-placenta is now characterized by the disappearance of its degenerated epithelium, by the fusion of the epithelium of the deep portions of its glands into a new continuous layer, and by the development of peculiar monster cells in its central area facing the placenta. The resorption of the epithelium by vacuolization has already been described in the account of the nine days' uterus, § 3. The epithelium, Fig. 6, *gl*, is everywhere re-formed as a continuous layer; portions, Fig. 6, *h.ep*, of the degenerated layer remain especially near the peri-placenta, but for the most part the new epithelium is entirely uncovered, and in the central region it has grown, so that the glands are already deepened. But the most remarkable feature is the accumulation, opposite the placenta, where the mucosa is much thickened, of the curious bodies, to which I apply the term *monster cells*. They are round or oval masses many times the size of any other histological element of the uterus or embryo, and possess huge nuclei. They are shown in Fig. 17, which represents them at a later stage, when they are further enlarged. I regard these bodies as detached epithelial cells, undergoing degenerative hypertrophy. In

spite of long searching for the phases representing their early history, I have failed to ascertain positively their origin. In the next section the question is recurred to. The monster cells vary in size: the smallest ones lie near the epithelium; the larger ones, for the most part, deeper down and even among the muscular fibres, but a few large cells lie next the surface. The body of the cell is evenly and coarsely granular and resembles the hyaline degenerated protoplasm of the epithelium; its external outline is distinct, well-rounded, and without processes; the nucleus, which often has a slight space around it, as if it had shrunk a little, has a clear regular outline, being apparently provided with a membrane; it is well colored by cochineal, and contains an indistinct network with imbedded granules of various sizes; in the smaller cells the nuclei have one or two granules much larger than the rest, and which may be spoken of as nucleoli; the size of the nucleus increases with that of the cell, and at the same time the granulation becomes coarser.

The description of the placenta at ten and eleven days given by Masquelin and Swaen I have not been able to follow in all respects. Owing to their conclusion that the epithelium of the uterus gives rise to blood, they apply the term *cavités hœmatoblastiques* to apparently all the cavities of the placenta except those of the maternal blood-vessels. I have compared their description very carefully with my own preparations: so far as this enables me to judge, their "cavités hœmatoblastiques" include the foetal blood-vessels, the vacuoles in the degenerated glands, the spaces included within the epithelial U's described in the next section, and which are supposed to be the tips of foetal villi, the multinucleate cells and perhaps also the sub-placenta. Why the multinucleate cells are included among the blood-forming organs the authors do not render clear. Their failure to recognize the variety of constituents in the glandular layer of the placenta must be ascribed to the want of the perfected methods at present at our disposal. With the means now at command there is no difficulty in obtaining preparations which show indisputably that the glands though degenerated persist intact, and do not give rise to blood cavities nor blood corpuscles as Masquelin and Swaen have erroneously believed.

§ 8. **Embryo at eleven to thirteen days.**—As known already, the embryo is completely separated from the yolk sack, and the



allantois has grown forth and attached itself to the placenta. The relations of the extra-embryonic structures have been represented by Bischoff in the diagrams of Pl. XVI. of his classical memoir on the development of the rabbit. These diagrams have since been reproduced again and again, sometimes with modifications as notably by Kölliker in his manual, and by Van Beneden and Julin. Guided by these and by my own preparations I venture to construct a new diagram, Pl. XXIX., which I hope will approximate more nearly to the actual relations of the parts, with which we are now concerned.

In the first place it is to be noted that most of the section is occupied by uterine tissue:—compare Fig. 9, Pl. XXVIII. The largest space is occupied by the placenta, on the surface of which is situated the embryo, lying upon its side. Opposite (above in the figure) the embryo is the ob-placenta, *ob-pl*, with its central area, containing the monster cells, *mo cl*; the inferior wall of the yolk sack is fitted upon, but not attached to, the ob-placental surface. The peri-placenta, *PP*, appears as the continuation of the outer zone, *oz*, of the placenta; it has no glands: its blood-vessels are enlarged, and all the space between them is filled with uninucleate decidual cells. This description of the peri-placental structure applies also to the outer zone, *oz*, of the placenta. A narrow space separates the surface of the peri-placenta from the side of the glandular zone, *gl*, of the placenta: the letters *a* and *b* lie in this space. The placenta consists of three zones: 1°, the upper glandular zone, *gl*, divided by a fissure, *f.*, into two lobes. This fissure is partly filled with an ingrowth of embryonic mesoderm, *mes*; the transversely expanded bottom of the fissure forms the sub-placenta, *sb.pl*; the glandular zone as a whole constitutes a protuberant mass with top and sides clearly distinguishable. Below the sub-placenta is the sub-glandular zone, *s.-glz*, with dilated blood-vessels and multinucleate decidual cells.

The embryo lies upon the surface of the placenta. From its ventral side spring the allantois, *all*, and the stalk of the yolk sack; for the sake of clearness the amnion and pro-amnion are entirely omitted, since they have no direct relation to the uterus.<sup>1</sup> The allantois expands upon the placenta; the yolk

<sup>1</sup> For diagrams of the pro-amnion, etc., see Van Beneden et Julin. Copies of their figures are given in Buck's *Reference Handbook of the Medical Science*, VI., 32.

sack expands over the ob-placenta. The cavity of the allantois, *all*, is of course lined by entoderm; it is, however, quite small, and in my preparations by no means the spacious vesicle commonly represented, for instance, by Kölliker in his *Grundriss* (2te Aufl., Fig. 88), or by Balfour (*Comparative Embryology*, II., Fig. 148). The allantoic mesoderm, *mes*, on the other hand, spreads out, over the surface of the placenta, down its sides, down into the fissure, *f*, between the two lobes, and penetrates between the glands, *gl*, of the placenta; wherever it goes, the mesoderm carries foetal blood-vessels. The free, *i.e.*, inner or cœlomatic, surface of the mesoderm bears the mesothelium, *msth*; as the extra-embryonic cœlom does not extend beyond the top of the placenta, there is, of course, no mesothelium upon the sides of the glandular zone (between *a* and *b*), but at the edge of the top of the placenta the mesothelium is reflected back, and after a short course joins the wall of the yolk sack near the *sinus terminalis*, *v.t.*

The yolk sack, as has been long known, consists of two parts:<sup>1</sup> 1st, the *area vasculosa* bounded approximately by the *sinus terminalis*, *vt*; within this area the entoderm is united with the mesoderm, which passes only a very short distance further out; 2d, the remaining portion without mesoderm, excepting always the pro-amnion, which is included in the *area vasculosa*; over this second region the entoderm, *en*, rests directly upon the outer germ-layer, *ecto*.

If we follow the ectoderm around, we find that it leaves the yolk sack, just before the *sinus terminalis*, *vt*, is reached, and being joined by the mesodermic lining of the cœlom passes down *b* on to the lateral surface between the peri-placenta, *P*, and the glandular placenta, *gl*, where, as already described, it bends inwards, and turning back runs a minute distance upwards; according to my hypothesis it continued earlier over the surface of the placenta, as indicated by the broad dotted line, *d*. The layer of embryonic epithelium upon the side wall of the rodent placenta has been seen by other observers, among whom may be mentioned Ercolani and Creighton; the latter, 77b, 560, directs especial attention to it, in the Guinea pig, but refers it to the entoderm. I consider it probable that it is really ectodermal in the Guinea pig, as in the rabbit. Underneath the

<sup>1</sup> Leaving the pro-amnion out of consideration.

ectoderm, *b*, to be seen at eleven to thirteen days at the sides on the placenta, is a layer of mesoderm without any coelom. Now, if my suppositions are correct, then the ectoderm forms at first an independent fold, *ba*, beyond the terminal vein, *vt*; the mesoderm, but not the mesothelium, extends into this fold, which covers the sides of the placenta. The disappearance of the foetal ectoderm from the surface of the placenta, and the penetration of the foetal blood-vessels between the glands, are changes which take place during the eleventh day. How those changes occur, observations on the development at that age must decide. Meanwhile let us make shift with two hypotheses. The first is: The whole of the ectoderm attached to the placenta degenerates and is resorbed. Since the uterine epithelium, as observation indicates, has likewise disappeared from the placenta, the mesoderm, *mes*, of the allantois, *all*, is brought into direct and free contact with the connective tissue and degenerated glands of the placenta, and is thus enabled to carry by its own ingrowth the foetal blood-vessels into the very substance of the placenta. The second hypothesis is that the ectoderm and mesoderm have produced villi, which have grown into the placenta. In favor of this latter hypothesis there is certain evidence which I have not yet alluded to. In the deep portions of the glandular layer of the placentas of both eleven and thirteen one finds narrow loops of epithelium like a tuning-fork in shape; the open ends of the U-loops are towards the top of the placenta; the epithelium composing them is a cylinder epithelium, which gradually thins out towards the upper end of the legs of the U; it differs altogether in appearance from the degenerate gland epithelium, the interiors of the U's contain vessels with foetal blood; so far, then, these structures might be longitudinal sections of the ends of foetal villi. Towards the surface of the placenta the epithelium of the loops thins out, and I have not been able to follow them. If we have to do with villi, we must assume that the ectoderm has become exceedingly thin over their basal portions, but is preserved as a thicker layer over their tips, and my failure to trace the villi would be attributable to the imperfection of my preparations and observations. Balancing the *pros* and *cons* leads me to favor the second hypothesis. Let me add that the mesoderm of the embryo is continuous without a break with the interglandular connective tissue;

this statement is correct beyond any doubt, for I have several sections, in each of which the direct passage is observable under the microscope without even displacing the slide. By hypothesis this mesoderm is, however, really separated by a very thin covering of foetal ectoderm from the uterine tissue, and the whole constitutes a system of villi which have grown down like roots into the placental soil.

That there is no communication between the foetal and maternal circulations must be deduced from the fact that the two bloods are never mingled in one vessel, although found side by side in adjacent vessels. The separation of the foetal and maternal blood has already been insisted upon. The full elucidation of the double placental circulation must be left for injections to bring.

In brief: The rabbit embryo is attached to the placenta by the ectoderm, which disappears from the surface of the placenta during the eleventh day; the vascular connective tissue of the allantois grows probably by forming true villi into the placenta, and so comes close to the maternal circulation.

In other rodents the placenta contains foetal vessels; its surface is covered after a certain stage by a thin epithelium like the mesothelial layer of the rabbit, and by a layer of vascular connective tissue. Hence it seems probable that the structure in the rabbit is typical of the class — compare § 12.

§ 9. **Uterus at thirteen days and three hours.** — The placenta and embryo are considerably bigger than at eleven days, but the structure of the parts is comparatively little changed.

A complete section is drawn in Fig. 9. The longitudinal muscles, *l.m.*, and the circular muscles *c.m.*, form the external covering. They differ in microscopical appearance from the muscles of the resting uterus, but I have not investigated the change in them.

The placenta is very bulky. Its two lobes have begun to form separate protuberances, so that the top of the placenta is no longer a nearly plane surface. The placental surface is covered by the mesothelium, which is a little thicker than in the previous stage, the cells having a greater vertical diameter. Between the mesothelium and the glandular layer, *gl*, is the vascular mesoderm, several of the large vessels of which are shown in Fig. 9. The central fissure, *f*, of the placenta is very

deep; it is completely filled with the ingrowth of mesoderm and its accompanying large vessels. At the bottom of the fissure next the outer placental zone, *o.z.*, is situated the sub-placenta, *sb.pl.* The section drawn in Fig. 9 does not show the connection between the fissure and sub-placenta, which appears in sections 208-214 of the same series. The thickness of the mesodermic covering of the placenta has increased very considerably, and the larger vessels are now provided with well-marked muscular as well as endothelial walls. Many of the foetal vessels run in spaces which stretch down nearly vertically from the placental surface; in some cases the vascular columns can be followed until they enter a cap of epithelium which forms a sort of U. These relations suggest the presence of a series of foetal villi covered in part by a very thin epithelium, and covered at their tips by a relatively thick epithelium. This interpretation has been discussed in the previous section. Beside the normal-looking epithelium, we find the degenerated glands not much changed from eleven days. The sub-glandular zone, *sgl.z.*, shows further enlargement of the blood-vessels, so that they are now larger than those of the outer zone, *o.z.*, thus reversing the earlier relative proportions; the multinucleate cells have increased in number and size, and contain more nuclei than at eleven days; they occupy all, or nearly all, the room between the vessels. Towards the outer zone the vessels are surrounded by the uninucleate perivascular cells, but the intervening tissue consists of multinucleate cells, so that there is a boundary region which cannot be assigned strictly either to the subglandular or to the outer zone. The outer zone, *o.z.*, is solidly packed with perivascular cells.

The sub-placenta, *sb.pl.*, lies still deeper than before, being now close to the outer zone. Its epithelium is undergoing hyaline degeneration, and accordingly is irregularly thickened, and its nuclei are multiplied: the substance of the layer stains deeply with eosine.

The peri-placenta, *P.*, differs from that at eleven days, principally in having the perivascular cells as a solid packing throughout the whole of its extent, except just where it adjoins the glandular layer of the placenta. As at eleven days, its covering epithelium is reconstituted on the part towards the sub-placenta, and is in the phase of degeneration towards the placenta.

The ob-placenta, *ob.pl.*, shows everywhere a marked growth of its glands; as illustrated by Fig. 10, the glands are follicular; their cavities wide. The glands are not branched or pouched, as the appearances in the sections suggest; they are broad tubes closely packed, and are necessarily cut obliquely in most cases. The rather ragged-looking epithelium is composed of long cylinder cells (Fig. 10), with the nuclei at various heights, and the protoplasm a good deal colored by the cochineal. The connective tissue of the mucosa has also grown, and forms both thin inter-glandular dissepiments and a thickened sub-glandular stratum. In the centre of the ob-placenta the mucosa is still further thickened to make room for the monster cells, which lie for the most part below the glands, but are found also between the glands and in the superficial portion of the muscularis. At one point the ob-placenta is interrupted by a protuberant mass, *x*, resembling the peri-placenta in structure; it consists of crowded perivascular cells with dilated blood-vessels, and is covered by epithelium. As I have seen nothing analogous to this mass in any other specimen of any age, it must be regarded as a singular sporadic variation from the normal processes of development.

The origin of the monster cells I am inclined to seek in the uterine epithelium, as stated in § 7. The appearance of their cell bodies, and of their nuclei at once suggest this origin on account of the similarity with the appearance of the degenerated epithelium elsewhere. We find, also, the smallest monster cells near the epithelium. In Fig. 11 portions of the epithelium of the peri-placenta are represented. The cells are all multinucleate, as seen both in vertical section, *A*, and surface views, *B*; occasionally, but very rarely, there is a cell with the nuclei gathered together in a central mass, with an indistinct line enclosing the bunch, Fig. 11, *c*. These cells are larger than the rest, and their protoplasm is somewhat degenerated. If such a cell were to detach itself, and hypertrophy and the bunch of nuclei to break down, it would resemble a monster cell. Yet I can find no evidence that such a metamorphosis actually takes place in the ob-placenta. In the ob-placenta itself there appear a few epithelial cells with a single nucleus which are slightly enlarged, and are possibly the initial stages of monster cells, but between them and the youngest monster cells observed I have failed to

discover any intermediate stages. The difficulty of finding the first stages of the monster cells indicates that their development must be extremely rapid, almost sudden.

§ 10. **Uterus and embryo at fifteen days and four hours.** — The swelling of the uterus has considerably increased; the placenta is larger; the cavity containing the embryo is very much larger; the peri-placenta has grown but little. We notice now that of the six folds of the uterus, the two placental have expanded both in width and thickness to a far greater extent than the remaining four folds, except that the lateral expansion of the two ob-placental folds, by attenuation of their walls, has enabled the ob-placenta to occupy an extent of the circumference of the uterus which is about equal to that taken up by the placenta proper; only about one-sixth of the whole circumference is allotted to the peri-placenta. With the naked eye one can see that the fissure of the placenta has opened so that the surfaces of the two lobes of the placenta now face each other like the sides of a V; the surface of each lobe, though somewhat irregular, is as a whole arched. The glandular zone is perhaps slightly thicker than at thirteen days, but the diameter of the sub-glandular zone is markedly lessened, owing apparently to the opening of the interlobal fissure and the consequent flattening of the surfaces of the lobes. With a hand-lens one easily recognizes that the blood-vessels of the vascular zone of the placenta are of much greater diameter than at thirteen days, while the dissepiments between the vessels are not only relatively but absolutely thinner than before: this observation does not necessarily involve the conclusion that there has been an actual loss of tissue, for the placenta as a whole has increase in bulk. Let us turn now to the microscopical examination.

The placenta differs but little, except in the respects above mentioned, from the stage last described. The mesodermic covering of the placenta is well marked, Fig. 12, *mes*, and the foetal mesothelium, *msth*, is perfectly distinct; it leaves the placenta at its edge to curl over on to the yolk sack, just as at an earlier stage, Fig. 8, *msth*. The side of the lobe next the peri-placenta is clothed by ectoderm essentially as described at eleven days and partially shown in Fig. 8, *ecto*; but the ectoderm is now more irregular than at earlier periods and is thrown into small folds near the point where it is reflected back on the pla-

centa; similar appearances are clearly indicated in Ercolani's memoir, **89**, Tav. IV, Fig. 1, *i, i*, for the Guinea pig. It is quite possible that the folds are more developed in the rabbit later. The placental glands are very much contorted, Fig. 12, *gl, gl*; very coarsely granular, with numerous irregular vacuoles and with the nuclei lying for the most part against or near the outer surface of the gland, Fig. 13, *gl*: the nuclei no longer stain deeply as they do during the first stage of the gland degeneration, Fig. 7. In the upper part of the placenta the glands are much narrower and more widely separated than in the deep part of the layer, as can be seen in Fig. 12, which takes in about half of the glandular layer from the surface down; towards the surface the glands often form wide loops, Fig. 12, and join one another, making a network with closed meshes. As regards the supposed foetal villi, I find the columns of the foetal mesoderm running down more distinctly than at thirteen days, but as before, the only epithelium which I clearly distinguished, is that in the deepest part of the glandular layer disposed as if covering the tips of the villi. The blood-vessels are very numerous, and some of those above the glands in the foetal mesoderm are very large, Fig. 12, *v*. It will be remembered that these vessels belong to the foetal system and that the plexus of vessels, which is so conspicuous upon the surface of a freshly excised placenta, pertains therefore to the embryo. At certain points there rise thin membranes from the surface of the placenta, which carry good-sized vessels: whether these are accidental or constant, I am unable to say. Examined with a still higher power, Fig. 12, the glandular layer shows the peculiarities of its structure still more clearly; the mesothelium, *msth*, upon the surface, though composed of flat cells, has considerable thickness; the mesodermic cells, *mes*, are for the most part spindle-shaped and their processes anastomose; the foetal blood-vessels, *v, v*, come close against the glands, *gl*; if, therefore, there is a layer of foetal ectoderm separating the foetal mesoderm from the uterine tissues, it must be very inconspicuous from extreme thinness.

As to the relations of the sub-placenta, my preparations are unsatisfactory.

The sub-glandular layer shows the vascular endothelium advanced in degeneration, the cells projecting far from the surface.



Many parts of the vessels are filled with coagulum, suggesting thrombi formed during life, as has been asserted to occur normally in the human placenta. For the most part, the vessels contain normal blood, save that there is an excess of leucocytes; in some vessels, however, there are large clear refringent bodies which look like vesicles. What these bodies are I am unable to say—possibly they come from breaking down of the endothelium. The multinucleate cells, Fig. 14, are large and very much crowded; they contain each a dozen nuclei, more or less. I have nothing of importance to add to the previous descriptions.

In the outer zone we notice at once that the expansion of the blood-vessels is far less active near the muscularis than further in; indeed, we might subdivide the zone into an outer compact and an inner cavernous layer. The vascular epithelium is far degenerated, Fig. 16; A is a surface view; B and C vertical sections; each cell forms a more or less independent projection; the cells vary extremely in size; the nuclei are either single or multiple; in the former case they may be small and comparatively regular, or large and very irregular in shape; in the latter case they are of unequal sizes. The perivascular cells are innumerable; their appearance is indicated by Fig. 15; but where the blood-vessels are wider, or, in other words, towards the glandular zone, they exhibit signs of breaking down; the signs in question are indistinctness of outline, granular appearance of the protoplasm, and the difficulty of staining the nuclei. As the changes are slight, they are perhaps accidental. It must be left for future examination of later stages to show whether they do break down or not. I also think that there is a tendency for the multinucleate cells to invade the territory of their uninucleate neighbors.

The peri-placenta agrees with the outer zone of the placenta in its parenchymal structure, except as to two points: 1°, it is now invaded to a slight extent by the multinucleate cells, at the spot nearest the placental glands; I have no reason to suppose that these cells actually migrate into the peri-placenta, but presume that they arise *in situ*; 2°, near the ob-placenta there are in some parts young monster cells lying close under the epithelium; the evidence is better here than anywhere else I have observed that the monster cells arise from the epithelium.

The ob-placenta now has monster cells throughout almost its

entire extent, but the greatest accumulation is where they first are developed, directly opposite the placenta. In this region (Fig. 17) they occupy not only the connective tissue of the mucosa, *a*, *b*, but also the territory of the circular muscular coat, where they lie, *c*, between the bundles, *musc*, of muscular fibres, which they have forced apart to make room for themselves. The smallest monster cells, *a*, are found nearest the lining epithelium, *ep*; those at the base of the mucosa, *b*, are bigger, but the biggest of all are those which lie in the outer part of the muscularis, *c*; if, therefore, the cells arise from the epithelium and migrate outwards, they must grow while they move. My preparations show in the nuclei of the monster cells certain large, deeply stained fragments which are perhaps chromatine, Fig. 18. Owing to the stretching of the uterine walls, the regenerated glands of the ob-placenta are no longer follicular as at thirteen days (Fig. 10), but are again stretched out, so as to approximate a second time to the form of shallow, open cups, which they had at eleven days (Fig. 6); but where the monster cells have accumulated most (Fig. 17), the only distinct trace of the glands is the irregularity of the free surface covered by epithelium, *ep*.

The embryo and its appendages do not show much alteration in the parts concerning us in the present article. We may, however, note especially two changes in the outer germ layer. 1°. On the strip of ectoderm between the *vena terminalis* of the yolk sack and the points where the ectoderm joins the placenta, there are a number of thickenings, which form small papillæ upon the outer surface of the layer. These outgrowths are solid ectoderm, and like the buds of the villi of the human chorion contain no mesoderm. Whether these structures do become actual villi in later stages, I am unable to say. 2°. Over the yolk sack the ectoderm has become a cylinder epithelium, of which the outer surface is irregular, each cell projecting a little more or less than its neighbors. A similar modification occurs in the opossum according to H. F. Osborn, **61 A**, 378-379, Pl. XVII., Fig. 4, and Selenka (*Entwickelungsges. d. Thiere*, Taf. XXVIII., Fig. 5). It is probable that the ectoderm assumes this modification in other mammals, where it remains attached to the yolk sack owing to failure to form a complete chorion.

§ 11. **Summary.**<sup>1</sup>— In the resting uterus of the rabbit there are six longitudinal folds. The ovum attaches itself on or between the two folds nearest the mesentery, and the placenta is there developed; the two adjacent lateral folds form a cushion (the peri-placenta) about the placenta, but the two folds opposite the mesentery are flattened out by the stretching of the walls to form the swelling to contain the embryo; they constitute the ob-placenta. In the region of the placenta the mucosa undergoes an enormous hypertrophy: there is likewise an enlargement, but much slighter, of the peri-placenta.

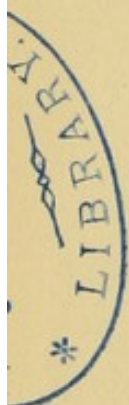
The entire epithelium lining the uterine swelling degenerates; its nuclei proliferate, and its protoplasm hypertrophies, becoming at the same time hyaline and granular. The degeneration affects the glands also. The degenerated epithelium becomes vacuolated and in large part resorbed. The process goes on with distinctive features in each of the three primary divisions of the swellings.

The connective tissue increases by hyperplasia in the peri-placenta and to a still greater degree in the placenta, and is transformed for the most part into uninucleate perivascular decidual cells, but also in part, — namely, immediately below the glandular layer of the placenta, — into large multinucleate cells. In the placenta, and to a less extent in the peri-placenta, there is a new formation of blood-vessels, which subsequently enlarge to great size, although their only walls are an endothelium which undergoes rapid hypertrophic degeneration.

In the placental region the uterine epithelium degenerates and disappears, but the glands are preserved as irregular anastomosing rows of coarse granular matter, with numerous vacuoles and scattered nuclei, but without central lumina. Below the glands is a zone containing wide vessels and large multinucleate cells. The outer layer has wide blood-vessels, with numerous uninucleate decidual cells, which arise from the connective tissue cells and arrange themselves in successive coats around the blood-vessels until they occupy the entire room between the vessels.

The embryo is attached at first to the surface of the placenta

<sup>1</sup> It will be remembered that the observations cover the period of from six to fifteen days *only*, and do not include the eleventh day, when several important developments occur.



only by the ectoderm, to which the mesoderm soon joins itself. As soon as the cœlomatic fissure appears, we can speak of a foetal chorion adhering to the placenta. When the allantois grows out, it forms the stalk of connection between the embryo and the placental chorion. After the development of the chorion, the free surface of the placenta is, of course, covered by mesothelium (the epithelium of the cœlom). Outgrowths of the chorion penetrate the glandular layer of the placenta; whether these outgrowths are in the form of villi in the sense that they preserve a covering of foetal ectoderm was not ascertained, although the tips of the outgrowths appear to have such a covering, and there is no mingling of the foetal with the maternal circulation. The cœlom of the embryo does not extend to the edge of the placenta next the peri-placenta, but the mesoderm does, and is covered by ectoderm.

In the peri-placenta, the glands degenerate and disappear completely, but the covering epithelium is reconstituted except on the part near the placenta. The blood-vessels and connective tissue change as in the outer zone of the placenta, though later. At the fifteenth day a few young monster cells were found near the surface.

In the ob-placenta the degeneration and resorption affect only the surface epithelium and the upper part of the glands; the deep portions remain as a series of shallow cups, having been stretched transversely by the expansion of the ob-placenta; the epithelium of the cups unites into a new continuous layer; the glands grow up into follicles and are again stretched out by the expansion of the walls. Meanwhile there appear monster cells, which probably arise by the hypertrophy and migration of single cells of the epithelium; they are characterized by the granular hyaline appearance of their bodies, by the coarse granulation and large scattered fragments of chromatine of their nuclei, and by their hugeness. The monster cells continue to enlarge and subsequently invade the whole thickness of the annular muscularis. They appear first and are always most numerous directly opposite the placenta, but they are ultimately present throughout the ob-placenta.

The relations of the embryo having been outlined in § 8, with the aid of Plate XXIX., it is not necessary to recapitulate them again.

§ 12. **Comparison with other rodents.**—The history of the rabbit's placenta elucidates also that of the Guinea pig, of which we possess descriptions by Bischoff, Ercolani, **89**, Creighton, **77a**, **77b**, Tafani, **134**, and others. These authors being unaware of the nature of the metamorphoses of the uterine glands, and not knowing the disappearance of the foetal ectoderm over the placenta, but, on the contrary, seeking for foetal placental villi, lacked the necessary basis for a correct interpretation. Ercolani was further misled by his erroneous belief that the placental tissues of the mother arise as new formations, not as metamorphosed constituents of the uterine mucosa, but coming after the assumed but non-occurrent complete destruction of the mucosa. Tafani's work betrays gross inaccuracy, for he based his figures and descriptions upon schematic notions, based in their turn upon very superficial, and often entirely false, observations. To justify a judgment so severely unfavorable, it is necessary only to direct examination to some of Tafani's plates. His drawings of the human placenta, for instance, *l.c.* Tav. VII., leave a great deal to be desired; in Fig. 1 the sections of the villi are altogether too large and too few; the separate triangle of tissue at the edge of the placenta does not exist; the decidua is represented without any compact layer, and its gland cavities are made into blood-vessels. The section of the rabbit's placenta (Fig. 2, Tav. IV.) is even more open to criticism, since it is impossible to determine the foundation of observation. Ercolani, on the other hand, was an observer of considerable ability, and his numerous memoirs on the placenta are valuable, although his hypothesis of *neoformazione* led him to adopt an unfortunate terminology which makes it difficult to follow him. Creighton observed with more impartial objectivity. That Bischoff was a first-class observer every one knows; he never leaves any confusion between what he saw and what he inferred; for us he has the disadvantage of having written before the developments of recent histology. On the whole, we probably do best to turn to Ercolani, who figures **89**, Tav. IV., Fig. I., a section of a placenta of a Guinea pig near full term. Let us compare it with the rabbit's placenta.

It is discoidal, pedunculate, and bilobed. The upper surface is covered by a thin epithelium beneath which is a layer of vascular connective tissue, *Z*, extending over the sides of the pla-

centa, *g, f, f*, and down between the lobes, *q*: the epithelium therefore corresponds entirely with the placental mesothelium of the rabbit. The upper portion of the placenta, *p*, corresponds to the meshwork of degenerated glands in the rabbit's placenta. The layer of epithelium, *i, i, m*, covering the side of the placenta, corresponds to the foetal ectoderm in a similar position in the rabbit; at an earlier stage it resembles very closely in appearance what I find in the rabbit (Creighton, **77a**, p. 560, Pl. XIX., Fig. *b, c, c, c*). Deep down under the space between the lobes of the placenta comes the sub-placenta, Ercolani's cotyledonary organ, *O*, which was compared above with the sub-placenta of the rabbit; the thick pedicle of the placenta, *e, n, n*, corresponds to the sub-glandular layers of multinucleate decidual cells, which has encroached upon and apparently replaced the outer zone of uninucleate decidual cells, which is present earlier, as it is in the rabbit. At the side of the placenta is the peri-placental thickening, *g.d*, and springing from it the so-called reflexa, *c*, which is probably only the peri-placenta hypertrophied. The reflexa is entirely absent in the rabbit. In regard to what I suppose to be the glands, *P*, neither the descriptions nor the figures of Ercolani suffice to indicate their character.

The interpretation offered differs in nearly every respect from Ercolani's own; and yet though I have no preparations of the Guinea pig's placenta, and am acquainted with the organ only through the publications of others, I think the homologies drawn may be accepted with considerable security; but let me add that I am well aware that their actual justification can come only from the specimens.

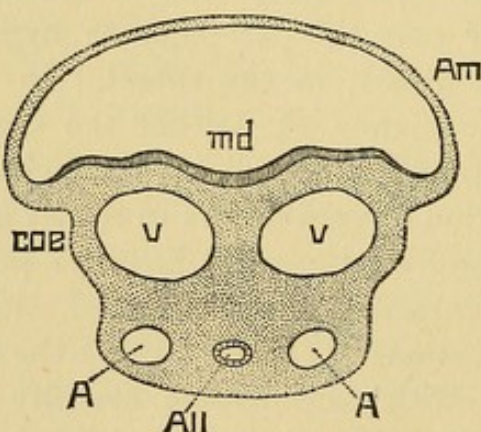
Sections of the rat's placenta near full term show that the structure in that species is strictly comparable to what exists in the rabbit. The surface is covered by a thin epithelium overlaying a vascular connective tissue layer; the vacuolated tubular glands, very much degenerated, occupy the greater part of the placenta, leaving only a thin vascular zone from which the outer zone is lost, and which is therefore occupied solely by the much altered sub-glandular zone of multinucleate cells. There are many differences in details of structure from the rabbit, but the fundamental likeness is self-evident.

As the similarity of the placenta of various rodents has been noted by previous authors, it is probable that the type of placental organization is the same throughout the class.

## II. MAN.

The following observations are of a fragmentary character, but may serve to round out our information in certain respects. Some of the facts have already been recorded in the series of numerous embryological articles contributed to Dr. Buck's *Reference Handbook of the Medical Sciences*; but as that work is for consultation rather than the publication of original observations, it will hardly seem a mistaken repetition if I include here some things already published there.

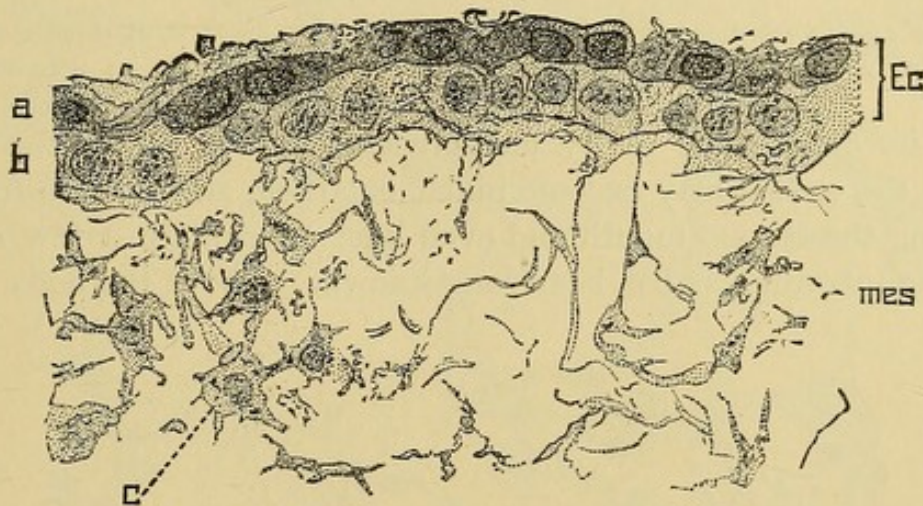
§ 13. **Allantois and umbilical cord.**—Prof. W. His has shown that the entodermal cavity of the allantois is the terminal stretch of the entodermal canal; the posterior end of the body is prolonged into a mass to which he gives the name of "Bauchstiel" (*Anatomie menschlicher Embryonen*, III., 222–226), and which develops in the same general manner as the



*Cut 2.*—Diagrammatic section of the Bauchstiel of a human embryo, modified from W. His. *Am*, amnion; *md*, medullary groove; *v, v*, veins; *A, A*, umbilical arteries; *All*, allantois; *coe*, coelom.

body proper, having a rudimentary medullary groove, a somatopleure and splanchnopleure, *Cut 2*. It is morphologically the hind portion of the body. After its closure and separation from the amnion it appears as the umbilical cord. Its development requires that the umbilical cord should be covered, not by the amnion, as it is almost universally stated, but by an extension of the foetal epidermis. Histological examination shows that this is the case. The amnion is characterized by the ectoderm remaining a single layer of cuboidal or low cylinder cells, and by the matrix of mesoderm being distinct, owing to its high refran-

gibility. The foetal skin is characterized by the ectoderm becoming many layered, while the cutis remains for a long time undifferentiated from the mesoderm below, and the matrix is of low refrangibility. In comparing the ectoderm of the umbilical cord with the skin, therefore, we do not expect to find any differentiated cutis. The epithelium of the cord is at first, of course, single layered, the condition which is permanent over the amnion. In the cord of a three-months embryo, Cut 3, I find the two-layer stage. The outer layer is granular, and in some parts each cell protrudes like a dome. Dome cells also appear on the young epidermis, and as I learn from Dr. J. T. Bowen, who has

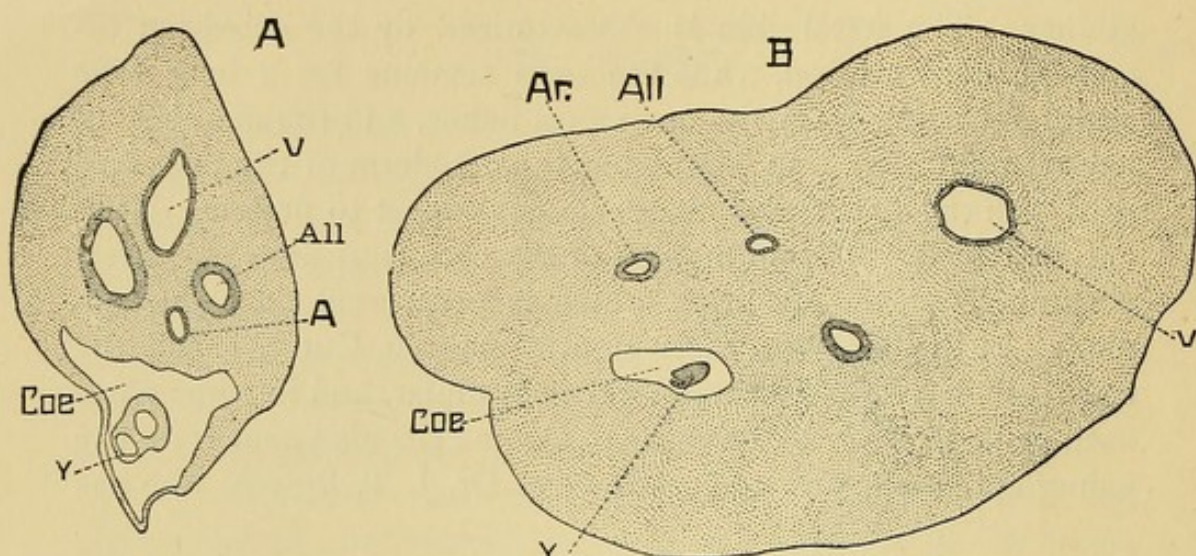


Cut 3. — Epithelial covering of the umbilical cord of an embryo of three months. X 545 diams.

been investigating the subject in my laboratory, are probably the precursors of the epitrichium. The cells of the inner layer are larger and clearer than those outside. By the fifth month the epithelium is distinctly stratified, and the superficial layers consist of flattened cells similar to those of the horny layer of the skin at an early stage. The ectoderm of the cord agrees therefore entirely with that of the embryo proper in its general development, but the differentiation proceeds more slowly, so that at any given age the ectoderm of the cord is at a less advanced stage than that of the embryo.

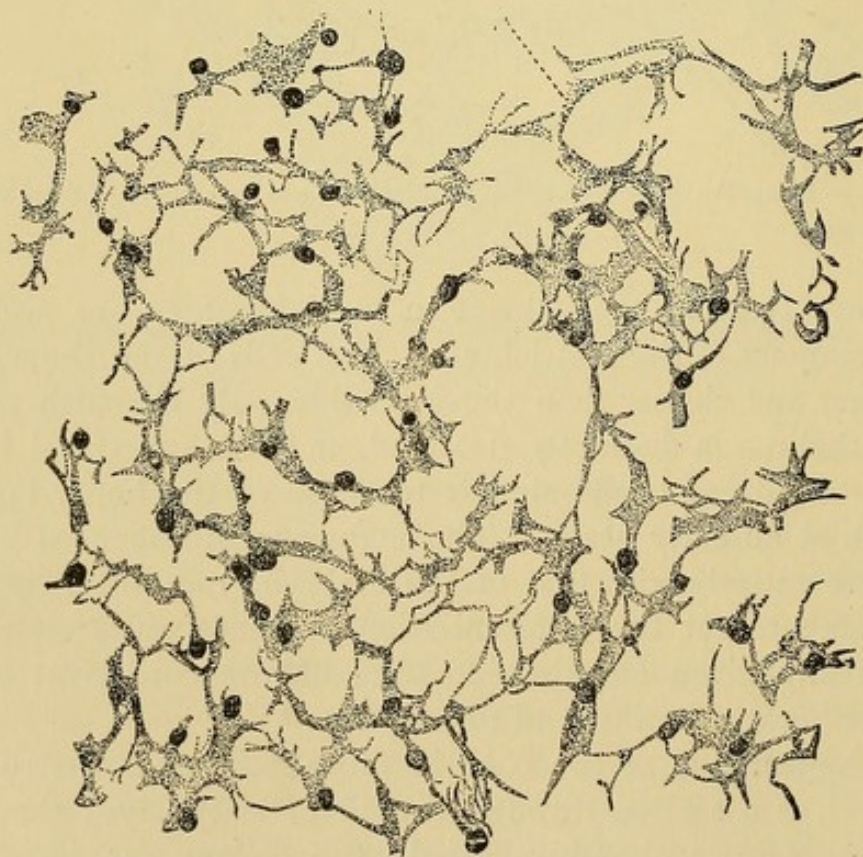
The appearance of the cord in cross-sections is instructive. Cut 4, *A*, is a section through a cord of sixty days; the right umbilical vein is already aborted; the coelom, *coe*, is a large cavity, and contains the yolk stalk, *Y.S*, with its two vessels,





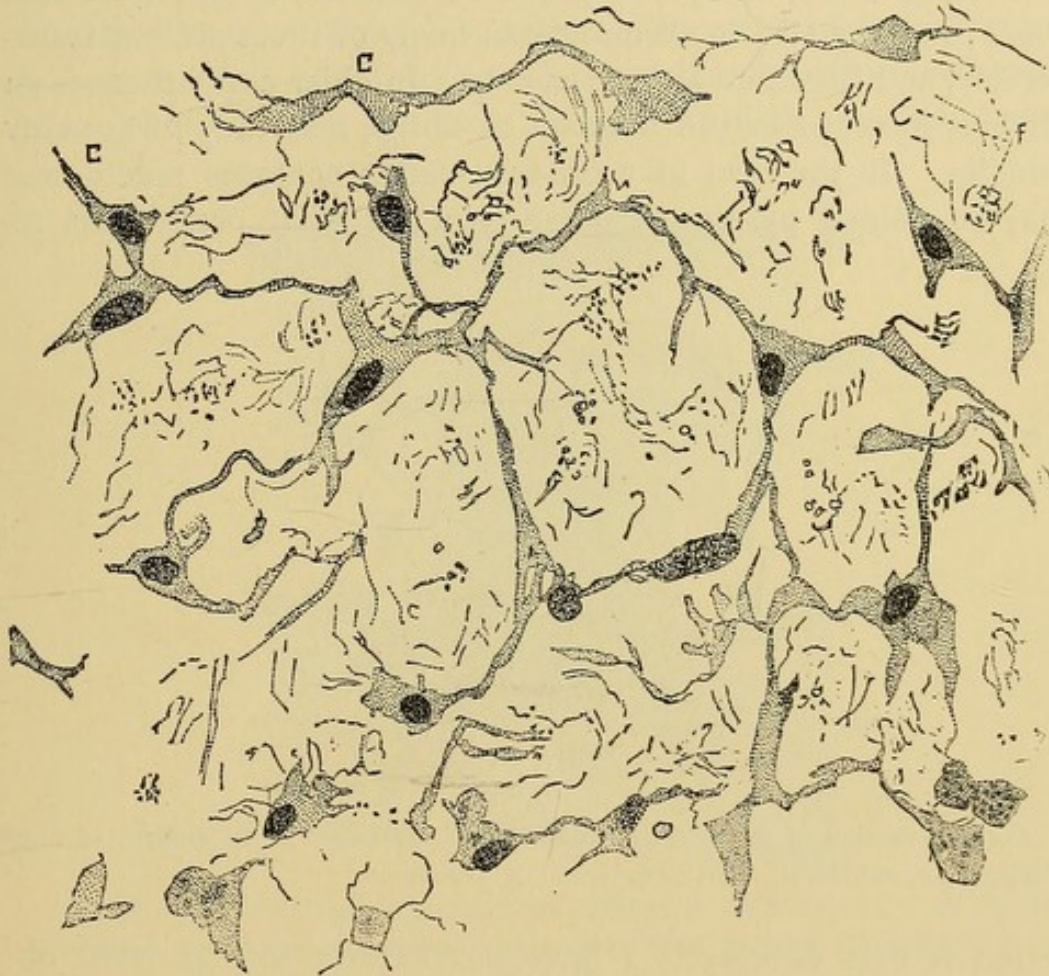
*Cut 4.*—Two sections of umbilical cord. A, at sixty days; B, at three months; V, vein; Ar, artery; All, allantois cavity; Coe, coelom; Y, yolk sack;  $\times 22$  diams.

and its entodermic cavity entirely obliterated. Near the embryo the coelom may become much enlarged, and is often found during the second month and even later to contain a few coils of the intestine, as has been long known. Above the body cav-



*Cut 5.*—Connective tissue of the umbilical cord of an embryo of 21<sup>mm</sup>;  $\times 540$  diams., stained with alum-cochineal, and eosine.

ity is the duct of the allantois, *All*, lined by entodermal epithelium; and in this region are situated the two arteries and single vein; the section is bounded by ectoderm.<sup>1</sup> The further development of the cord depends upon three factors: 1°, the growth of the connective tissue and blood-vessels; 2°, the abortion of the cœlom, yolk stalk, and allantoic duct in the order named; 3°, differentiation of the connective tissue and of the ectoderm.

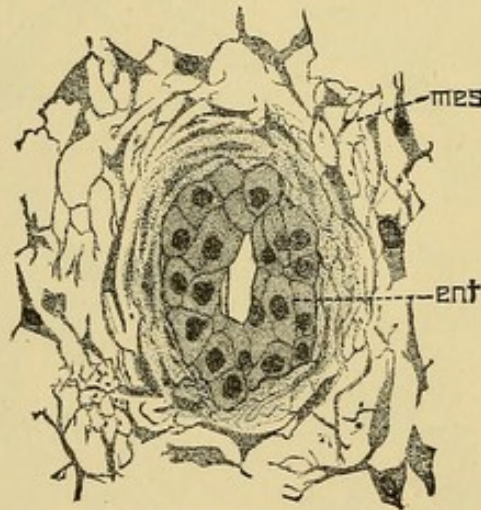


*Cut 6.* — Connective tissue of the umbilical cord of a human embryo of about three months,  $\times 511$  diams. Stained with alum-cochineal, and eosine.

The growth and differentiation of the mesoderm proceeds rapidly, encroaching upon the cœlom, which is obliterated (early in the fourth month). At first the connective tissue, *Cut 5*, is composed merely of numerous cells embedded in a clear substance; the cells form a complex network, of which the filaments and meshes are extremely variable in size; the nuclei are oval, granular, and do not have always accumulations of protoplasm about

<sup>1</sup> The ectoderm is often wanting, owing to its frequent destruction *post mortem*.

them, forming main cell bodies. I notice, also, a few cells which I suppose to be leucocytes, but see no other structures. By the end of the third month the cells have assumed nearly their definite form; the protoplasm has increased in amount, and forms a large cell body around each nucleus, Cut 6. The network has become simpler and coarser, the meshes bigger, and the filaments fewer and thicker; in the matrix are numerous connective tissue fibrils, not yet disposed in bundles, except here and there; as they curl in all directions many of them are cut transversely, and therefore appear as dots. In older cords there is an obvious increase in the number of fibrils, and they form many bundles. In the cord at term the matrix contains mucin, and may be stained by alum hæmatoxylin; at what period this re-



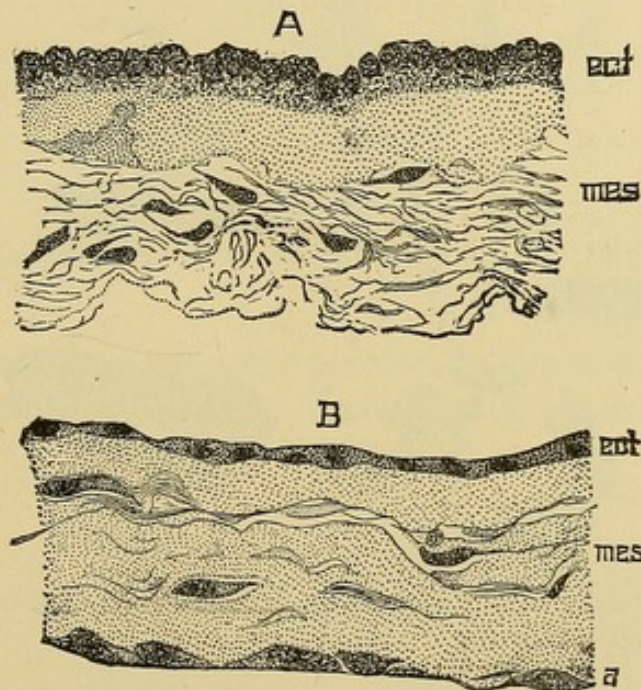
Cut 7.— Section of the allantois from the umbilical cord of an embryo of three months; *ent*, entoderm; *mes*, mesoderm.  $\times 340$  diams.

action is first developed I have not ascertained. I have observed nothing to indicate the presence of special lymph channels in the cord at any period, but I have not investigated the point. Tait's lymph channels are merely the intercellular spaces.

The tube of allantoic entoderm increases very little in diameter after the second month; compare A and B, Cut 4. It is very persistent, appearing usually even in the cord at full term, at least in the proximal end, according to Kölliker (*Entwicklungs-ges.* 2te Aufl., p. 34). After the second month it is a small group of epithelioid cells, with distinct walls, irregularly granular contents, and round nuclei; around the cells, *ent*, which may or may not show a remnant of the central cavity, there is a

slight condensation, *mes*, of the connective tissue to form, as it were, an envelope. This structure has been regarded by Ahlfeld and others as the persistent yolk sack. I think the correct interpretation was first suggested by Kölliker.

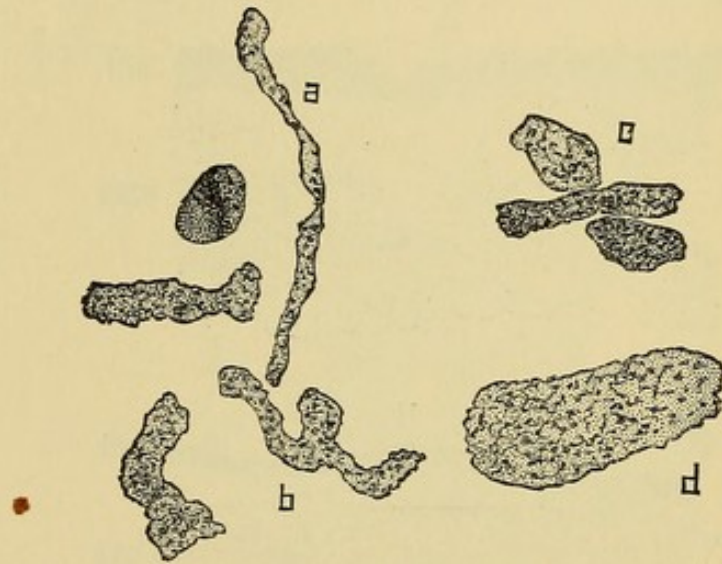
§ 14. **Amnion.**—The tissues of the amnion do not progress beyond an early embryonic stage; the ectoderm remaining at the one-layered stage, the mesoderm preserving much of the primitive matrix. Emery (*Arch. Ital. Biol.*, III., 37) has directed attention to the primitive homogeneous matrix of the vertebrate mesoderm, and especially to the separate sub-epidermal layer of the embryo, which contains no cells at first. In the human



Cut 8.—Two sections of the placental amnion: A, from an embryo of the eighth month; B, at term; *ect*, ectoderm; *mes*, mesoderm; *a*, layer of mesodermic cells.  $\times 340$ .

amnion there is a non-cellular layer under the epithelium, as is well shown in Cut 8, A and B. Sometimes this layer is invaded to a certain extent by connective tissue cells, B; in other cases the portion of the matrix towards the chorion acquires a fibrillar character, A, as if partially resorbed, but in no case have I seen the matrix entirely altered from its primitive character. The cells of the mesoderm lie in lacunæ; they are flattened in the plane parallel to the surface, and hence in vertical sections, Cut 8, appear more or less fusiform. They present no special features, so far as I have observed, to distinguish them

from other embryonic connective tissue cells. Their bodies have little affinity for coloring-matters, hence it is difficult to follow the processes by which the cells are united. Their nuclei are at first round or oval. After the third month they often show a great variety of alterations in shape and size, Cuts 9, 10; some of the nuclei are then very large, with a distinct net-work, *d*; others are smaller and differ but slightly from the normal; some are very irregular, *b*, and others again strangely elongated, *a*; many other forms beside those represented in Cut 9 are to be found. The changes indicated I consider of a degenerative character, and in fact many of the nuclei are



Cut 9. — A natural group of nuclei from the mesoderm of the amnion of a foetus of the fifth month.  $\times 1225$  diams.

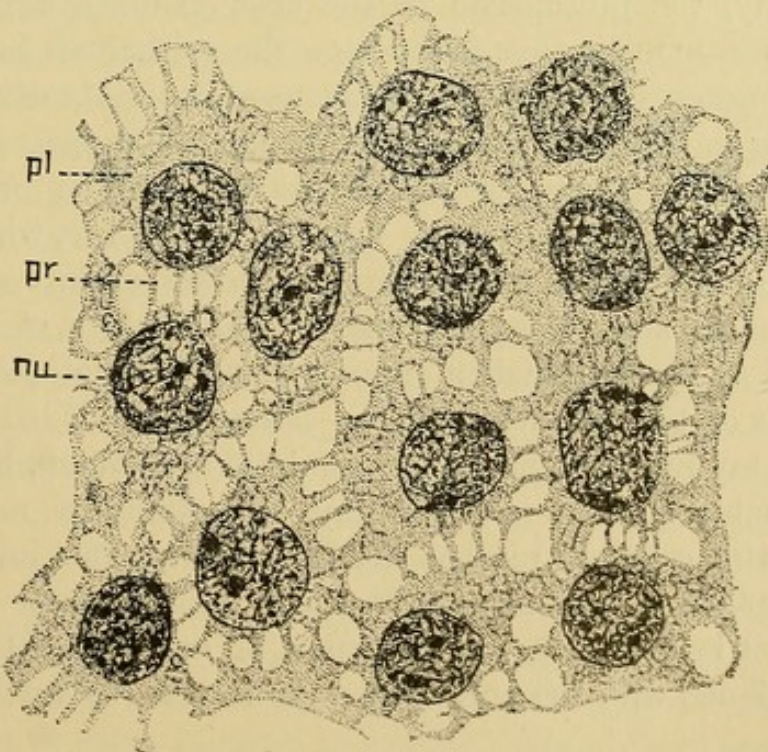
breaking down, for one finds in some specimens every stage between a nucleus and scattered granules, — nuclei, nuclei with indistinct membranes, nuclei without membranes, masses of granular matter, clusters of granules crowded together, and finally other clusters more or less scattered. This degenerative process may be compared with that described by Phisalix (*Arch. Zool. Expt.*, Sér. II., T. III., 382) as occurring in the blood cells of the spleen of teleosts. Compare also the chromatine degeneration observed by Flemming to occur in ova of the vertebrate ovary (*His and Braune's Archiv.* 1885, 221-244). In the human amnion the nuclear degeneration described is not always to be recognized so clearly, although the nuclei in all amnia older than three months, which I have observed, are more or less

irregular and distorted. Finally it is to be added that not infrequently the cells form a distinct epithelioid layer upon the surface of the amnion next the chorion, as represented in Cut 8, B, *a*.



*Cut 10.*— Mesodermic nuclei of the amnion of an embryo of about four months.  $\times 713$  diam.

The epithelium of the amnion varies in appearance, as seen in transverse sections. Usually the cells are cuboidal or low cyl-



*Cut 11.*— Surface view of the amniotic epithelium of an embryo of 144 days; stained with alum — hæmatoxyline, and eosine. *pl*, protoplasm; *pr*, intercellular processes; *nu*, nucleus.  $\times 1225$  diams.

inders, Cut 8, A, each one with a rounded top, in which is situated the more or less nearly spherical nucleus; sometimes, however, the nuclei lie deeper down. Less frequently the epithelium is thin, Cut 8, B, and its nuclei, which are transversely elongated, lie further apart. It is probable that these differences are not structural, but conditional upon the greater or less degree to which the amnion is stretched. I have observed no constant differences between the placental and the remaining amnion. The most interesting peculiarity of the epithelium is best seen in surface views; namely, the intercellular bridges. They display themselves with a clearness which I have never seen in other epithelia; see Cut 11.

The nuclei, *nu*, are relatively large, rounded with distinct outlines; they have a more or less well marked intra-nuclear network, with thickened nodes, and a small number of deeply stained granules, which are probably chromatine. Each nucleus is surrounded by a cell body, *pl*; and the adjacent cell bodies are separated from one another by clear spaces. With high powers, as represented in the cut, one sees that these spaces are separated from one another by threads of material, *pr*, stretching across as bridges, connecting neighboring cells. Examined attentively, the protoplasm of the cells exhibits a vacuolated appearance. One is thus led to view the epithelium as a sponge work of protoplasm somewhat condensed around each nucleus; according to this interpretation the intercellular spaces are large meshes of the sponge work, and the intercellular bridges are protoplasmic. A recent paper<sup>1</sup> by M. Manille Ide, which I owe to the kindness of the author, brings a series of interesting observations to show that the intercellular bridges of the Rete Malpighi of the mammalian epidermis are not protoplasmic, but processes of the cell membranes. This paper has led me to re-examine my preparations of the amniotic epithelium, but I have been unable to find in them any indications of membranes around the cells or reasons for considering the intercellular bridges as other than protoplasmatic in constitution. Whether this result is due to the imperfection of my preparations, or is in accordance with the truth, must be decided by further investigation.

<sup>1</sup> Manille Ide, La membrane des cellules du corps muqueux de Malpighi. *La Cellule*, IV., 2me fasc., 1888.

Meola, **59**, ascribes a much more complex structure to the amnion than his predecessors, in which he is followed by Viti, **21**. Both of these authors subdivide the mesodermic stratum into three layers: a *lamina connetivale*, next the ectoderm, a *sostanza intermedia*, and a *membrana limitante*. As to the histological details, Viti differs somewhat from Meola, but agrees with him in finding a histological distinction between the three layers enumerated. The extent to which I can distinguish three layers is indicated by the description of the mesoderm given above: I have been unable to find the marked structural differences affirmed by Viti. Viti's paper is to be commended for its excellent historical reviews, particularly for his summary of the various theories as to the origin of the amniotic fluid.

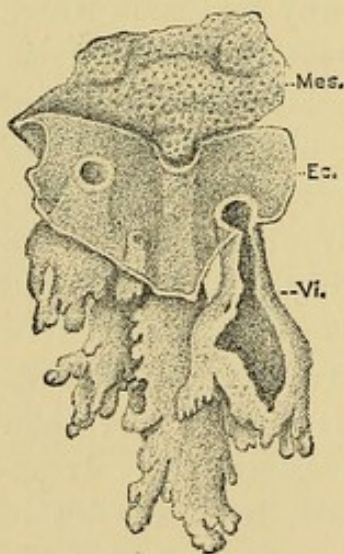
§ 15. **Chorion.** — The human chorion has been the object of greater misconception than perhaps any other organ of the body. Even at the present time there prevail numerous false conceptions concerning it, nor do I know of any text-book which gives a satisfactory or even tolerably correct account of its structure. This singular confusion is not due to deficiency of observations, for from the vast literature of the subject (by trusting the accurate observers, such as Coste, Farre, Kölliker, Turner, Langhans, Waldeyer, etc.), we may cull a fairly complete and exact history of the development of the chorion. But the literature of the chorion consists chiefly of papers of little value, and often remarkable for the gross crudeness of the observations they record, and for the proofs they are of their author's ignorance of other and better investigations. It appears that the anatomists and physiologists, by a species of tacit understanding much to be regretted, have regarded the uterus and placenta outside of their province, and have left the investigation of the anatomy and functions of these organs to gynæcologists and others, whose capacities have lain rather in the direction of medical practice than of original research, although among them are some notable exceptions. The majority of the practitioners who have written on the uterus and foetal appendages have done at least as much harm as good. It would be a sheer waste of time to subject this mass of literature to a critical revision in order to extract from it what little there may be of value. I have, however, read a large number of the articles, and studied those which seemed worthy of it. Upon



this course of reading and a study of my own extensive material I have based the following history of the chorion, which passes briefly over what is known, and dwells upon what is founded on my own observations.

The human chorion as I have defined it<sup>1</sup> is "the whole of that portion of the extra-embryonic somatopleure, which is not concerned in the formation of the amnion." The human chorion is remarkable for its very early complete separation from the yolk sack, and for its precocious development of villi. Both of these developments had already taken place in His' youngest embryo, and in Reichert's ovum, which is supposed to be normal and the youngest known, there were chorionic villi, though no embryo was distinguished. Reichert's description is not satisfactory, his long memoir<sup>2</sup> being principally concerned with speculations.

The villi of the chorion, as shown long ago by the obser-



Cut 12. — Portions of the chorion of an embryo supposed to be about eighteen days; *mes*, mesoderm; *ec*, ectoderm; *vi*, hollow villi. After Coste.

ervations of Coste, are formed at first only by the ectoderm. I reproduce here Fig. 6, of Pl. II., referring to the human species from Coste's great work. The hollowness of the villi and their clumsy shape are to be especially noted. The mesoderm grows into the villi subsequently. The branches of the villi grow out in a similar manner, the process being led, as it were, by the ectoderm. Orth, in a special paper, 118, has used these facts to argue against Boll's *Princip des Wachstums*. Kollman's observations<sup>3</sup> on the growth of villi during the fourth week are particularly instructive. The outgrowth of the branches is very rapid and occurs with every degree of participation of the connective

tissue. The two extremes are: 1°, a bud consisting wholly of epithelium, which may become a process with a long, thin pedicle, and a thickened free end remaining entirely with-

<sup>1</sup> Buck's *Reference Handbook, Medical Sciences*, — Art. Chorion.

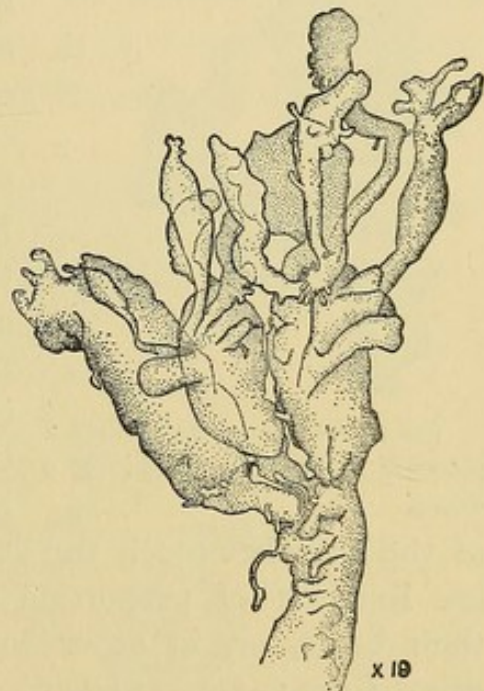
<sup>2</sup> Reichert, *Berlin Akad. Abhandlungen*, 1873.

<sup>3</sup> Kollman, *Arch. Anat. Physiol. Anat. Abth.*, 1879, 297.

out mesoderm; 2°, a thick bud with a well-developed core of connective tissue, and having a nearly cylindrical form. Between these extremes every intermediate state can be found. Other observers have noted this peculiar manner of growth, which I have found still going on in the placental chorion during the fourth month. Robin, **125**, appears also to have crudely observed both the young hollow villi, and the solid epithelial buds. The blood-vessels he traces to the division of the cavity of the villi into an artery and a vein; from the nature of things he offers no observations in support of this assertion.

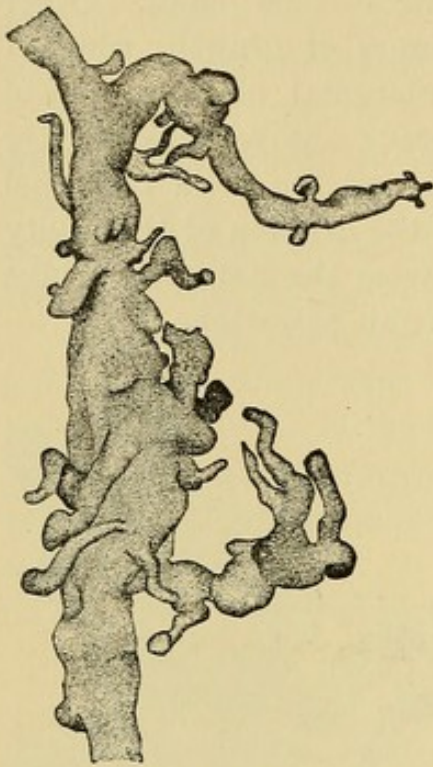
Only the tips of the villi touch the surface of the decidua, either at first or subsequently, except of course, over the chorion læve during the abortion of the villi. The tips of the villi are attached to the uterine surface; they penetrate the decidua for a short distance, but even in the placental area at the close of gestation, the penetration is slight, and the villi make their way only into the surface stratum of the decidua serotina. There is no evidence of any sort that the villi penetrate the glands at any period. The relation of the villi to the decidua has now been so accurately ascertained, that there can be, I think, no longer any question whatsoever on this point. The best discussion is by Langhans, **110**, p. 231 ff.

The shape of the villi varies according to the part of the chorion and the age of the embryo. They gradually abort over the chorion læve, and gradually grow over the chorion frondosum. Let us begin with the placental villi: At first they are short, thick-set bodies of irregular shape, as shown in Cut 12; at twelve weeks their form is extremely characteristic, Cut 13; the main stem gives off numerous branches at more or less acute angles, and these again, other branches, until at last the termi-



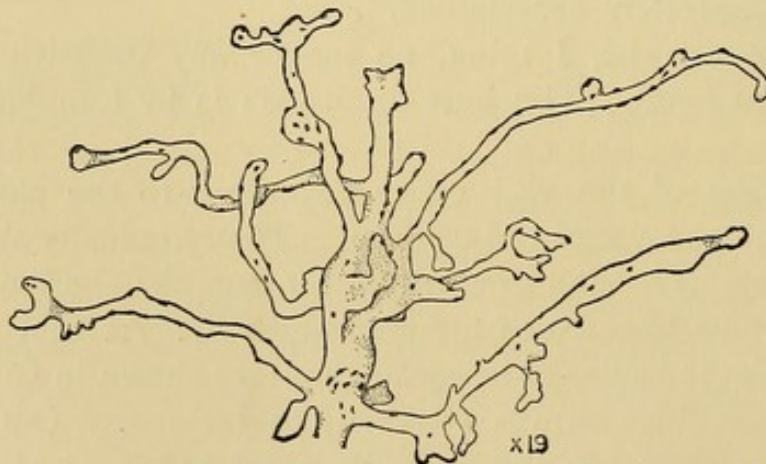
Cut 13. — Isolated terminal branch of a villus from the chorion of an embryo of twelve weeks.

nal twigs are reached; the whole of the space between the chorion and decidua is occupied by these ramifications; the



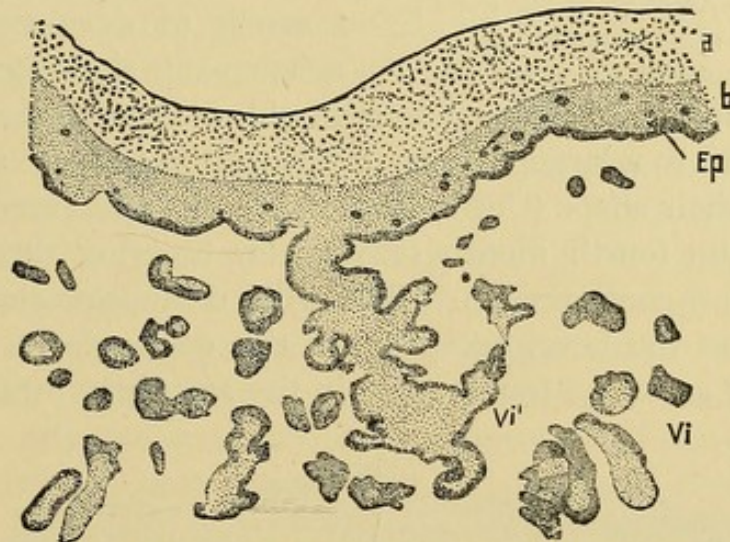
*Cut 14.*—Villous stem from a placenta of the fifth month.  $\times 9$  diams.

branches and twigs, as the illustration shows, are extremely irregular and variable, although in general they may be described as club-shaped, being more or less constricted at their bases. The branches may be bigger than the trunk which bears them, or of any less size; some of the smallest are merely slender outgrowths of the epithelial covering of the villus, such as have already been alluded to. Gradually there is a change. During the fifth month we find the irregularity, though still very marked, decidedly less exaggerated, *Cut 14*; the branches tend to go off at more nearly right angles; one finds very numerous free ends, as of course only a small proportion of the branches touch the decidual surface; the branches, too, are less out of proportion to the stems, less constricted at their bases, or, in other words, less remote from the cylindrical form; the awkward cucumber shapes of the twelfth week are no longer found except here and there. The change continues in the same direction; that is, is towards



*Cut 15.*—Terminal villi of a placenta at full term. The little spots represent the proliferation islands of the covering epithelium.

greater regularity of configuration. It is hardly necessary to describe the intermediate phases that have been examined, but it will suffice to describe the form at full term, Cut 15, when the branches are long, slender, and less closely set, as well as less subdivided, than at earlier stages; they have nodular projections, like branches arrested at the beginning of their development; there are numerous spots upon the surfaces of the villi; microscopical examination shows that these spots are *proliferation islands*, as we may call them, or little thickenings of the ectoderm with crowded nuclei. It appears that not all the villi change to the slender form; for some villi, having still the earlier, thicker form, are found even in the mature placenta, a fact already noticed by Jassinsky, 105, 346. These thick villi



Cut 16.—Section of the chorion at three weeks. *a*, layer of coagulum; *b*, mesoderm of chorion; *Ep*, epithelium, also extending over the villi; *Vi* and *Vi'*; the mesoderm, *b*, contains a number of blood-vessels, nearly all in transverse section.  $\times 65$ .

usually show also a distinct "cellular layer" in their ectoderm, a peculiarity to be considered below again. Seiler, 131a, has given figures of the villi at various ages, but fails to show the characteristic forms. Langhans has observed the alteration in the villi, 110, 199, and even justly remarks that many of the villi in so-called "moulds" are not pathological, as they have been frequently considered, but normal young villi. The differences in the villi, according to age, are very conspicuous in sections. The sections should of course be made so that the fragments of the villi will remain *in situ*; imbedding in celloidine is convenient for this purpose; if this end be attained, one

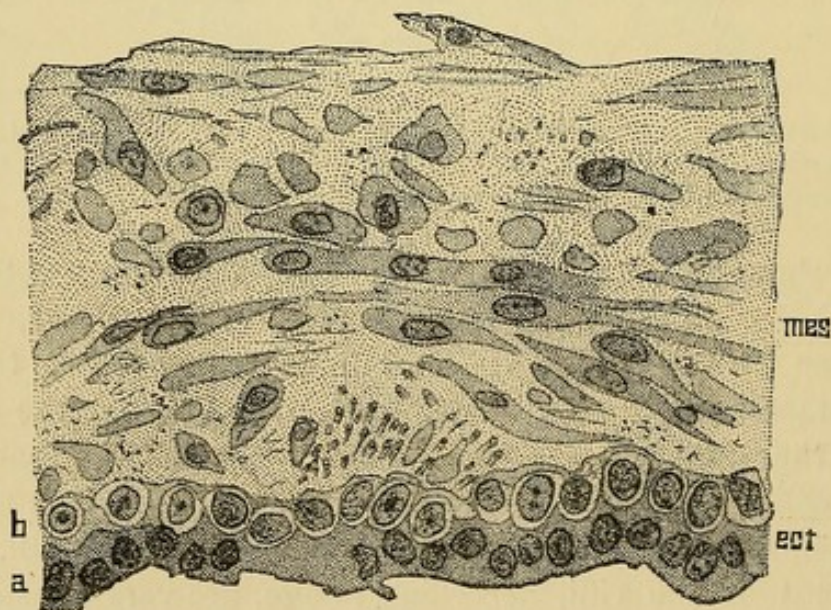
finds below the chorionic membrane numerous sections of villi; if the specimen be a young chorion, — first to third month, — the villi are large, with a good deal of room between them; their outlines are very irregular, and there are relatively few small branches (Cut 16). The older the specimen, the larger the



Cut 17. — Aborting villus from a chorion of the second month.

proportion of small branches. In an old chorion — seventh to ninth month — the number of small villi of nearly uniform size is very striking (see the figure of a section through a placenta *in situ*, given in Cut 35).

The abortion of the villi of the chorion læve takes place by an arrest of development and a subsequent slow degeneration of the tissues, which lose all recognizable organization in the protoplasm, and to a large extent of the nuclei; at the same time they alter their shape (Cut 17), becoming more and more filamentous; by the fourth month only a few tapering threads, with very few branches, remain. The villi disappear almost completely from the læve, except near the edge of the placenta, where they are to be found, even in the after-birth, imbedded in



Cut 18. — Section of the chorionic membrane of an embryo of three weeks; stained with osmic acid; *mes*, mesoderm; *ect*, ectoderm; *a*, outer, *b*, inner layer of ectoderm. From a section prepared by Prof. Theodor Langhans.  $\times 445$  diams.

the degenerated epithelium of the chorion and the upper layers of the decidua, as shown in Cut 25, *vi*, the epithelium and decidua being so fused at this point that it is impossible to determine any line of demarcation between them.

The chorion, being a portion of the somatopleure, consists, of course, of two primary layers, the mesoderm and ectoderm. During the second half of the first month, the earliest period concerning which we have any accurate knowledge, the mesoderm is already a vascular layer of considerable thickness (Cuts 16 and 18, *mes*), and the epithelium (ectoderm) has two layers of cells (Cut 18, *a* and *b*); of which the outer is the darker in specimens stained with osmic acid, carmine, cochineal, or hæmatoxyline, and has also smaller and more granular nuclei. The same distinction exists in the two-layered stage of the ectoderm of the umbilical cord (Cut 3), and of the foetal skin. Hitherto most authors have entirely overlooked the inner layer at early stages. It was first clearly recognized by Langhans, who directed attention to it in a special memoir, **111**, he having already described its later history, **110**. In some earlier writers are allusions to the layer. Kastschenko, in his paper on the chorionic epithelium, has also described it, although he has not followed its history very far. The interpretation to be offered seems to me clearly to be, that the chorionic epithelium advances in its differentiation to a stage equivalent to the two-layered stage of the epidermis and there stops; whatever further change occurs is degenerative.

The two primitive layers of the chorionic epithelium have been more or less clearly observed at later stages by several anatomists, and have been variously interpreted. Ercolani and Turner regard them as absolutely distinct, assigning the deep layer to the chorion as its true and only epithelium, and the outer layer to the uterus, thus enabling themselves to conceive the villi as covered by a maternal as well as a foetal epithelium, so that maternal blood found between the villi is still within the maternal tissue. After accepting the outer layer as maternal, the question as to its origin still remained. Some authors affirmed it to be the uterine epithelium, others to be the lining of expanded uterine blood sinuses. So far as I am aware, no one has made observations to show by the developmental history of the layer, that one or the other of the last mentioned hy-

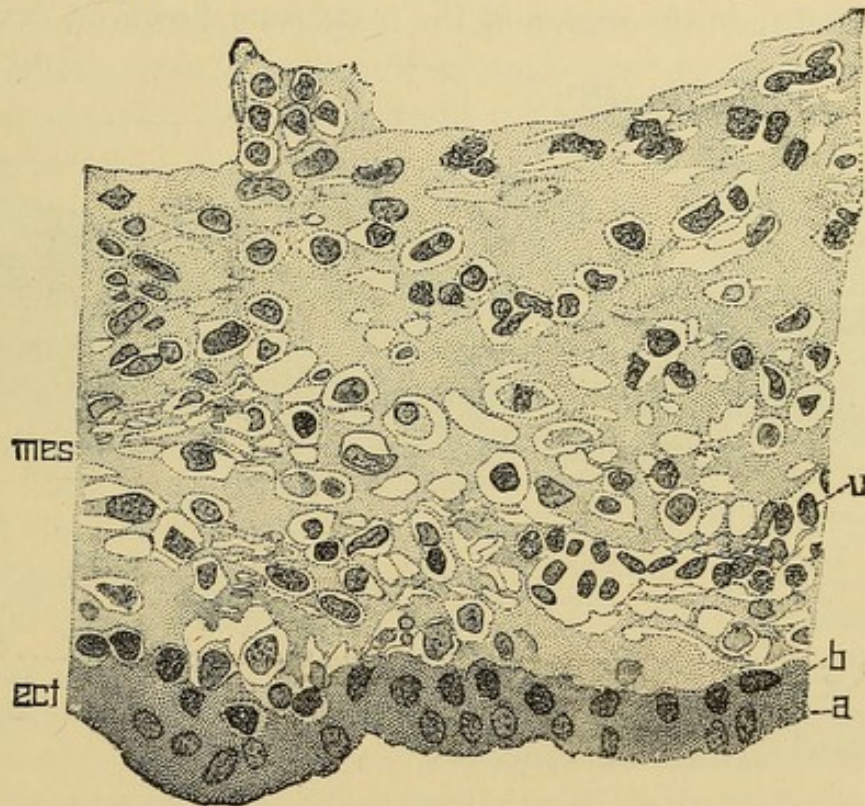
potheses is correct. When we consider the precision and exactitude of Kastschenko's observations, which actual specimens enable one to verify, there is in my judgment no reason left for differing from the conclusion that both layers are parts of the foetal ectoderm.

Governed by the difficulty of accounting for the presence of maternal blood in the intervillous spaces, and therefore apparently outside the maternal tissues, several investigators have been led to seek for at least an endothelium outside the chorionic epithelium. Some authors, as for instance Winkler, have asserted the existence of such an endothelium, but after a prolonged and careful search, I fail to find anything of the kind, and in this result it seems to me the best observers are agreed.

The conclusion, I think, may now be safely formulated that the chorion is covered externally by the foetal ectoderm, and has no other covering in any part except, of course, where the chorion læve rests upon the surface of the decidua, and where the tips of the villi touch the serotina; but the morphological distinction holds, and the decidua is no more the covering of the chorion, than are clothes morphologically the covering of the body. I believe further, on grounds stated below, that the conclusion just formulated holds true of the chorion at all periods.

The further history of the chorionic mesoderm is so fully given by Langhans in his invaluable memoir, **110**, and Kastschenko, **107**, that there is little to be added. In the earliest stage I have been able to examine, an ovum of the third week, the matrix of the chorionic connective tissue, in a preparation stained with cochineal or hæmatoxyline, and imbedded in paraffine for cutting, appeared hyaline and glistening, owing to its refrangibility (Cut 19); it has lacunæ in which the cells lie; the cell bodies are either shrunken or colorless, so that lacunæ, except for the staining of their contained nuclei, are clear and light. This appearance I find again in specimens a little older. The image is entirely distinct from that of the same layer later, for then the cells are stained darker than the matrix, which at the same time has lost its homogeneous character, and acquired a fibrillated look. Very different from my own sections are several which I owe to the kindness of Professor Langhans of Bern, and which that distinguished investigator informs me are from a three-weeks ovum, which had been preserved in osmic

acid (see *ante*, Cut 18). In Professor Langhans' preparations the cells are all stained much deeper than the matrix; they have an elongated form, and run in various directions more or less parallel to the epithelium *ecto*; hence many of them are cut transversely or obliquely. Whether the differences noted are due to the methods of preparation must be decided by preserving the same chorion in part with osmic acid, in part with Müller's fluid or picrosulphuric acid, the latter being the reagents I have used. In specimens of the tenth week, the matrix of the chorionic mesoderm has quite altered in character, being no longer homo-

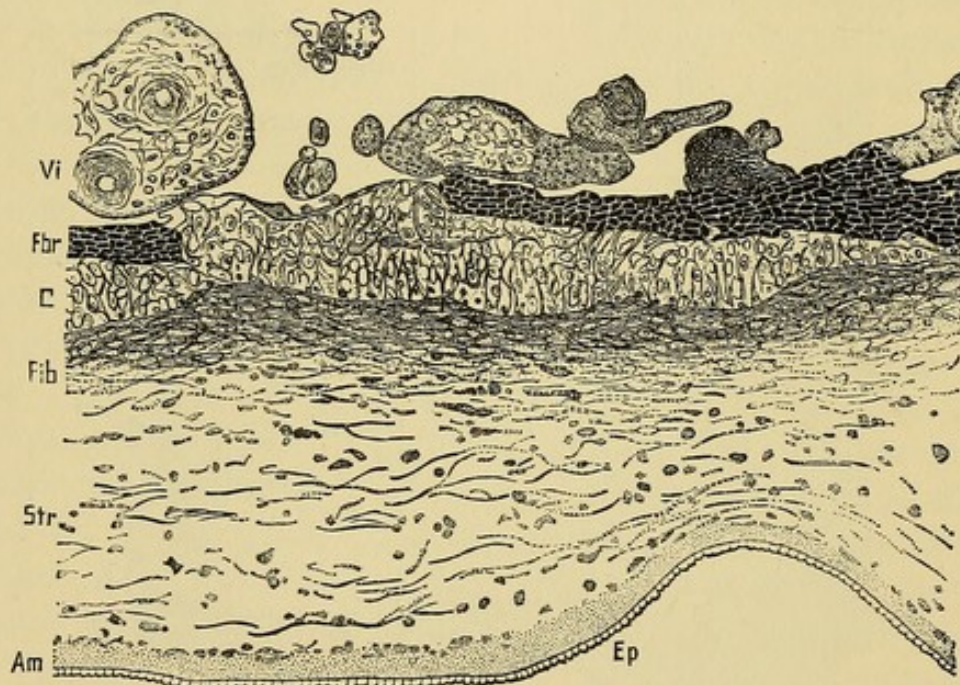


*Cut 19.* — Section of the chorionic membrane of an ovum supposed to belong to the third week; *ect*, ectoderm; *mes*, mesoderm; *a*, outer, *b*, inner layer of ectoderm; stained with alum-cochineal.  $\times 445$  diams.

geneous, and at the same time it has increased in thickness. For the most part the matrix stains lightly, and where it is lighter it contains fibrils of extreme fineness, and running curly courses; there are also streaks of lightly stained matrix, giving the impression of fibres resulting from portions of the primitive colorable matrix being left. In other parts of the layer the primitive matrix is still present, and we find a homogeneous well-colored basal substance, the cell lacunæ of which appear light by contrast, as in Cut 19. One can distinguish also the



commencement of the perivascular coats, at least of the larger vessels, the matrix being quite dense around them, and the cells elongated almost into fibres, and possessing a slightly increased affinity for coloring-matters. The larger blood-vessels and unmetamorphosed part of the layer occupy a middle portion between the two surfaces, but the smaller blood-vessels lie near the ectoderm (compare Cut 19, *v*), thus presaging the formation of Langhans' vascular layer (*Gefässschicht*). The development of the mesoderm of the *chorion læve* stops at about this stage, or at the stage when the matrix has completely changed from its first state; in the region of the frondosum, however, develop-



Cut 20. — Section of the amnion and placental chorion of the fifth month. *Ep*, amniotic epithelium; *Am*, amnion; *Str*, stroma; *Fib*, fibrillæ layer; *fbr*, fibrine layer; *c*, cellular layer; *Vi*, villi. (From a section cut in celloidine, and stained with Weigert's Hæmatoxyline. The drawing is only approximately correct as to details.  $\times 71$  diams.).

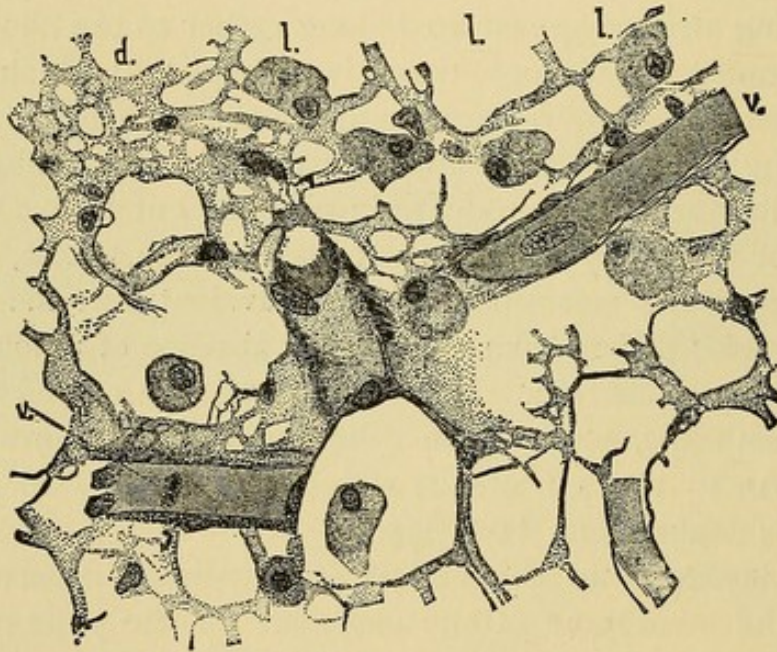
ment proceeds much further by the production of fibres throughout the whole of the layer; usually, but not invariably, the fibres become much more numerous near the ectoderm than in the inner part of the mesoderm, thus differentiating a well-marked sub-epithelial fibrillar layer, Cut 20, *fib*, from the deeper and wider stroma, *Str*. The fibrillar layer is that commonly spoken of as the connective tissue layer of the chorion: for details of its structure, including the "*Gefässschicht*," see Langhans and

Kastschenko. The inner layer, *Str*, is called the *Gallertschicht* by many German writers, and seems to be what Kölliker (*Entwickelungsgeschichte*, 2te Aufl., p. 322) designates as "Gallertgewebe zwischen Chorion und Amnion"; it usually contains a considerable number of large granular wandering cells. Jungbluth, **106a**, describes a network of capillaries, which exist during the first half of pregnancy, apparently in the upper part of the stroma, — *i.e.* next the amnion — but I fail to find any. Where the amnion comes into contact with the chorion the adjacent parts of the two membranes are more or less loosened, forming a network of strands by which the membranes are united: most of the uniting strands appear to belong rather to the chorion than to the amnion. This loose tissue is perhaps that which Kölliker designates as a *Gallertgewebe* distinct from the chorion.

Although the chorion bounds the cœlom, I have observed no mesothelium upon its mesodermic surface; but I have not made search for it by any special methods. In the rabbit, it will be remembered, the mesothelium is very evident over the placenta, but the rabbit differs from man by the absence of union between the amnion and chorion. Nor have I been able to find any basement membrane, properly so called, under the chorionic ectoderm. As to the appearance which suggests it, I accept Kastschenko's explanation, **107**, 455.

The mesoderm in the villi is differentiated otherwise than that of the membrane of the chorion. In the youngest stage I have examined there is some of the primitive matrix present in the villi; and I presume that earlier the whole mesoderm has the same character. In my specimen (three weeks) the change is progressing. I have not succeeded in satisfying myself as to the process of change which takes place, but I think it probably essentially as follows: The cells gradually develop large bodies and acquire a more decided affinity for coloring-matters; meanwhile vacuoles appear in the matrix, presumably by its modification into a new substance; the vacuoles increase in size and number, transforming the matrix into a network and ultimately causing its total disappearance, leaving the intercellular spaces filled entirely with the new substance, which has come from a metamorphosis of the original matrix; probably this new substance is more or less fluid, since wandering cells are scattered freely through it. Leaving this half-hypothetical history, let us

pass on to direct observations. In the placental villi of embryos of four months and older, the mesoderm exists in two principal forms,—adenoid tissue and fibre-cell tissue around the blood-vessels. The adenoid tissue, Cut 21, is that of which the supposed development has just been sketched; it may be considered as the proper tissue of the villus. It consists of a network of protoplasmic threads, which start from nucleated masses (cells). There are many large meshes, which are partly occupied by the coarsely granular wandering cells, *l, l*, which are scattered about, and are usually present in large numbers. About the capilla-



Cut 21.—Adenoid tissue of a villus from a placenta of four months. *l, l, l*, wandering cells; *v, v*, capillary blood-vessels; *d*, finer meshwork from near a capillary.  $\times 352$  diams.

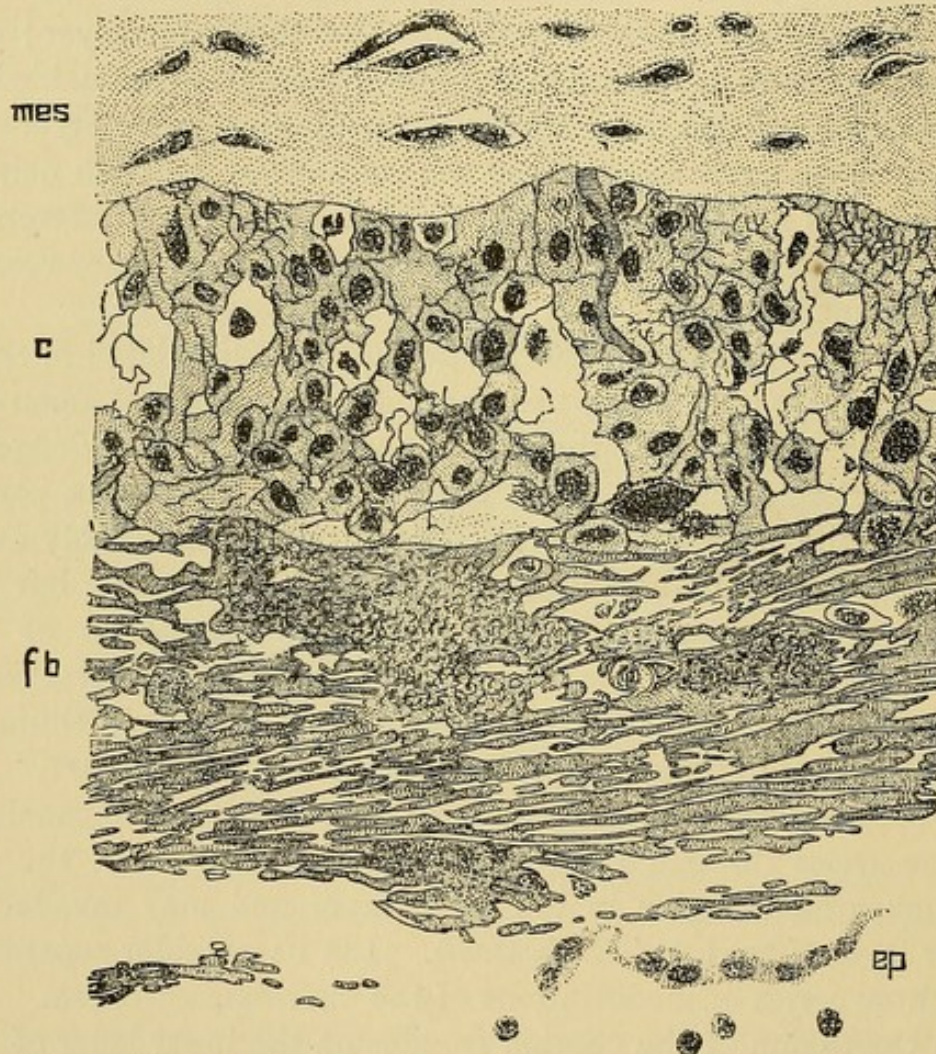
ries the network is much more finely spun. Kastschenko, **107**, 454, found the wandering cells most abundant near the epithelium, but I have noticed no such peculiarity, except that they do not often enter the dense perivascular tissue; and as the blood-vessels are centrally situated, the adenoid tissue and the wandering cells in it are of course more peripheral. It seems to me that the leucocytes are distributed more or less evenly throughout the adenoid tissue. I fail to recognize any intercellular substance. The abundance of nuclei deserves special mention. Around all the non-capillary vessels the mesoderm is very different, for it exhibits distinct intercellular substance, with a ten-

dency to fibrillar differentiation in quite a wide zone around the blood-vessels; in this zone the cells become elongated and irregularly fusiform; around the larger vessels the cells are grouped in lamina, making the structure similar to that already described in the walls of the vessels of the umbilical cord; after the perivascular coats acquire a certain thickness, the cells of the inner layers are more elongated, more regularly fusiform, and more closely packed than those of the outer layer; the transition from the denser to the looser tissue is gradual. We are perhaps entitled to recognize in the denser inner layer the *media*, in the outer looser layer the *adventitia*, although neither of the layers has by any means the full histological differentiation characteristic of the like-named layers of the blood-vessels of the adult.

The epithelium of the chorion becomes differentiated in three different ways: 1°, upon the chorion frondosum; 2°, upon the chorion læve; 3°, upon the villi. For a correct knowledge of the remarkable changes which the epithelium undergoes, particularly in the placenta, we are indebted to the remarkably exact investigations of Langhans, **110** and **111**. This author left two points of importance unsettled; namely, the origin of his "*Zellschicht*," and of the "*canalisirtes Fibrin*." Kastschenko has traced the cellular layer (*Zellschicht*) to the epithelium, as already stated: compare pp. 463-469 of his memoir, **107**. My own observations show, I think conclusively, that the canalized fibrine arises through a degenerative metamorphosis of the epithelium, which begins in the outer layer and may invade the inner layer (Langhans' *Zellschicht*). Let us consider separately the three series of modifications of the chorionic ectoderm.

In the region of the chorion frondosum the inner layer of the ectoderm (the cellular layer of Langhans) becomes irregularly thickened in patches, which present every possible degree of variation as to number and as to their breadth and thickness. Although at first the cellular layer is more or less continuous and composed of uniform cells, this is not the case in later stages. We must assume that with the growth of the membrane the epithelium increases in area, but remains in many places single layered, developing no "*Zellschicht*." The patches of cells have been well described by Langhans, **110**, and Kastschenko, **107**, 466, and are represented with lower power in

Cut 20, *c*, and with a higher power in Cut 22, *c*. They vary much in appearance: the cells are more distinct in the small patches, but are less individual in the large patches, owing to the spread of the process of degeneration into the layer, Cut 22, *c*. The cell bodies are lightly stained, and the granular nuclei are not very sharply defined and vary in size and shape. The cellu-



*Cut 22.* — Placental chorion of an embryo of seven months; vertical section through the ectoderm and portion of the adjacent stroma. *mes*, mesodermic stroma; *c*, cell layer; *fb*, fibrine layer; *ep*, remnant of epithelium.  $\times 445$  diams.

lar layer is always sharply defined against the stroma, although there is no true basement membrane, but towards the outer layer of the ectoderm its boundary is sometimes distinct, sometimes lost in a gradual transition.

The outer layer of the ectoderm of the frondosum is even more variable. As stated by Kastschenko, it is primitively a dense protoplasmic reticulum, with nuclei in a single layer and

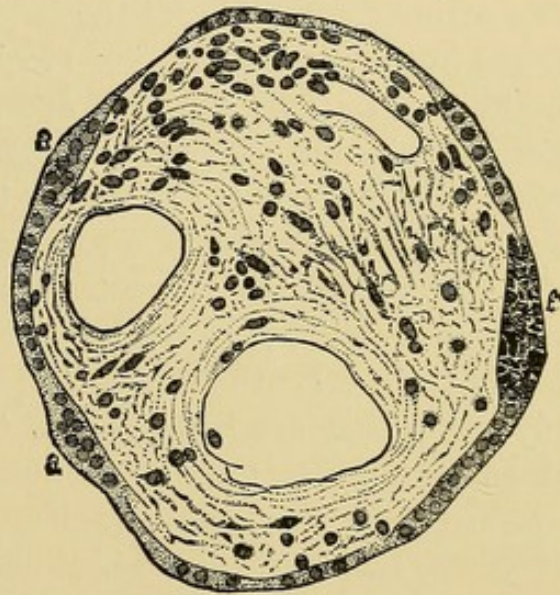
without any cell boundaries. In the chorion frondosum at four months and after I find spots where this structure still prevails, either with or without an underlying cellular layer; in other spots the layer is thickened and contains an increased number of nuclei, which are sometimes crowded in a bunch; elsewhere the layer is thinned out and has no nuclei; in still other spots the thickening has gone on much further, and usually, but not always, where the outer layer is much thickened the cellular layer under it is also thickened; wherever it is thickened, and occasionally where it is thin, the outer layer of the ectoderm shows a marked tendency to degenerate into canalized fibrine, Cut 20, *fbr*, and Cut 22, *fb*. It is not difficult to assure one's self that the fibrine arises by direct metamorphosis of the ectoderm. I now think that its formation begins in the outer layer and thence spreads into the cellular layer; for, in fact, when both layers are distinguishable, as in Cut 22, the fibrine layer, *fb*, is always external, and the external layer of nucleated protoplasm has either totally disappeared or is represented by mere remnants, as in Cut 22, *ep*. The fibrine layer consists of a hyaline, very refringent substance permeated by numerous channels, Cut 22, *fb*; the substance has a violent affinity for carmine and hæmatoxyline, and is always the most deeply colored part of a stained section; the channels tend to run more or less parallel to the surface of the chorion and are connected by numerous cross-channels; some of the channels contain cells or nuclei. This complex system of canals is by no means of uniform appearance in all parts of the placenta, both the spaces and dissepiments varying in size and shape. The fibrine often sends, as shown in Cut 22, long outshoots into the cellular layers upon which it seems to encroach. The frequency of these images in my preparations led me to the opinion<sup>1</sup> that the fibrine arises from the cellular layer only, and I concluded that the ectoderm was first transformed into the so-called cellular layer, which was then transformed into fibrine. It still appears to me that much of the degeneration goes by these stages; but, on the other hand, it seems clear that the degeneration begins, as above stated, in the outer layer. Another appearance is presented by the ectoderm where it is thickened and wholly transformed into the cellular layer. In brief: the ecto-

<sup>1</sup> *Anatom. Anzeiger*, ii. 23.

derm of the placental chorionic mesoderm undergoes patchwise manifold changes; it exists in three chief forms: 1°, the nucleated protoplasm; 2°, the cellular layer; 3°, canalized fibrine. A patch of the ectoderm may consist of any one of these modifications, of any two or of all three, but they have fixed relative positions, for when the nucleated protoplasm is present, it always covers the free surface of the chorion; when the cellular layer is present, it always lies next the mesoderm; and when all three forms are present over the same part, the fibrine is always the middle stratum. In general terms it may be said that the amount of canalized fibrine increases with the age of the placenta, but it is very variable in its degree of development. The peculiar layer into which the ectoderm is transformed has long puzzled anatomists. E. H. Weber recognized the fibrine layer and described its appearance correctly; it has probably been often seen, but generally regarded as either pathological or a blood coagulum. Robin, for instance, may be cited, **125**, 70-71, as one who saw, without observing correctly and understandingly, the tissue in question. An important gain was made when Winkler recognized the modified ectoderm as a constant layer, and in 1872 directed especial attention to it under the name of "*Schlussplatte*," **152**. Kölliker (*Entwicklungsgeschichte*, 2te Aufl., 337) added essentially to our knowledge of its structure, but it is to Langhans that we owe the first clear light. Meanwhile, other writers, following the lead of Ercolani and Turner, **146**, 551-553, have been influenced chiefly by the presence of the cellular layer, in the large size of the elements of which they found a resemblance to the decidual cells, which has guided them to the conclusion that the cellular layer is derived from the wall of the uterus. This error has been definitely corrected by Kastschenko, as already stated. In further support of the conclusion that the chorionic cellular layer is not decidual, may be brought forward the fact that there is a certain immigration of decidual cells into the placenta at its margin; but they remain entirely distinct from the cells of the cellular layer. This is readily seen in radial sections through the margin of a placenta from a normal after-birth—compare below, the account of the ectoderm of the chorion læve. The origin of the canalized fibrine from blood, which Langhans left in his first paper as an open possibility, and which

even so recent a writer as Ruge, **129a**, 123 and 130, has advocated, cannot be maintained. Of course, there may be a deposit of blood fibrine (coagulum), but it would be pathological, and therefore to be distinguished from the normal fibrine of ectodermal origin. Moreover, the microscopic appearance of a blood clot or thrombus is so extremely characteristic that one can readily distinguish it from the placental canalized fibrine.

The ectoderm of the villi of the placenta differs from that of the chorionic membrane in several respects: 1°, the cellular layer after the first month becomes less and less conspicuous, and after the fourth month is present only in a few isolated patches, known as the *Zellknoten*, and carefully described by Langhans and Kastschenko; both of these authors were impressed by the resemblance of the cells to those of the decidua serotina; Langhans concludes that the *Zellknoten* arise from the serotina, but Kastschenko, having traced their development from the chorionic epithelium, denies his predecessor's conclusion, but still clinging to the idea of a genetic connection



Cut 23. — Cross-section of a villus from a placenta of seven months; three blood-vessels are shown; *a, a*, thickenings of the ectoderm; *f*, a thickening transformed into canalized fibrine.  $\times 222$  diams.

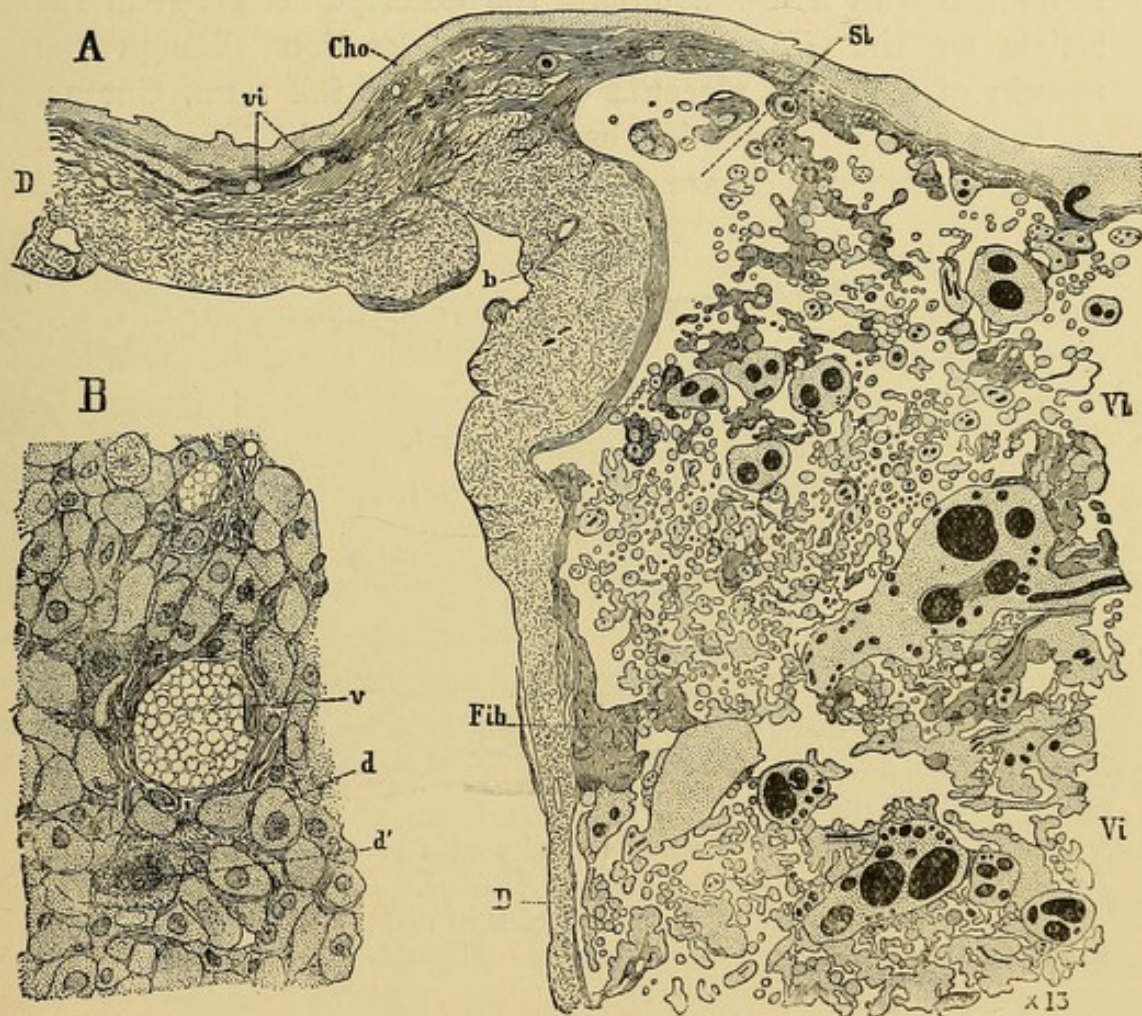
between the *Zellknoten* and the decidua, reverses the reasoning, and concludes that the decidual cells arise in part at least from the *Knoten*. Neither of these authors have found the intermediate forms between the two types of cells, and when we examine their descriptions critically we find that they have really no evidence except the likeness of the cells to offer in favor of their genetic relationship, and accordingly Langhans expresses himself with characteristic caution. To me the resemblance appears altogether superficial; hence my conclusion that the *Zellknoten* are remnants of the cellular layer. 2°, For the most part the villi remain covered by the nucleated protoplasm, which in many places is thickened. In the later stages these thicken-



ings are small and numerous, constituting the so-called "*Proliferations-inseln*": compare Cut 15. Many of the little thickenings appear in sections of the villi, Cut 23, *a, a*, and here and there are converted into fibrine, *f*. I have interpreted them (Wood's *Reference Handbook of the Medical Sciences*, V., 695) as commencing buds, and consider that in earlier stages they grow into branches, but in later stages are in part at least arrested in their development. 3°, The proliferation islands are converted into canalized fibrine, and at the same time grow and fuse, forming larger patches, particularly on the larger stems: in this manner are produced the large areas and columns of fibrine found in the placenta at four months and after; they have been well described by Langhans, and form a striking feature in sections of placentæ. Some of the columns, as stated by Langhans, stretch along the villi from the chorionic membrane to the surface of the serotina as if to act as supports. Ercolani appears, if I understand his account, to have seen the fibrine columns, without, however, ascertaining either their structure or their origin. 4°, Over the tips of the villi, which are bent considerably where they are imbedded in the decidua serotina, the relations are not clear; the epithelium is certainly not present in its original form over the imbedded ends of the villi, which are, however, surrounded by a hyaline tissue of the character of the canalized fibrine, except that the canals are often indistinct or even wanting; the hyaline tissue forms an almost continuous coat over the decidual surface; in earlier stages the ectoderm of the terminal villi is often considerably expanded. The natural interpretation of these facts is that the ectoderm of the villi expands over the decidua serotina and degenerates. In this manner we account for both the absence of any cellular ectoderm over the ends of the villi and the presence of canalized fibrine upon the serotinal surface—but the hypothesis must await the final test by observation.

The ectoderm of the chorion læve loses by the seventh month all traces of the protoplasmic layer, and is without any canalized fibrine, except near the placenta; *cf. infra*. It is transformed into a *Zellschicht*. In a section of the læve *in situ* at seven months, Cut 33, the chorionic ectoderm, *c*, rests directly upon the decidua, which has no epithelium of its own. The ectodermal cells lie two or three deep; they are described by Kölli-

ker and Langhans, the former designating them as the chorionic epithelium, while the latter doubtfully traces their origin to the uterus. That Kölliker (*Entwicklungsgeschichte*, 2te Aufl., p. 322) is right, I am confident. It is easy to follow the layer of cells in question at the edge of the placenta, and see that it is directly continuous with the cellular layer of the frondosum, which it resembles in character. On the other hand, the ecto-

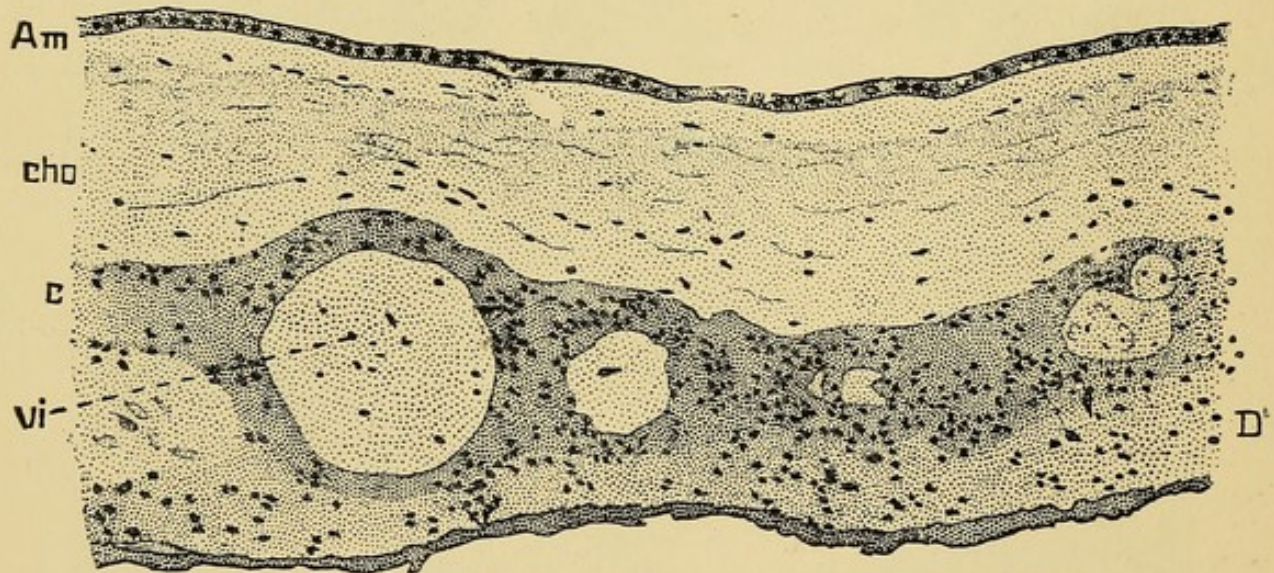


*Cut 24.* — Placenta at full term. A, vertical radial section through the margin; D, decidua; *vi*, aborted villi outside the placenta; *Cho*, chorion; *Sl*, circular sinus; *Vi*, placental villi; *Fib*, canalized fibrine. B, portion of A more magnified to show the decidual tissue near *b*; *v*, blood-vessel; *d.d'*, decidual cells; *d*, with one, *d'*, with several nuclei.

dermal cells of the læve are distinct in character from the decidual cells next to them, *Cut 34*, having smaller and more darkly stained nuclei, and much more coarsely granular protoplasm; the ectodermal cells are much smaller than the decidual. The ectoderm is sharply marked off from the decidua, but its surface

is often corrugated, and then the line of separation between the tissues is irregular, and in sections it may even appear that there is a true interpenetration and mingling of the decidual and ectodermal cells; but it is only apparent, and the demarcation is always preserved.

At the edge of the placenta, as shown by examination of after-births, the relations of the layers are somewhat different. I reproduce with a few additions the descriptions given in my article on the *Placenta*<sup>1</sup> of a radial section through the margin of a normal placenta discharged at full term, Cut 24, A, from which the amnion had been removed. The chorion, *Cho*, and decidua, *D*, are in immediate contact at the left of



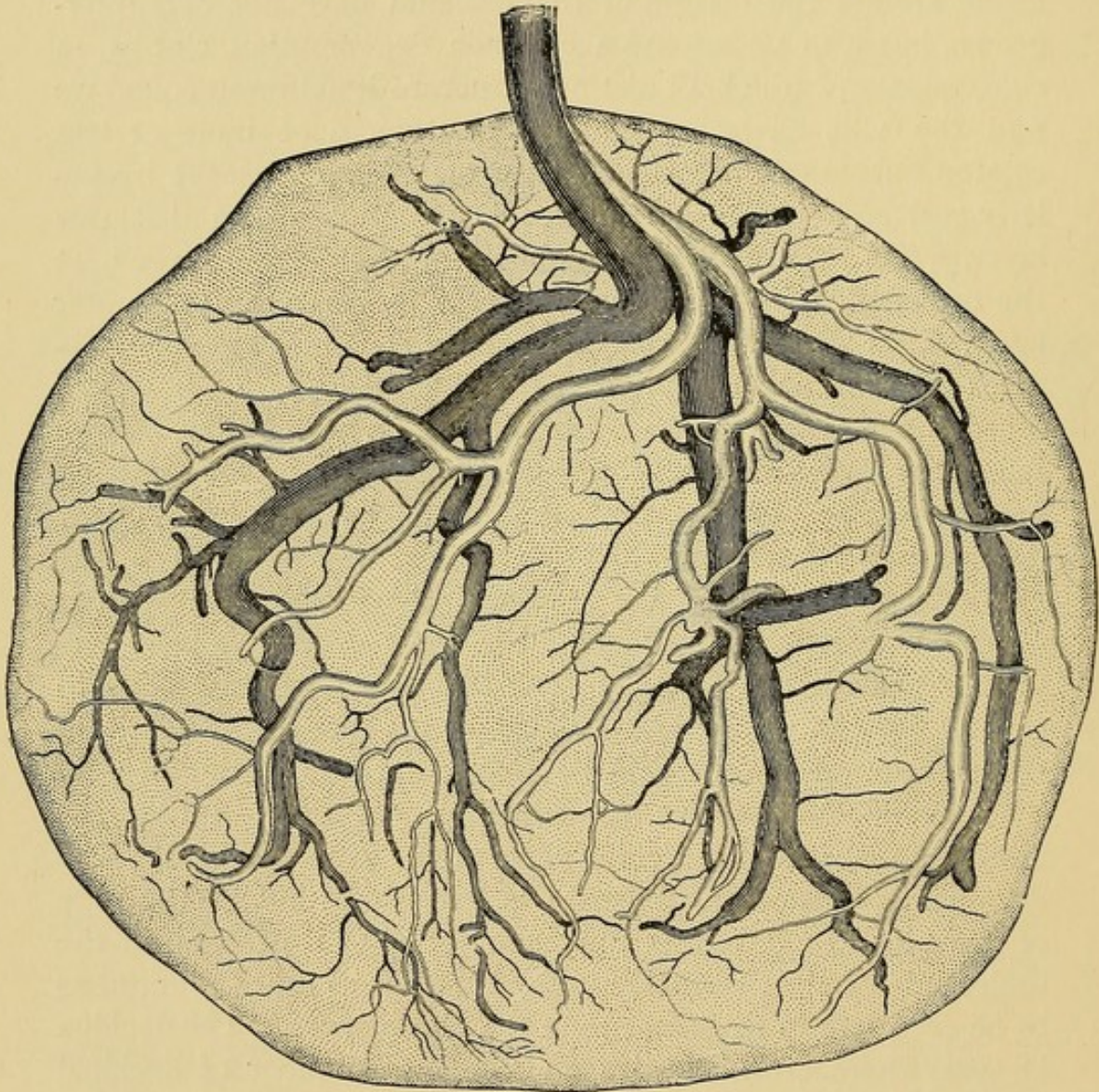
Cut 25. — After-birth at full term; vertical section of the amnion, chorion, and decidua in their natural relations near the placenta. *am*, amnion; *cho*, chorion; *c*, cellular layer or ectoderm; *f*, fibrine and decidual tissue, degenerated; *D'*, decidual tissue.  $\times 125$  diams.

the figure; that is, outside of the placenta, though remnants of the aborted villi, *vi*, are still plainly recognizable; but, as stated previously, they occur only in the immediate neighborhood of the placenta. These villi are surrounded by hyaline matter which resembles and can be followed into continuity with the canalized fibrine layer, *Fib*, covering the surface of the decidua serotina and the fibrine layer of the chorion frondosum. Below the aborted villi, *vi*, of the chorion læve, the fibrine layer is broken down and penetrated by the decidual tissue, so that the demar-

<sup>1</sup> Wood's *Reference Handbook Medical Science*, V., 694, 695.

cation between the foetal and maternal tissues is here lost, and in fact, at the edge of the placenta the decidual cells make their way into the chorionic tissue, and for a certain distance towards the centre of the placenta they are found lying chiefly in the ectoderm. In other placentæ the fibrine layer and the decidual tissue around the margin of the placenta have not only intergrown, but also undergone a common degeneration, Cut 25, in consequence of which all distinct structure is obliterated, and we find the villi, *vi*, imbedded in a stratum, *f*, of more or less colored substance, without definite organization except irregularly scattered nuclei. Attentive examination shows that this layer, *f*, has unmistakable remains, *c*, of the cellular layer next the mesoderm of the chorion, and that it passes into an outer layer, *D'*, in which the traces of decidual structure are unmistakable; the dark line at the lower edge of the decidua, *D'*, is merely detritus and coagulum, as is often found on after-births. If we follow the layers in this, or a similar specimen, in the direction away from the placenta, the layers gradually alter, losing their degenerated character, until we reach a point where the chorionic ectoderm and the uterine decidua both exhibit their normal features. Returning now to the placenta we were previously considering, Cut 24: The placental chorion begins to exhibit its characteristic stratification a short distance within the margin. I have found, however, that the distinctness of that stratification varies considerably, not only in different placentæ, but also in different parts of the same placenta. The decidua, *D*, outside the placenta is very thick, but at the edge of the placenta it begins to thin out, and as it passes over the under side of the placenta, rapidly becomes so much reduced as to be even less in thickness than the chorion, *cho*. The decidua is everywhere crowded with an immense number of decidual cells, but in some other specimens they are less crowded. The surface of the decidua serotina is covered by a layer of fibrine, easily recognized by its deep staining; this coat of degenerated material has not yet received the attention it deserves, as a feature of the human placenta, which is quite constant, so far as my observations go; as stated previously, I consider its origin to be the epithelium of the ends of the villi imbedded in mucosa. Up to the edge of the placenta the chorion læve and decidua are united; at the edge they separate, to make room for the

villi, *Vi, Vi*, of the frondosum. In the angle, *Si*, where the two membranes first separate there are very few villi, so that there is a comparatively clear space left, which is known as the circular sinus. It is not, as some of the older writers have believed, a distinct vessel, nor does it extend as a clear space completely



*Cut 26.* — Placenta at full term, doubly injected by Dr. H. P. Quincy, to show the distribution of blood-vessels upon the surface; the arteries are drawn light; the veins dark.  $\times 0.7$  diams.

around the placenta; but, on the contrary, it is interrupted here and there by an ingrowth of villi. In the cut, the spaces occupied of maternal blood are left white; the foetal blood-vessels are drawn black.

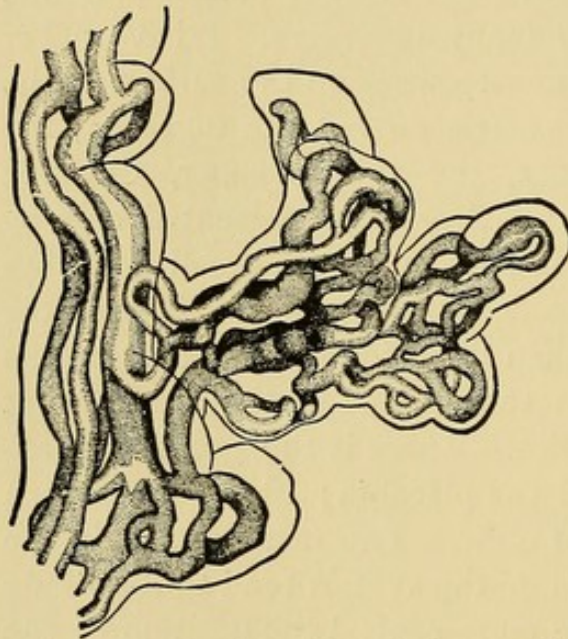
The chorionic circulation is complete in itself. The single vein and the two arteries of the umbilical cord spread out over

the surface of the chorion, marking their course by projecting ridges. The insertion of the cord is always, so far as I have observed, obviously eccentric; the degree of eccentricity varies from a nearly central position to the so-called velamentous insertion,—compare B. S. Schultze, **159**; the degree of eccentricity is easily seen to be related to the distribution of the vessels,—a point not mentioned in current text-books. The arteries come down together from the cord, and are usually connected, but not invariably, by a short transverse vessel, situated about half an inch above the surface of the placenta, and which has been noted by many observers. I have never noticed any arterial or venous anastomoses on the surface of the placenta. The two kinds of vessels do not run together; the arteries lie nearer the surface, the veins deeper, Cut 26; the arteries fork separately until they are represented only by small branches and fine vessels; some of the small branches disappear by dipping down suddenly into the villi below; the veins are considerably larger than the arteries, and some of the larger branches disappear from the surface in the same abrupt manner as do the smaller arteries. There is the greatest possible variability in the vessels of the placenta; I have never seen two placentæ with the vessels alike. The more eccentric the insertion of the cord, the more do the vessels tend to distribute themselves symmetrically; the more central the position of the cord, the less can any vascular symmetry be made out.

The two following paragraphs are copied without change from my article on the placenta (Buck's *Reference Handbook of the Medical Sciences*, V., 696, 697):—

“To follow the course of the foetal blood-vessels within the placenta, the best method is by corrosion injections. These may be made either with fusible metal, wax, or celloidine. The first is specially suited for the study of the large trunks; the latter, for that of the smaller vessels also. I have a very beautiful celloidine injection by Dr. S. J. Mixer, which, with others of wax and metals, has served as the basis of the following description: The veins leave the surface somewhat more abruptly than do the arteries, which gives off more small branches to the surface than do the veins, Cut 26. Both kinds of vessels leave the surface by curving downward for a short distance into the trunk of a villus; the vessels then divide, and their branches

again take a more horizontal course; the branches then curl over downward, and, after a second short descent toward the decidua, again send out horizontal branches. The result of this arrangement is a terrace-like appearance in the course of the vessels; they approach the uterine side of the placenta in this very characteristic manner. The number of terraces is variable; usually there are two or three, but sometimes there is only one, or they may number four or even five. Arrived at the end of its terraces, the main vessel takes a more nearly perpendicular

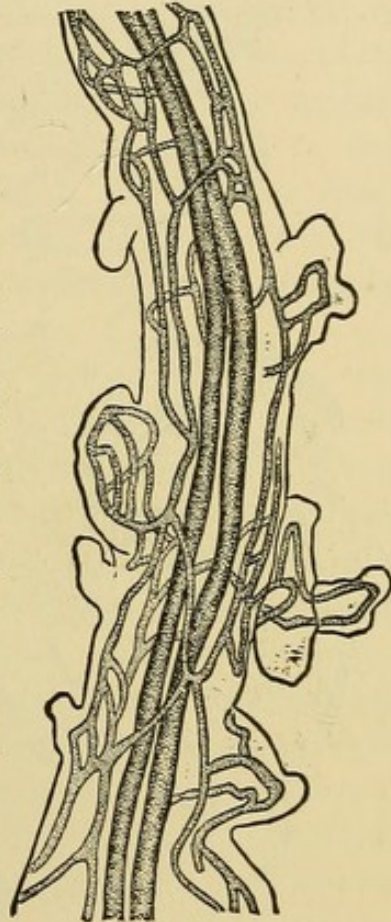


*Cut 27.*—Portion of an injected villus from a placenta of about five months; magnified 210 diams.

course, and rapidly subdivides. Immediately after entering the villi, the arteries and veins give off but few capillaries, but after a short course in the main stalk of the villus, the vessels give rise to many branchlets, and gradually the character of the circulation changes, until in the smallest villous twigs there are capillaries only, *Cut 27*. The vascular trunks have a marked tendency to dichotomous division, which is maintained within the

villi to a certain extent; the arterioles and veinlets in the mature placenta go from their trunks at wide angles for the most part, and subdivide in the same manner, so that they spread out through the whole substance of the placenta. The vessels next the decidua take a more horizontal trend, like the top branches of a wind-swept tree. As the vessels run in the villi, of course the way in which the latter branch out determines the paths of the former; hence by following the distribution of the vessels we inform ourselves as to the ramifications of the villi. Thus the horizontal course of the vessels on the uterine side of the placenta corresponds to the well-known fact that the ends of the villi attached to the uterus become bent and adhere by their sides to the decidual surface."

“The capillaries of the villi are remarkable for their large size, and on this account have been described as arteries or veins by E. H. Weber, Goodsir, and other writers. Their calibre is often sufficient for from four to six blood-disks abreast. They are very variable in diameter, and also peculiar in exhibiting sudden restrictions and dilatations, Cut 27. In the short bud-like branches there is often only a single capillary loop, but as the branch becomes larger, the number of loops increases, and they form anastomoses. In branches large enough to serve as a stem, some one or two of the vessels may be enlarged, as may be seen in Cut 27; in the branches large enough to admit of it, there are two (or sometimes only one) longitudinal central vessels, an artery and vein, and a superficial network of capillaries, Cut 27*a*. Goodsir and other early writers laid great stress on the formation of the capillary loops, but this feature is a common one in the development of the foetal vascular system, as is also the width of the capillaries. In my opinion these peculiarities are characteristic rather of the foetus than specifically of the placenta. In some of the older writers (Goodsir, Farre, *et al.*) it is asserted that the true capillary system disappears toward the end of gestation. I am unable to confirm this, but find instead that in the slender terminal villi of the placenta at term there is often only a single, sometimes long, capillary loop; the capillary is very wide, and its width is probably the reason of its having been held formerly to be a vein or an artery.”

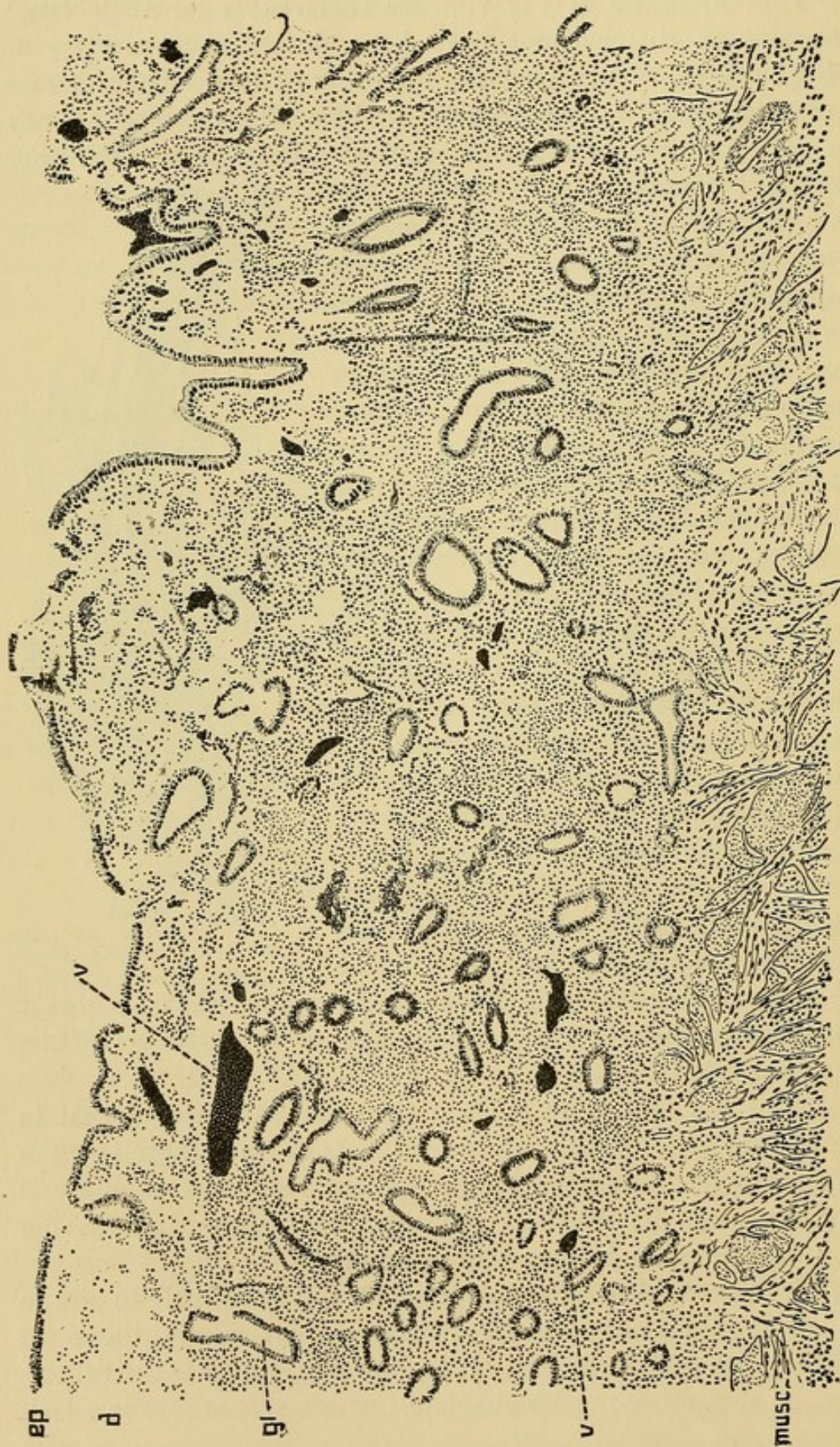


Cut 27*a*. Placenta of about five months; portion of a small villus, to show the central vessels and superficial capillaries.  $\times 105$  diams.

§ 16. **Uterus during menstruation.** — I have little to add to the descriptions of previous authors, particularly those of Leopold, 36, and Kölliker.<sup>1</sup> It is, however, worth while to present the accompanying illustration, Cut 28, since there is a lack

<sup>1</sup> Kölliker's *Handbuch der Gewebelehre*, 5te Aufl., p. 563.





*Cut 28.* — Mucous membrane of a virgin uterus during the first day of menstruation. *ep*, epithelium; *d*, disintegrated layer; *v*, *v*, blood-vessels; *musc.*, muscularis.  $\times 65$  diams.

of figures. The cut represents a transverse section of the *corpus uteri* of a fine specimen, for which I am indebted to Dr. W. W. Gannett. The woman died from acute miliary tuberculosis; the autopsy was made almost immediately after death, and within four hours from death the complete genitalia were placed in Müller's fluid, the uterus having been first carefully opened by a single median ventral incision. Death is said to have occurred on the day of the regular period. The hymen was intact. There was no sign of pathological change in any of the genitalia. In one ovary, the right, there was a fresh *corpus hæmorrhagicum*. These data afford a sufficient basis for the belief that the uterus was well preserved in a perfectly normal condition.

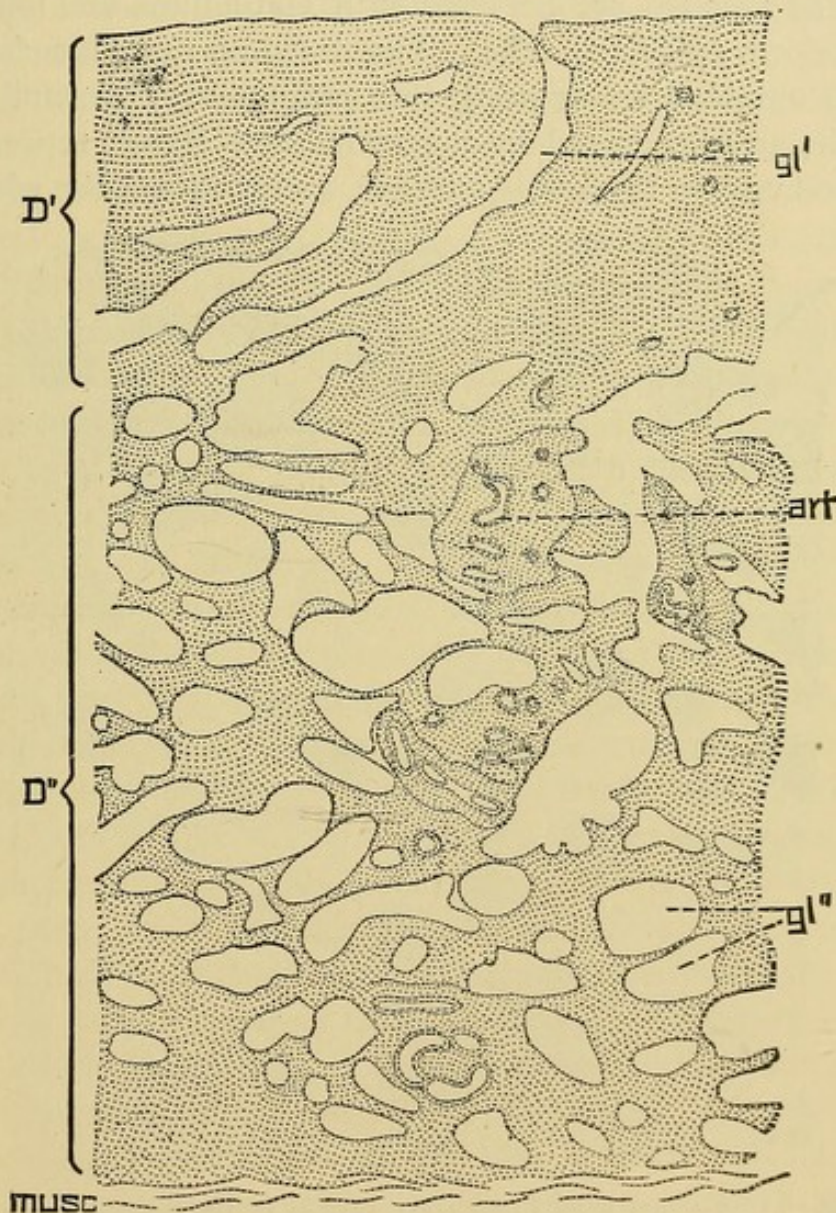
The mucous membrane is from 1.1–1.3 mm. thick; its surface is irregularly tumefied; the gland openings lie for the most part in the depressions. In the cavity of the uterus there was a small blood-clot. The mucosa is sharply limited against the muscularis, Cut 28. In transverse sections one sees that the upper fourth of the mucosa is very much broken down and disintegrated, Cut 28, *d*; the cells stain less than those of the deep portions of the membrane; as represented in the cut the tissue is divided into numerous more or less separate small masses; some of the blood-vessels appear torn through, but it is difficult to make sure observation: Overlach, 39, considers it probable that the infiltration of blood takes place by diapedesis, not by rupture of the capillaries. The superficial epithelium, *ep*, is loosened everywhere; in places fragments of it have fallen off, and in some parts it is gone altogether; it stains readily with cochineal and its nuclei color well, the epithelium differing in this respect from the underlying connective tissue, which does not stain well; the blood-vessels in the disintegrated layer are for the most part small.

The deeper layer of the mucosa is dense with crowded well-stained cells, which lie in groups separated by clearer lines; in the cut this grouping shows less plainly than in the preparation; the lighter channels are perhaps lymph-vessels, a suggestion which occurs to me, because in so-called "moulds" one sometimes finds similar channels crowded with leucocytes. The cells appear to be the proliferated interglandular tissue; there are very few leucocytes, so far as I can distinguish; the cells have

small, oval, or elongated, darkly stained nuclei, with a very small granular protoplasmatic body each; there is certainly no noticeable enlargement of the cells, but only a remarkable multiplication. The point is important; I see nothing to suggest the presence of decidual cells, nothing even like definite enlargement of any of the cells. The image of the tissue is comparable to that of the connective tissue of the rabbit's placenta at six days, except that there the cells are widely separated, here closely crowded, but in each case the cells are small, with little protoplasm, and connected by their processes. In another specimen in my possession of a normal uterus at the close of menstruation, the condition of the mucous membrane agrees with that of the specimen we have considered, except, of course, that the disintegrated superficial layer is lost, and that the superficial layers stain poorly. In this second specimen, also, the interglandular cells are small and very crowded; there are few leucocytes and no decidual cells. The two specimens further agree in having the glands distended and contorted; each gland is surrounded by a distinct basement membrane or layer of connective tissue cells closely investing the epithelium, as has been observed by Leopold, **36**. In my article on the decidua in the *Reference Handbook*, II., p. 390, is a summary of the changes occurring during menstruation, and stress is there laid upon two points emphasized by previous writers; namely, the increase in the number of leucocytes and the presence of decidual cells. Since my own observations have failed to confirm these statements, I can no longer accept them. The proliferated connective tissue cells are those, probably, which become decidual cells when the *decidua menstrualis* is changed into the *decidua graviditatis*—compare the account of the one month's uterus in the next section.

§ 17. **Uterus one month pregnant.**—The specimen to be described came from a woman who committed suicide by violence, not by poison, and I was informed that she was known to be about one month pregnant. Further information was not obtained, and I was requested not to seek it. The specimen was received in very fresh condition, but it had been opened, the reflexa was torn and pretty much gone; the embryo had been removed, and I was therefore unable to verify the age, or investigate the attachment of the villi of the chorion to the

uterus. There was a beautiful *corpus luteum* in one ovary, quite similar to that figured by Dalton in his Report on the *corpus luteum* in the transactions of the American Gynæcological Society for 1877, Fig. 9. The surface of the uterus seemed uninjured. The specimen was hardened in Müller's fluid, and found subsequently to be well preserved. It may be considered, I think, perfectly normal.



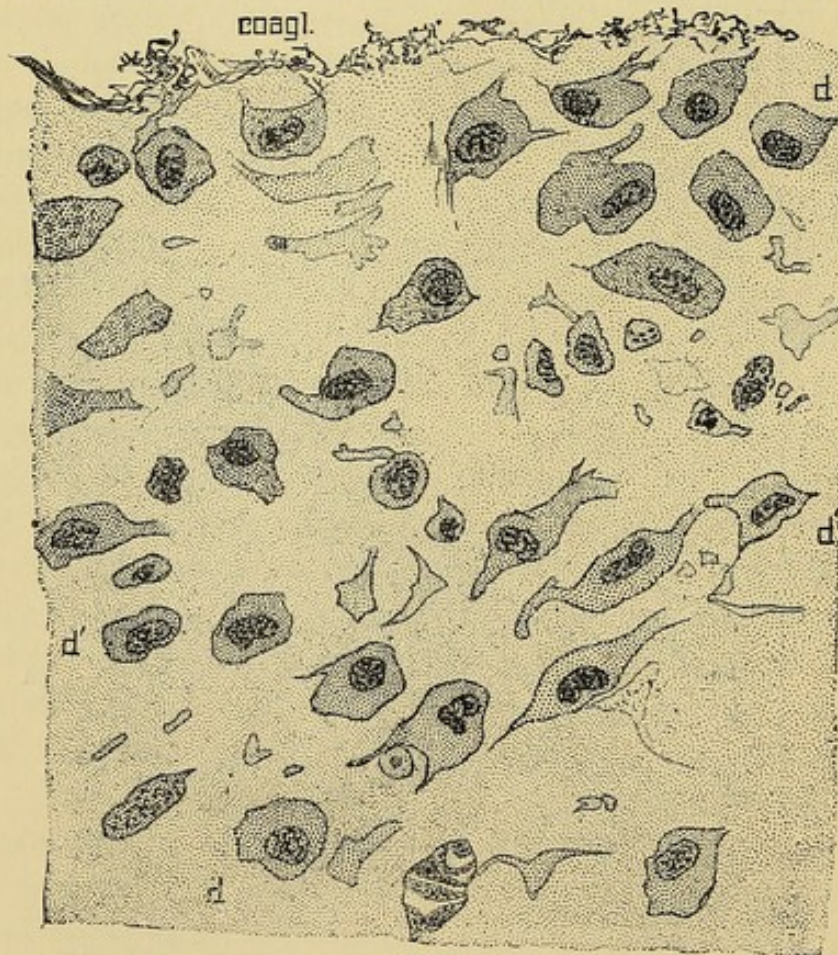
*Cut 29.* — Uterus one month pregnant; outlines of the glands from a vertical section: to show the division of the mucosa into an upper compact layer, *D'*, and a lower cavernous layer, *D''*; *gl'*, *gl''*, glands; *art*, spiral artery; *musc*, muscularis.

My specimen enables me to confirm in most respects Turner's accurate description of two uteri of about the same age, 146, 546-548. The inner surface shows the hillocks (*Inseln*) de-

scribed by Reichert in the uterus of two weeks, studied by him, which have been figured by Coste in slightly older specimens, and found by Turner also, **146**, 540.

The three illustrations given herewith are all from sections through what I suppose to be the placental region.

There is an upper compact layer, Cut 29, *D'*, and a lower cavernous layer, *D''*; the caverns, being gland cavities, which appear as rounded areolæ lined with epithelium, are filled with broken-down epithelial cells. The drawing, reproduced in Cut 29, was obtained by drawing the outlines very carefully, stippling the areas occupied by the connective tissue, representing the blood-vessels by double outlines, and omitting the glandular



*Cut 30.* — Uterus one month pregnant; portion of the compact layer of the decidua seen in vertical section; *coagl*, coagulum upon the surface; *d*, *d'*, decidual cells.  $\times 445$  diams.

epithelium altogether. It will be noticed that about three-fourths of the diameter of the mucosa is occupied by the cavernous layer, *D''*.

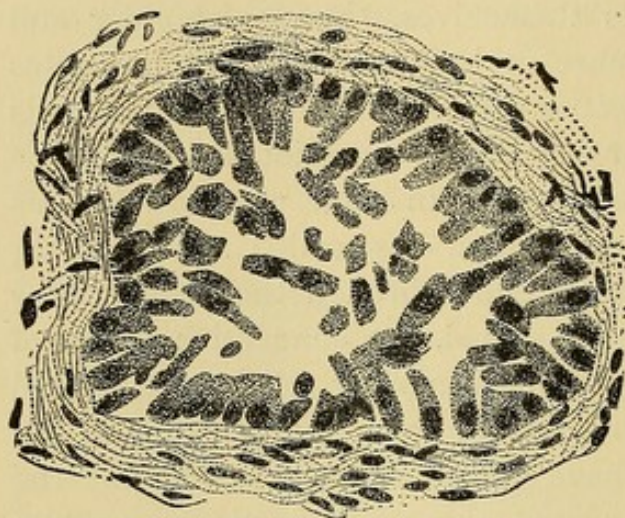
The upper or compact layer is shown in Cut 30. The surface

is without any trace of epithelium, but is covered only by a thin fibrous and granular coagulum, *coagl*; the tissue itself consists almost exclusively of young decidual cells, *d*, *d'*, with a clear homogeneous matrix; here and there are leucocytes, but they are nowhere numerous; the decidual cells are all quite large, with their bodies deeply stained by the eosine; the nuclei are round, oval, or slightly irregular in shape, coarsely granular, and sharp in outline; the cells themselves, though irregular and variable in shape, are all more or less rounded with processes running off in various directions; scattered between the cells are many sections of their processes; occasionally it can be seen that two cells are connected; in fact, we have in this tissue evidently a modified embryonic or so-called anastomosing connective tissue. Now, as we know through the observations of Leopold, **36**, which I have verified, the connective tissue of the uterine mucosa consists of anastomosing cells, and as stated in the previous section, the cells are found proliferated in the menstruating uterus; we have therefore only to imagine the cells enlarged with certain accompanying modifications, to obtain the tissue figured in Cut 30. There is no special formation of cells around the blood-vessels, where, according to Ercolani, the decidual tissue arises by new formation. In Turner's specimens the upper part of the compact layer was imperfectly preserved, but according to his description there appears to have been a coagulum similar to that which I have found, but thicker. In the deep part of the layer the cells are less enlarged, and when the cavernous layer is reached, there occurs a rapid transition in the character of the cells, which become smaller and more fusiform, and their nuclei more elongate, smaller, and deeper stained by alum-cochineal. The gland openings upon the surface of the uterus lead into tubes, Cut 30, *g''*, which run slightly obliquely through the compact layer, taking a more or less nearly straight course and joining the contorted gland tubes, Cut 30, *g'''*, of the cavernous layer. The gland ducts are completely devoid of lining epithelium, which has disappeared except for a very few loose cells, occasionally found lying free in the ducts; the cells have not fallen out from the sections, but were lost before the tissue was imbedded.<sup>1</sup> The ducts then

<sup>1</sup> The blocks to be cut were stained *in toto* with alum-cochineal and eosine, imbedded in paraffine, etc. The sections were fastened on the slide with celloidine, to keep the parts in place.

are wide tubes running nearly straight through the upper part of the decidua and bounded directly by the decidual tissue; they communicate below with a contorted cavity. Similar tubes appear in later stages and have been described as blood-vessels — see the next section.

The cavernous layer contains numerous spaces, the areolæ of Turner, **146**, **547**, who was uncertain as to their character,

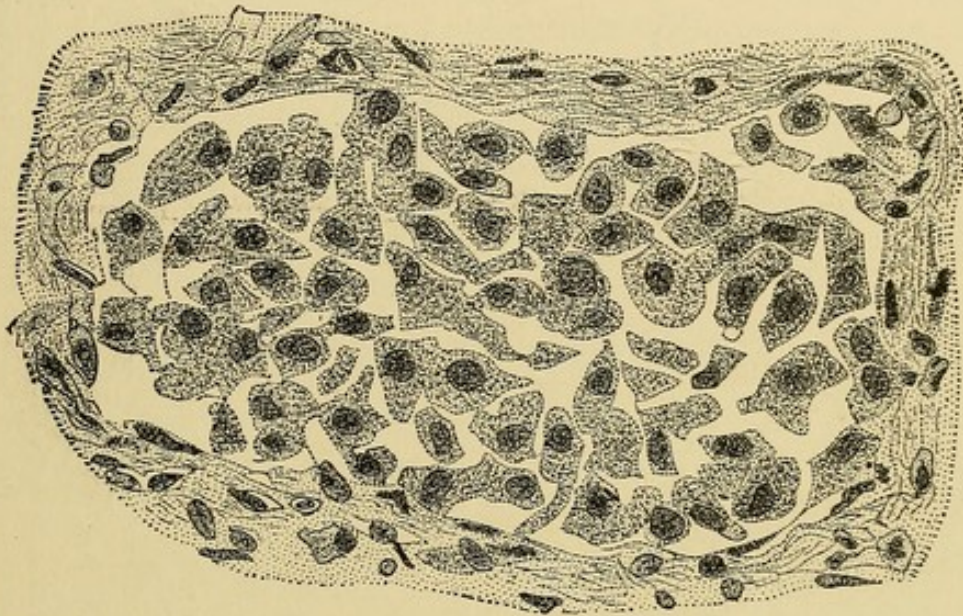


*Cut 31.* — Uterus one month pregnant; section of gland from cavernous layer, with the epithelium partly adherent to the walls.  $\times 445$  diams.

though he ascertained that many of them belonged to the glandular system. In my specimen it is perfectly clear that all the larger areolæ belong to the glands, which must be extremely distorted and distended to give the shapes shown in *Cut 29*. The thin dissepiments between the areolæ are composed of connective tissue, the long dark nuclei of which,

*Cut 31*, are strikingly different from those of the cells of the compact layer, *Cut 30*. The areolæ present two extreme modifications and all intermediate phases between these two. The smaller areolæ are lined by a well-preserved cylinder epithelium, or by one in which the cells are separated by small fissures; in other areolæ the cells are a little larger, *Cut 31*, each for the most part cleft from its fellows, and some of them loosened from the wall and lying free in the cavity. The other extreme is represented in *Cut 32*; the size of the areolæ is much increased, — compare *Cuts 31* and *32*, — both drawn on the same scale; the epithelium is entirely loosened from the wall, and the cells lie separately in the cavity which they fill; the cells are greatly enlarged, their bodies having three or four times the diameter of the cells in the small areolæ; they have not the cylinder shape, but are irregular in outline: their protoplasm is finely granular and stains rather lightly; the nuclei are large, rounded, glandular, and with sharp outlines; they are less darkly stained than the nuclei of the epithelium of *Cut 31*.

The obvious interpretation of the appearances described is, that the glandular epithelium is breaking down, that it is lost altogether from the ducts, but is still present in the deep portions of the glands; in breaking down the cells separate from



*Cut 32.* — Uterus one month pregnant; section of gland from cavernous layer, with the epithelium loosened from the walls;  $\times 445$  diams.

one another, and then from the wall, and falling into the gland cavity, there enlarge, the cavity enlarging also. Similar appearances are also found in “moulds” of the second month; very likely they have been often observed and mistaken for pathological changes.

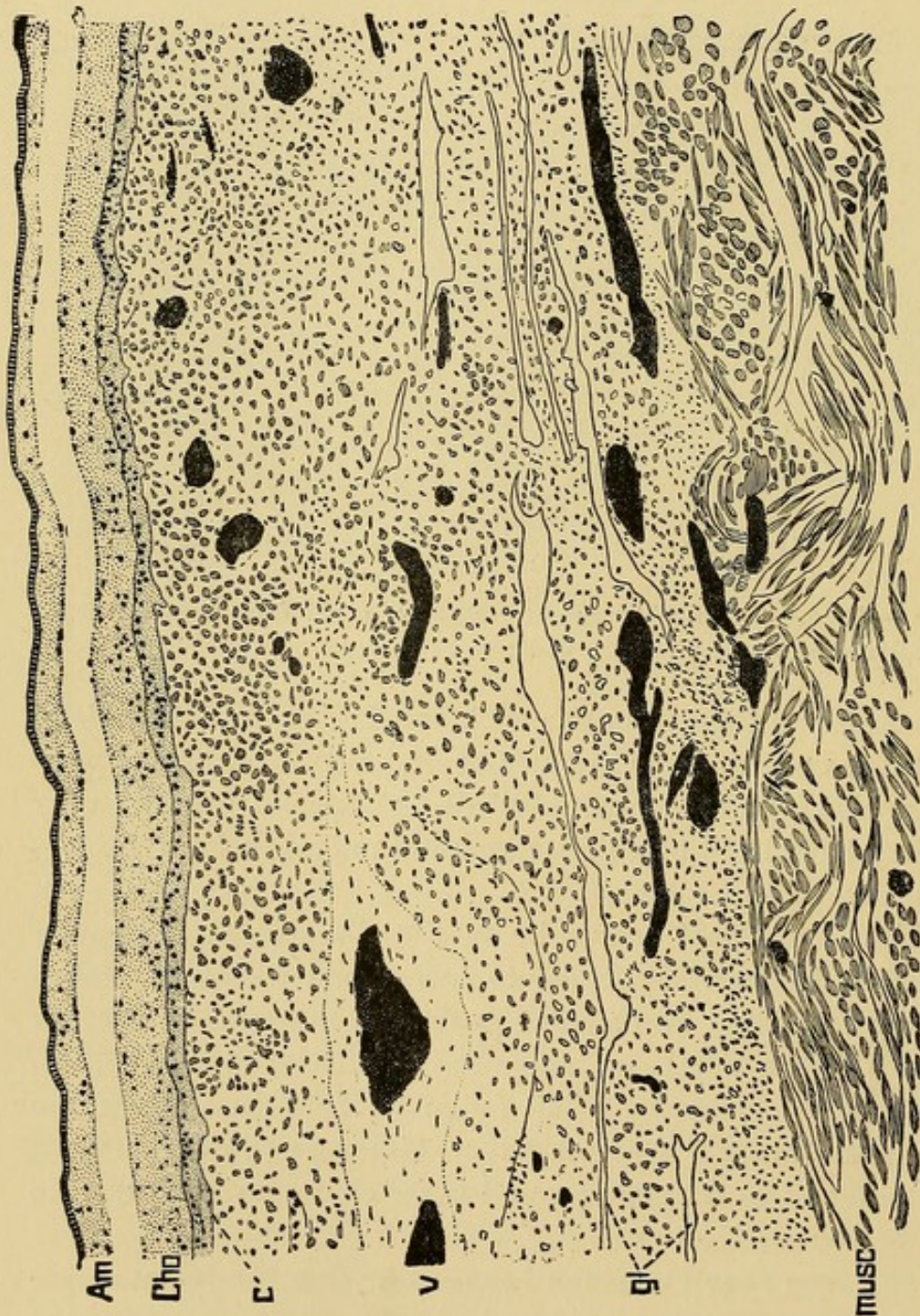
The blood-vessels of course lie in the dissepiments between the glands. I observed nothing to correspond with the “colossal capillaries dilated into small sinuses,” mentioned by Turner **146**, 548. Were not these supposed capillaries gland cavities, from which the epithelium had fallen out? Occasionally the sections pass through a spiral artery, *Cut 29, art*, which is cut again and again as it twists around in its characteristic separate column of connective tissue.

§ 18. **Uterus seven months pregnant, with the foetal membranes in place.** — The specimen to be described was obtained for me through the kindness of Dr. W. W. Gannett. It is an apparently normal uterus, which contained a normal embryo weighing 1150 grammes and having an umbilical cord 58 centimetres long, — probably about seven months old, or a little



more: there were no data as to the duration of gestation. The uterus was opened, and preserved in Müller's fluid without disturbing the membranes.

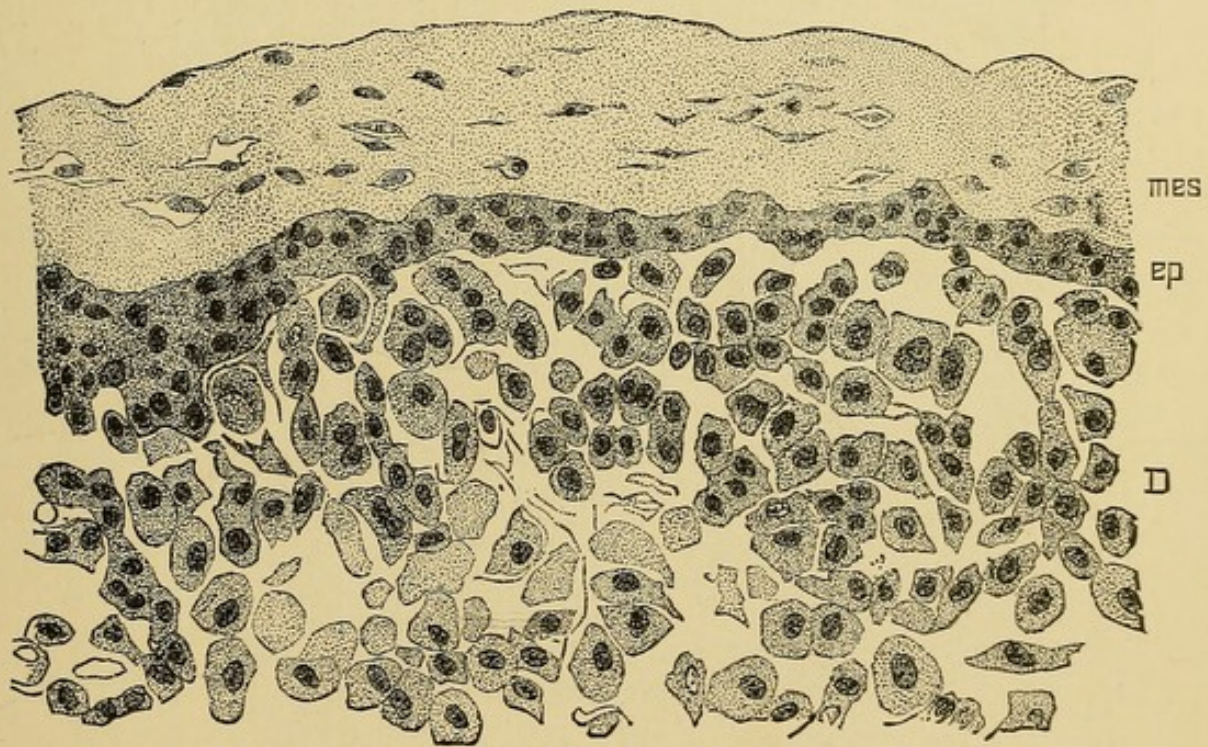
A section through the amnion, chorion læve, and uterine



Cut 33. — Uterus about seven months pregnant; vertical section through the decidua vera, with the chorion læve and amnion *in situ*. *Am*, amnion; *Cho*, chorion; *c*, epithelium (cellular layer of chorion); *v*, blood-vessel; *gl*, spaces supposed to be gland cavities; *musc*, muscularis: the blood-vessels are represented dark.  $\times 40$  diams.

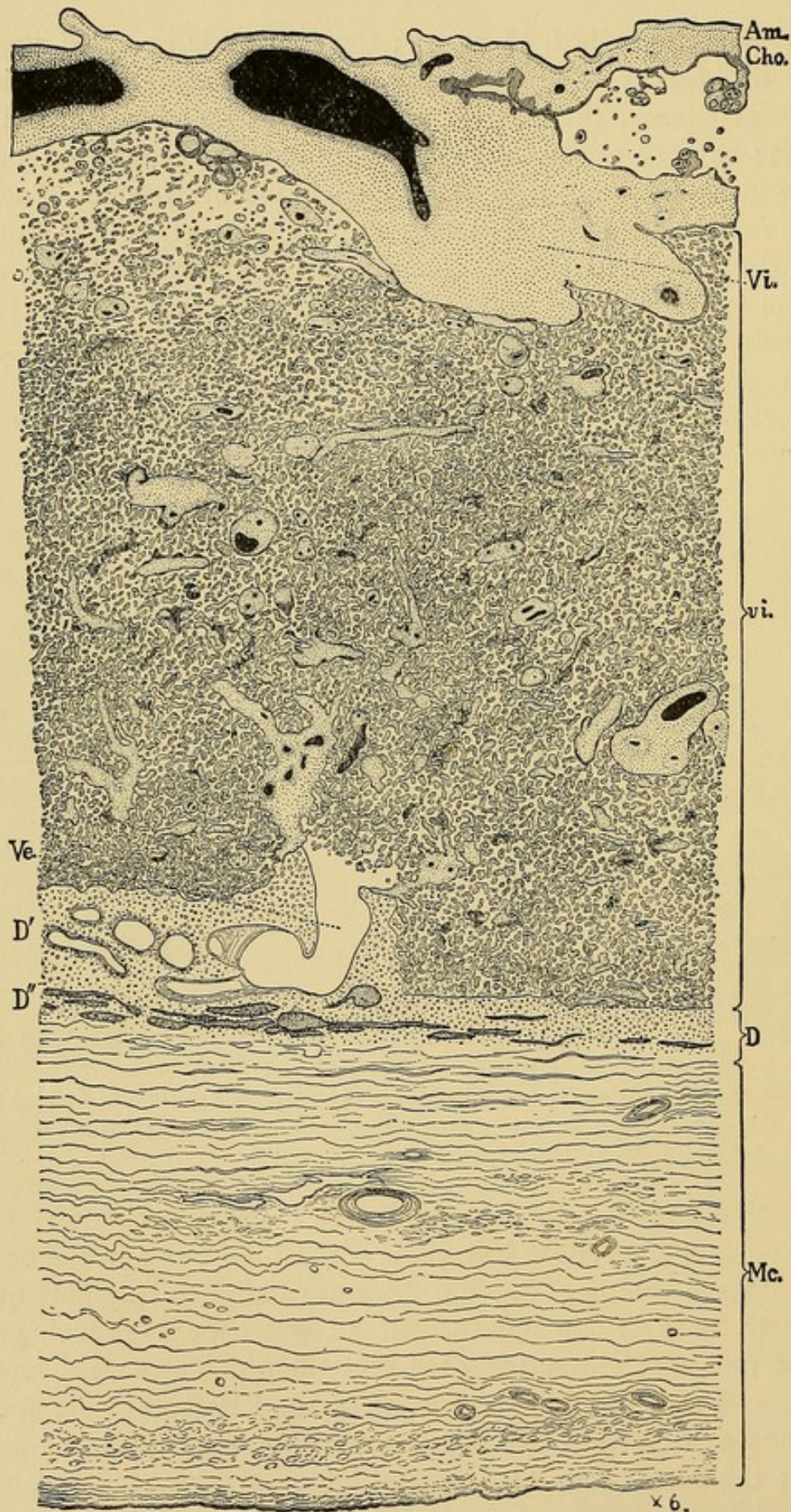
mucosa, stained with hæmatoxyline, and viewed with a low power, is represented in Cut 33; the dark spots are maternal blood-vessels, which have been shaded for the sake of clearness. The amnion, *am*, and chorion, *cho*, present the characteristics

previously described, §§ 14, 15; the chorion is bounded against the decidua by an epithelium *c*, which I interpret as the chorionic ectoderm; there is no trace of a second layer of epithelium; so that the uterine epithelium must be considered lost, a conclusion agreeing with the observations of Kölliker, Turner, and myself upon earlier stages, and the statements of Ercolani. The decidua has eight or nine times the thickness of the chorion; it has an upper compact and a lower cavernous layer; the former contains numerous decidual cells, most of which are a little larger than those nearer the muscularis; the compact layer contains a few blood-vessels of moderate calibre, and occa-



*Cut 34.*—Uterus about seven months pregnant; upper portion of decidua vera, with the chorion *laeve in situ*. *mes*, mesodermic layer of chorion; *ep*, epithelial layer of chorion; *D'*, decidua.  $\times 340$  diams.

sionally a large vessel, *v*, surrounded by connective tissue containing no decidual cells. Examined with a higher power, the decidual cells—compare *Cut 34, D'*—are found to resemble quite closely those at one month, *Cut 30*, but they are much more numerous and closer together, and their processes are fewer; they vary also more in size; some of the larger ones are multinucleate; it is probable that the cells are multiplying by division; the matrix presents a fibrous look, but whether it contains actual fibres, I am not sure; between the decidual cells are a



*Cut 35.*— Section through a normal placenta of seven months, *in situ*. *Am*, amnion; *Cho*, chorion; *Vi*, villus trunk; *vi*, sections of villi in the substance of the placenta; *D*, decidua; *Mc*, muscularis; *D'*, compact layer of decidua; *Ve*, uterine blood-vessel (or gland?) opening into the placenta. The foetal blood-vessels are drawn black; the maternal blood spaces are left white; the chorionic tissue is stippled, except the canalized fibrine, which is shaded by lines; the remnants of the gland cavities in *D''* are stippled dark. (Drawn from nature by J. H. Emerton.)

certain number of nuclei, some of which belong to leucocytes, others to blood capillaries, and still others, which I am uncertain about, which are few in number, and possibly belong to connective tissue corpuscles. The cavernous layer resembles now, in contrast to the first month, the upper layer of the decidua in histological constitution, but the decidual cells are smaller and at little wider intervals from one another; the cavernous layer is especially characterized by the slit-like spaces in it; some of these spaces, as indicated by the drawing, Cut 33, are undoubtedly blood-vessels or sinuses, but still others contain no blood, or at most three or four isolated corpuscles, although close to them are capillaries gorged with blood; once in a while a few epithelioid cells can be seen adhering to the walls of the spaces. These spaces can hardly be assigned to the vascular system; they have been held by Kundrat and Engelmann, **180**, and various subsequent writers, to be the gland cavities; we have not sufficient observations to establish the actual metamorphosis of the areolæ of the one month's uterus into the slits, *gl*, of Cuts 33 and 35, *D'*, but there is no ground to question the occurrence of the change, which appears to be a necessary consequence of the stretching of the decidua due to the expansion of the uterus during pregnancy.

A complete section through the placenta *in situ* and uterus is represented in Cut 35, which has already appeared in my article, "Placenta" (Buck's *Handbook*, V., 696), and been sufficiently described. The chorion is separated by a dense forest of villi from the decidua, *D*; the ends of some of the villi touch and are imbedded in the decidual tissue; these imbedded ends are without epithelium, but their connective tissue is immediately surrounded by hyaline substance. The decidua is plainly divided into two strata — *cf. infra*. The section passes through a wide tube, *Ve*, which opens directly into the interior of the placenta and contains blood; in my article, *l.c.*, this opening is referred to as that of a vein, the identification being in accordance with my understanding of the descriptions of Waldeyer,<sup>1</sup> **149**. Professor Langhans has since informed me, that according to his own observations the opening of the arteries are characterized by the absence of villi projecting into their openings.

<sup>1</sup> I am under much obligation to Professor Waldeyer for an opportunity to examine some of the injected specimens upon which his very important researches were conducted.

His pupil, Raissa Nitabuch, has since published a dissertation, **117**, confirming this opinion, according to which the vessel shown in Cut 35, *Ve*, is not venous, but arterial. Another possibility has occurred to me, viz.: that it is a gland duct; in fact, it resembles very closely the undoubted gland ducts of the one month's decidua: there is no reason apparent why the gland ducts, which pass nearly vertically through the compact layer, should be obliterated; on the contrary, one might expect to find them widened by the stretching of the uterus; as there is



*Cut 36.* — Uterus of seven months, vertical section of the decidua serotina from near the margin of the placenta. *mc*, muscularis; *D'*, *D''*, decidua serotina; *D'*, cavernous or spongy layer; *D''*, compact layer; *Vi*, scattered chorionic villi. The intervillous spaces were filled with blood, which is not represented in the figure,  $\times 50$  diams.

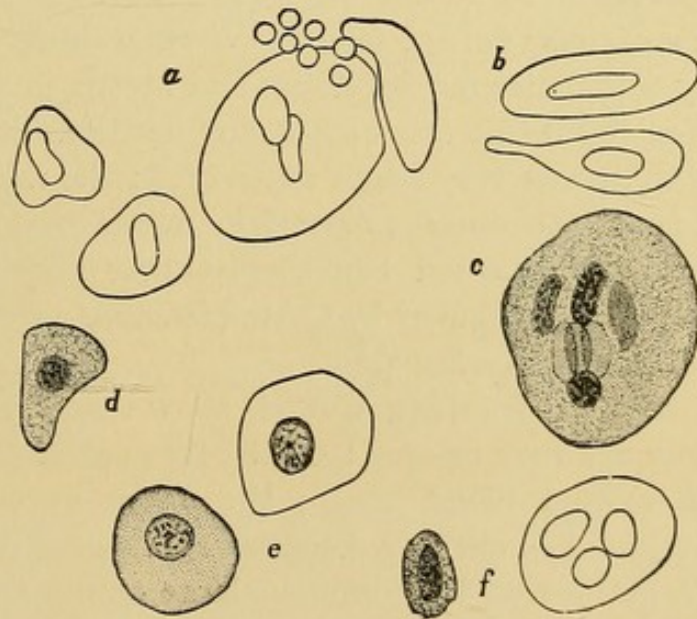
blood in the intervillous spaces, it could easily make its way into the distended glands, and its presence there would not prove the glands to be blood-vessels. While, therefore, I accept Waldeyer's researches, **149**, as well as those of Langhans and Nitabuch, **117**, as verifying Farre's neglected account, **172**, 722, of the placental circulation, I venture to express a note of caution as to the danger of mistaking glandular for vascular openings.

The following additional points deserve notice: The serotina is about 1.5 mm. thick, and contains an enormous number of decidual cells, Cut 36. The cavernous, *D'*, and compact layers, *D''*, are very clearly separated; the mucosa is sharply marked off from the muscularis, *mc*, although scattered decidual cells have penetrated between the muscular fibres. The muscularis is about 10 mm. thick, and is characterized by the presence of quite large and numerous venous thrombi, especially in the part towards the decidua. The decidua contains few blood-vessels. Upon the surface of the decidua can be distinguished a special layer of mingled hyaline and decidual tissue, which in many places is interrupted by the ends of the chorionic villi, as is well shown in Cut 36. The supposed gland cavities of the spongy layer, *D'*, are long and slit-like; they are filled for the most part with fine granular matter, which colors light blue with hæmatoxyline; they also contain a little blood, sometimes a few decidual cells.

I have seen in them also a few oval bodies several times larger than any of the decidual cells, and presenting a vacuolated appearance; what these bodies are, I have not ascertained. In places the glandular epithelium is distinct; its cells vary greatly in appearance, neighboring cells being often quite dissimilar; nearly all are

cuboidal, but some are flattened out; of the former there are some with darkly stained nuclei, but the majority of the cells are enlarged, with greatly enlarged hyaline, very refringent nuclei.

The decidual cells are smaller and more crowded in the cavernous layer, and mostly larger in the compact layer — compare



Cut 37. — Decidual cells from the section represented in part in Cut 36. *a, b, d, f*, various forms of cells from serotina; *c*, giant cell from the margin of the placenta; *e*, clear cells from chorion; at *a*, seven blood globules have been drawn in to scale.  $\times 545$  diams.

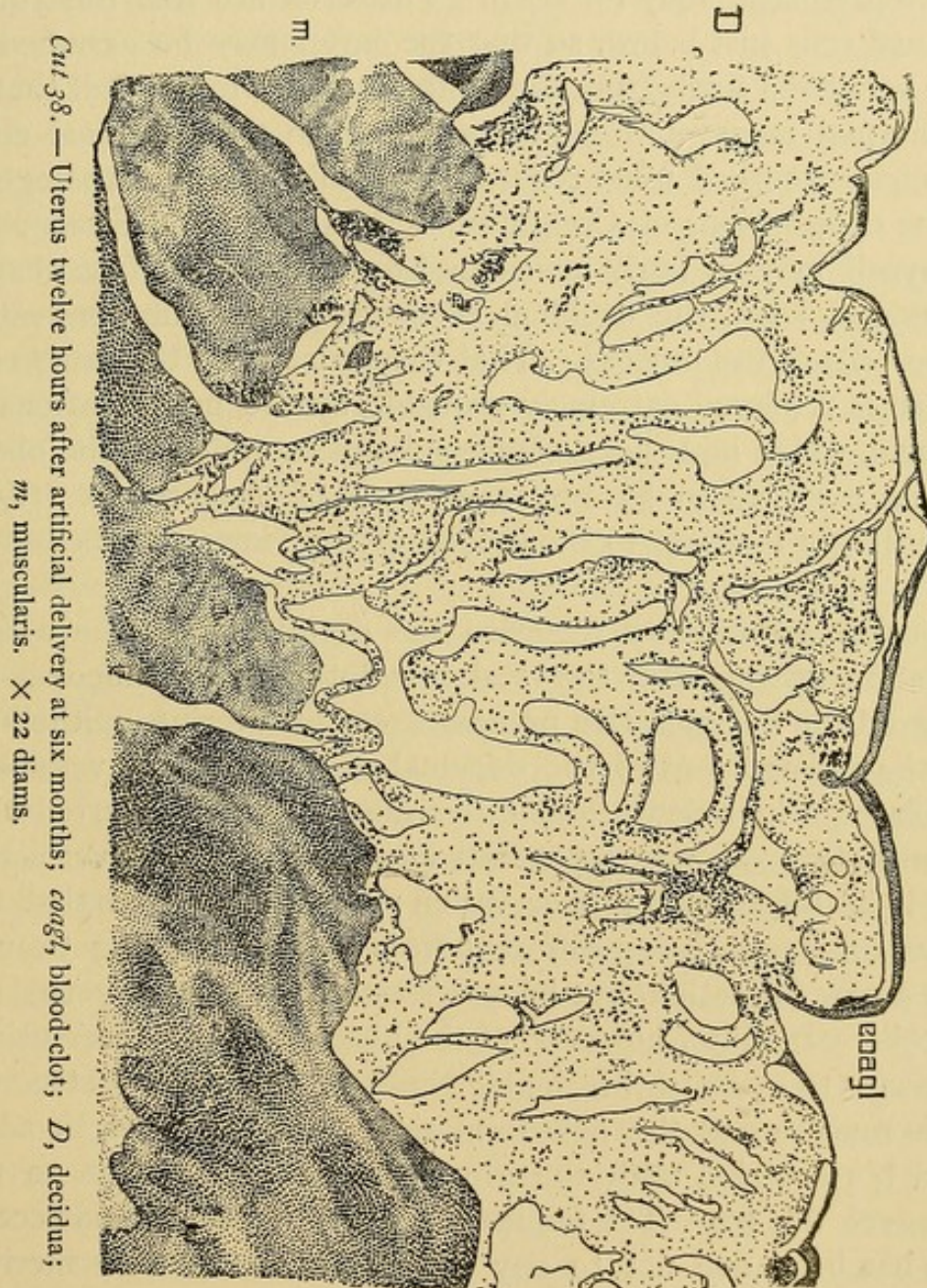
Cut 36. The largest cells are scattered through the compact layer, but are most numerous towards the surface. The decidua cells exhibit great variety in their features, Cut 37; they are nearly all oval disks, so that their outlines vary according as they happen to lie in the tissue; they vary greatly in size; the larger they are, the more nuclei they contain; but I observe no cells with more than ten nuclei. The nuclei are usually more or less elongated; the contents of the cells granular. Some of the cells present another type; these are more nearly round, clear, and transparent, *e*; the nucleus is round, stained lightly, and contains relatively few and small granules; such cells are most numerous about the placental margin.<sup>1</sup>

§ 19. **Uterus twelve hours after abortion at six months.** — For this specimen, also, I am indebted to Dr. W. W. Gannett. The woman was brought into the Boston City Hospital in a comatose condition; the fœtus, estimated to be about six months, was removed by the forceps; the mother died twelve hours later; the autopsy by Dr. Gannett showed death to have been caused by tubercular meningitis. The uterus is apparently normal; I received it in a fresh state, and hardened it in Müller's fluid. It was already very much contracted; the mucosa measured about 2 mm. in thickness; its surface was ragged and more or less covered with clotted blood, presenting very much the appearance so superbly figured by Coste (*Développement des Corps organisés*, Pl. X., *Éspèce humaine*).

Vertical sections, Cut 38, show that the surfaces of the mucosa are very uneven; on the free surface there is a thin layer of clotted blood, *coagl*; the upper or compact layer of the decidua has entirely disappeared, leaving only the deep portion, *D*, permeated by numerous large empty spaces, which I take to be in part gland cavities, in part blood sinuses, both changed from their slit-like form by the contraction of the uterus during and since the delivery of the child. Between the spaces are the brownish and hyaline cells, and a great many blood-corpuscles, which lie throughout the tissue itself as well as in the blood-vessels. In short, the conditions found agree with those described by Leopold as present in the uterus a short time after normal delivery at full term, **36**, and accordingly, further details concerning my specimen may be omitted.

<sup>1</sup>This and the preceding paragraph are taken with sundry alterations from my article on the placenta, *l.s.c.*

§ 20. **Origin of decidual cells.** — Besides the erroneous hypothesis of Ercolani, there are three views as to the origin of the decidual cells known to me, to wit: 1°, they are modified leucocytes (Hennig, Langhans, *et al*); 2°, they arise from the connective tissue cells of the mucosa (Leopold, **36**); 3°, they



*Cut 38.* — Uterus twelve hours after artificial delivery at six months; *coagl*, blood-clot; *D*, decidua; *m*, muscularis. X 22 diams.

are produced by the epithelium (Overlach, **39**). The first view is not supported by observation, even by its advocates, and may be dismissed. Overlach's observations certainly favor the third view, but inasmuch as he has studied only *one* uterus with pseudo-menstruation from acute phosphorus poisoning, his the-



ory cannot be accepted definitely until verified by further observations on normal uteri. Overlach found in the cervix of the uterus in question, the lining epithelial cells to contain an endogenous brood of small cells, one to fifteen in each parent-cell; the daughter-cells begin as nuclei, around which there gathers a protoplasmatic body for each. The cells are like the young decidual cells just below, so that the latter may be assumed to have wandered forth from the epithelium. I may recall that in the normal menstruating uterus I find no true decidual cells, and consequently I must regard Overlach's find as pathological.

The observations of Creighton, of Masquelin and Swaen, and of myself may be fairly considered to establish the fact that in rodents, at least, the decidual cells arise from the connective tissue cells of the mucosa. That they arise from the same cells in man is rendered extremely probable by the investigations of Leopold, which have been confirmed and extended by the observations recorded in §§ 16, 17, and 18, of the present article. Accordingly I assent to the second of the views above enumerated.

Ercolani erroneously regarded the decidual tissue as a new formation, arising after the total destruction of the mucosa. He observed the degenerative processes of the uterine epithelium, and the arrangement of the decidual cells around the vessels of the placenta in rodents and other mammals; he inferred that the whole mucosa was degenerated and lost, but he never established the inference by observation; he also inferred that the perivascular cells, being different from the surrounding tissues, were a new formation, but he never traced the actual genesis of the cells. In spite, however, of the absence of the observations necessary to establish his double thesis of the total destruction of the mucosa and the new formation of the decidua, he advocated his doctrine with the greatest earnestness, even to the last—see **91, 92**. The failure of his hypothesis to find acceptance has been due not to any unreadiness to bestow merited acknowledgment upon his researches, but to the incompatibility of the hypothesis itself with the ascertained facts of the structure and development of the placenta. While, therefore, we utilize Ercolani's numerous and valuable observations, it will be a distinct gain for science to set aside his theory of the new formation of the decidua.

§ 21. **General considerations.** — We are now in a position to compare the changes in the uterus during menstruation and gestation. In both cases the processes begin with tumefaction and hyperæmia of the mucosa; they continue with hyperplasia of the connective tissue (the decidua cells being regarded as modified connective tissue corpuscles) and with hypertrophy, accompanied by distention and contortion of the glands; they both close with casting off the superficial layers of the mucosa, after which follows the regeneration of the membrane. The essential steps, then, are the same in both cases. The difference is, that during the long life of the *decidua graviditatis*, changes supervene in the tissues which do not take place during the rapid menstrual cycle; the mucosa of gestation is distinguished by the loss of both its surface and glandular epithelium, and by the enlargement of its connective tissue cells into so-called decidua cells. We must accordingly view the changes in the uterus during gestation as a prolonged and modified menstrual cycle. The relation in time between menstruation and the commencement of pregnancy is attributable to the menstrual process rendering the uterus receptive; that is to say, capable of receiving and retaining the ovum. We must conceive that the ovum has no power of initiating the development of a *decidua*, but only of modifying the menstrual process; hence pregnancy *can* begin only at a menstrual period. The ovum, too, exercises this influence at a distance, for in all mammals, the earliest development of which is known, the ovum passes through its segmentation in the oviduct (Fallopian tube), and takes from three to eight days to reach the uterus; but during this period the change in the womb is going on. The most plausible explanation of this action of the ovum at a distance is a reflex stimulus passing from the oviduct to the central nervous system of the mother, and thence back to the uterus; the validity of this hypothesis must be tested by physiological experiment. That the nerves are able to effect morphological changes is already abundantly proven, not only by the influence of the secretory nerves upon gland cells, by the degeneration of muscular and other tissues, when their nerves are severed, but also by certain embryological observations tending to show that histological differentiation does not progress very far until the tissues are joined by the outgrowing nerves.

When the ovum reaches the uterus, it appears to exert a more direct influence, for one set of changes occurs in the placental area, where there is concrescence of foetal and maternal parts; another in the region around the placenta (peri-placenta, decidua reflexa), and still another in the rest of the uterus (decidua vera, ob-placenta). Whether the three zones enumerated can be distinguished in the pregnant uteri of all placental mammals, and whether they have more features in common than appear from a direct comparison between man and the rabbit, are questions to be decided by increased knowledge. However, it already seems very probable that the decidua reflexa and peri-placenta are homologous at least in rodents.

Concerning the evolution of the amnion nothing definite is known, nor do the speculations of Balfour (*Comparative Embryology*, II., 256) nor of van Beneden and Julin, 44, 425, seem satisfactory, although the view of the latter is suggestive. They say:—

“ ‘ Dans notre opinion, la cause déterminante de la formation de l’enveloppe amniotique réside dans la descente de l’embryon, déterminée elle même par le poids du corps. C’est par une accélération du développement que la cavité amniotique en est venu a se former quand l’embryon ne possède encore qu’un poids insignifiant.’ The chief objection to this theory is that it really gives no cause for the expansion of the somatopleure and chorion; there is no proof that a mere strain of weight can cause the cells of a membrane to proliferate, and since such proliferation is the immediate cause of the growth of the amnion, van Beneden and Julin must assume for their theory that the strain of weight does cause proliferation; but this assumption lacks support. Moreover, they give no evidence to show that the embryo *in utero* is situated in the primitive amniota upon the upper side of the ovum, although it is probable such is the case.”<sup>1</sup>

Ryder’s theory, 19, of the origin of the amnion, like that of van Beneden and Julin, to which he does not refer, is purely mechanical; but Ryder seeks the cause in a rigid *zona radiata*, forcing the embryo down into the yolk. See his summary, *l.c.*, p. 184. So far as we know, however, the embryo of the Sauropsida cannot be said to sink into the yolk, and so lead to the development of an amnion; but, on the contrary, the amniotic

<sup>1</sup> Quoted from Buck’s *Reference Handbook*, I., 140.

folds rise up clear above the yolk. Moreover, the formation of the amnion is really a very complex process, part arising from the pro-amnion, part by a dilation of the pericardial cavity (*Parietalhöhle*), and part as the extra-embryonic tail folds. These facts speak, in my judgment, unequivocally against the amnion having arisen by the sinking of the embryo into the yolk sack. Nor is there any justification, I think, for seeking these simple mechanical explanations, which are worthy of Herbert Spencer, since the formation of the amnion depends upon inequalities in the growth power of the germ layers, and only such explanation can be valid as explains that inequality — which Ryder's hypothesis fails to do, so far as I can see.

As regards the evolution of the placenta, we are in the dark. Contrary to prevalent opinion, it is not an organ of the allantois, nor is it an organ of the yolk sack. On the contrary, it is always, so far as we know, an organ of the chorion, and begins its development by a differentiation of that membrane. The allantois is a secondary and later structure. Its primitive rôle is apparently only that of a stalk of connection between the chorion and embryo. There is no evidence to show that the tissue of the allantois spreads out over the chorion to form the mesodermic layer thereof, but the mesoderm of the chorion is proper to it as much as to any part of the somatopleure the mesoderm thereof. When the allantois becomes a large sack, we have a subsidiary change, so that we are brought squarely to the conclusion that the foetal placenta is chorionic. From this premise phylogenetic speculation must start. Further, we know through the discovery of fundamental importance by His that the allantois cavity is at first a small entodermal tube lying in a posterior prolongation of the body (*Bauchstiel*), and that at this time the so-called allantoic vessels run to and branch out upon the chorion; the placental differentiation of the chorion has already begun, without participation of the allantois, the enlargement of which, when it occurs at all, occurs at a later stage. To speak, therefore, of an allantoic chorion as do Balfour and Selenka (*Studien über Entwicklungsges.*, p. 135) is unjustifiable. Nor can we trace the origin of the placenta to the yolk sack, since in most mammals the mesoderm does not spread over the yolk until quite late, so that the yolk sack consists, as in the rabbit and opossum, in large part of ectoderm

and entoderm only, and is without vessels, and therefore unable to form a placenta, which, however, is developing meanwhile from the chorion.

We seek nowadays, following the lead of Professor Cope, to deduce mammalia from the reptilia. Since the reptilia have a free allantois, it is a temptation for embryologists to seek to trace the placenta to a modification of the allantois; but the placenta of mammals appears in the embryo before the allantois becomes free, and the great size of the allantoic vessels is connected primitively not with the allantois, but with the already important chorionic circulation. The placenta is interpolated in the ontogeny of mammals before the specialization of the allantois, which functions as the vascular pathway between the embryo and the chorion, both primitively and permanently. The enlargement of the allantois, which takes place in certain mammals, is a supervening change, probably a survival of reptilian ontogeny. The question is, not how is the connection of the allantois with the placenta (chorion) established in mammals, for it exists from the start,<sup>1</sup> but what becomes of it in reptiles and birds.

Ryder's theory, **128a**, of the origin of the discoidal placenta<sup>2</sup> by constriction of the villous area of the zonary placenta, is difficult to accept. The placenta, being chorionic, cannot of course develop, except so far as the chorion is differentiated; that is to say, so far as the ectoderm (exochorion) is underlaid by mesoderm. Now, in mammals, the chorion, as mentioned above, does not go at first but part way over the yolk sack, even at the period when the development of the placenta has begun. Accordingly, so far as our present knowledge enables us to judge, the discoidal is probably the primitive placental type. If the chorion is completed by the further extension of the mesoderm around the yolk sack, then the placental formation also may spread, and a diffuse type arise. At present, the whole subject is very obscure, but there is certainly no sufficient evidence to prove that the diffuse placenta is the primitive type.

In conclusion, let me point out that we have no satisfactory

<sup>1</sup> This is beautifully shown by Selenka's investigations on the opossum, cited in the text.

<sup>2</sup> The human placenta is *not* discoidal, but metadiscoidal.

knowledge of the nutrition of the embryo. We know positively scarcely more than that the maternal and foetal circulations are brought very close together in the placenta. We infer that there must be a transfer of nutritive material from one blood to the other. As to *what* material is transferred and *how*, we have only theories, but of them an abundance. Under these circumstances, the best beginning is undoubtedly a frank acknowledgment of our ignorance.

§ 22. **Summary.**—The following paragraphs attempt to give the more important of the conclusions reached in the second part of this paper.

§ 13. The umbilical cord is not covered by the amnion, but by an extension of the foetal epidermis. Its coelomatic cavity is completely obliterated during the third month, and a little later the stalk of the yolk sack is resorbed. The allantoic epithelium persists as a tube or cord of cells for a long period. The blood-vessels have specialized walls derived from the surrounding mesoderm, but have no true adventitia. Connective tissue fibres begin to develop during the third month.

§ 14. The amnion is covered by a single layer of ectodermal cells, which are connected by conspicuous intercellular bridges. It has no true stomata. Its mesoderm consists of anastomosing cells, with a dense matrix; it is imperfectly divided into three strata, of which that next the ectoderm is without cells, that furthest from the ectoderm is often of a loose texture.

§ 15. The chorion consists of two layers, mesoderm and ectoderm, both of which are present over all parts of the chorion throughout the entire period of pregnancy. The mesoderm has at first a dense colorable matrix, with cells, which color very slightly. During the second month the matrix loses its coloring property, and subsequently the cells acquire a greater affinity for coloring-matters; the matrix assumes a fibrous appearance, and ultimately in the region of the chorion frondosum connective tissue fibrils appear in it, most numerous next the ectoderm, so that the mesoderm is differentiated there into an outer fibrillar layer and an inner and thicker stroma layer. The ectoderm during the first month divides into two strata, an outer dense protoplasmic layer and an inner less dense cellular layer. In the latter part of pregnancy the whole ectoderm of the chorion l ave has acquired the character of the cellular layer, except close

to the margin of the placenta; at the same period the cellular layer forms a number of irregular patches over the chorion læve, while the protoplasmic layer remains over the entire surface, both where the cellular is present and where it is absent; the protoplasmic layer may undergo complete or partial degeneration into canalized fibrine, which is developed in irregular patches. The cellular layer remains on the villi only in a few patches (*Zellknoten*) and over the tips of certain villi; the protoplasmic layer of the villi remains everywhere and develops numerous nodular thickenings; it changes partially into canalized fibrine. It is probable that the fibrine covering the surface of the decidua serotina is derived from the ectoderm of the ends of the villi imbedded in the decidua. The villi are at first of awkward and irregular forms, but their branching gradually becomes more regular, and the twigs acquire a slender and more uniform shape.

§ 16. The menstruating uterus is characterized by hyperæmia, by hyperplasia of the connective tissue of the mucosa, and by hypertrophy of the uterine glands; the upper fourth of the mucosa is loosened and breaks off: there are no decidual cells.

§ 17. The uterus one month pregnant has lost its epithelium from its surface, and from the ducts of its glands; owing to the dilatation and contortion of the deep parts of the glands, it is divided into a lower cavernous or spongy layer and an upper compact layer; the connective tissue of the upper layer is transformed into decidual cells; in sections the glands of the lower layer appear as crowded areolæ, which are lined by a cylinder epithelium more or less disintegrated, or else filled with isolated enlarged epithelial cells.

§ 18. The uterus seven months pregnant is without epithelium either on its surface or in the glands, except a few isolated patches in the deep parts of the latter; there is no trace of the decidua reflexa; the decidua vera is covered by the epithelium of the adherent chorion læve; the decidua serotina is covered for the most part by a layer of fibrine, which is probably derived from the degeneration of the chorionic ectoderm covering the imbedded ends of the villi; the decidua is divisible into an upper compact and a lower cavernous layer, in which latter the gland cavities are reduced to slits; the decidual cells are very numerous and crowded; the larger ones lie near the chorion;

the multinucleate decidual cells are found chiefly in the serotina; at the edge of the placenta decidual cells are found in the chorion.

§ 20. The decidual cells arise by direct enlargement of the connective tissue cells of the mucosa. All parts of the decidua and placenta arise in place by metamorphosis of the tissue; the mucosa is preserved, and there is no production of placental tissues by new formation.

§ 21. The changes of the uterus during menstruation and gestation are homologous, the menstrual cycle being prolonged and modified by pregnancy; hence it is that conception takes place only at the menstrual period, for the ovum can only modify the menstrual change, not initiate the formation of a decidua. No satisfactory explanation of the origin of the amnion has yet been offered. The placenta is an organ of the chorion; its evolution cannot be traced to modifications of either the allantois or the yolk sack; the allantois is originally the intestinal canal of the *Bauchstiel*, which serves as the means of vascular communication between the chorion and embryo; the enlargement of the allantois is secondary. We possess no positive information as to how the placenta performs its nutritive functions.

BOSTON, Aug. 3, 1888.



§ 23. **Preliminary Bibliography of Works and Articles specially relating to the foetal envelopes of mammals, exclusive of general works.**

\*\*\* I shall be much obliged to any who will inform me of errors in and omissions from this list. I have other titles, but the following are all I have been able hitherto to verify.

**ALLANTOIS.**

(See also FETAL MEMBRANES.)

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2. Beddard, F. E.	Note on the presence of an Allantoic (Anterior Abdominal) Vein in Echidna.	Zool. Anz., VII., 653-654.	1884.
3. Budge, A.	Ueber die Harnblase bei Vogel-embryonen.	Deutsche med. Wochenschrift, VII., 69-70.	1881.
4. Cadiat.	L'allantoide.	Gaz. med. Paris, 4 Sér., VI., 97-98.	1887.
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7. Krause, W.	Ueber die Allantois des Menschen.	Arch. f. Anat. u. Phys., 1875, 215; 1876, 204-207.	1876.
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## AMNION.

(See also FETAL MEMBRANES.)

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21. Viti, Arnaldo.	L' amnois umano nella sua genesi e struttura ed in rapporto all' origine del liquido amniotico.	Siena, pp. 59. Pl. I.	1886.
22. Winkler, F. N.	Die Zotten des menschlichen Amnions.	Jenaischr. Z. Med. u. Naturu., IV., 535-540.	1868.
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## DECIDUA.

(See also PLACENTA and UTERUS.)

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29. Ercolani, G. B.	Delle glandole otricolari dell' utero e dell' organo glandulare di nuova formazione, etc.	Mem. Accad. Sci. Ist. Bologna. 4to. Sér. 2, VII., 133-207. Tav. I.-X.	1868.

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## FOETAL MEMBRANES.

(See also ALLANTOIS, AMNION, and PLACENTA.)

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## PLACENTA.

(See also FETAL MEMBRANES, AMNION, ALLANTOIS, and DECIDUA.)

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## EXPLANATION OF PLATES.

Nearly all the figures were drawn by Mr. E. Stanley Abbot under my supervision. The outlines were drawn with the camera lucida, and the details added free-hand. The drawings are all accurate representations of the preparations, and though of course not photographically exact, are not diagrammatic, except in the case of a few figures expressly specified below. I owe much to Mr. Abbot's patient skill.

*Reference Letters.*

<i>all</i> , allantois.	<i>mes</i> , mesoderm.
<i>cm</i> , circular muscles.	<i>mo.cl</i> , monster cells.
<i>conn</i> , connective tissue.	<i>msth</i> , mesothelium.
<i>ecto</i> , foetal ectoderm.	<i>muc</i> , mucosa.
<i>emb</i> , embryo.	<i>musc</i> , muscularis.
<i>en</i> , entoderm.	<i>ob.pl</i> , ob-placenta.
<i>endo</i> , endothelium.	<i>o.z</i> , outer zone of placenta.
<i>ep</i> , epithelium.	<i>P</i> , periplacenta.
<i>f</i> , placental fissure.	<i>per.v</i> , perivascular cells.
<i>f.v</i> , foetal blood-vessel.	<i>sp.pl</i> , sub-placenta.
<i>gl</i> , gland ; glandular layer.	<i>Sgl.z</i> , subglandular zone.
<i>h.ep</i> , hyaline epithelium.	<i>V</i> , blood-vessel.
<i>l</i> , leucocytes.	<i>vac</i> , vacuole.
<i>lm</i> , longitudinal muscles.	



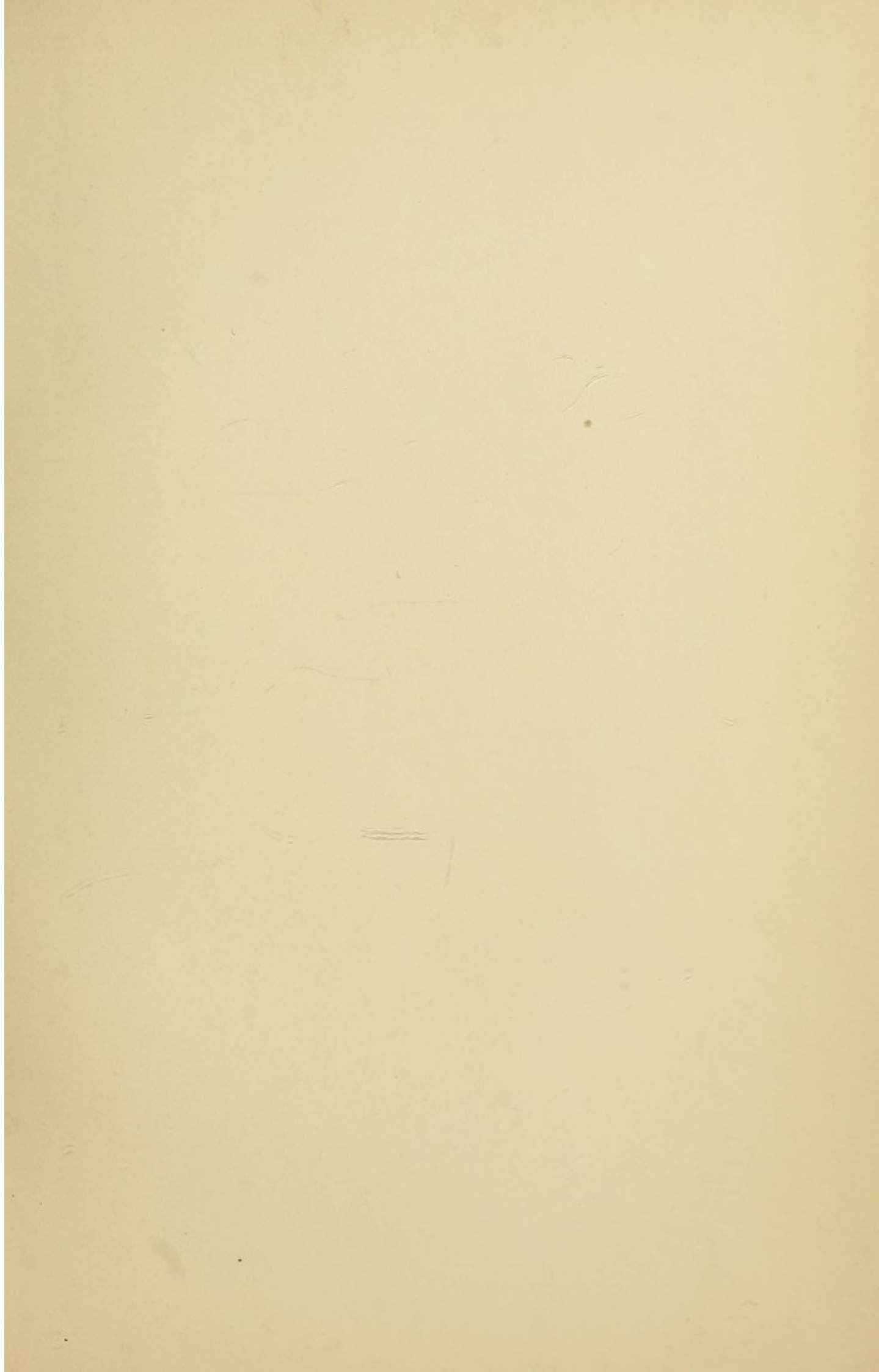
## EXPLANATION OF PLATE XXVI.

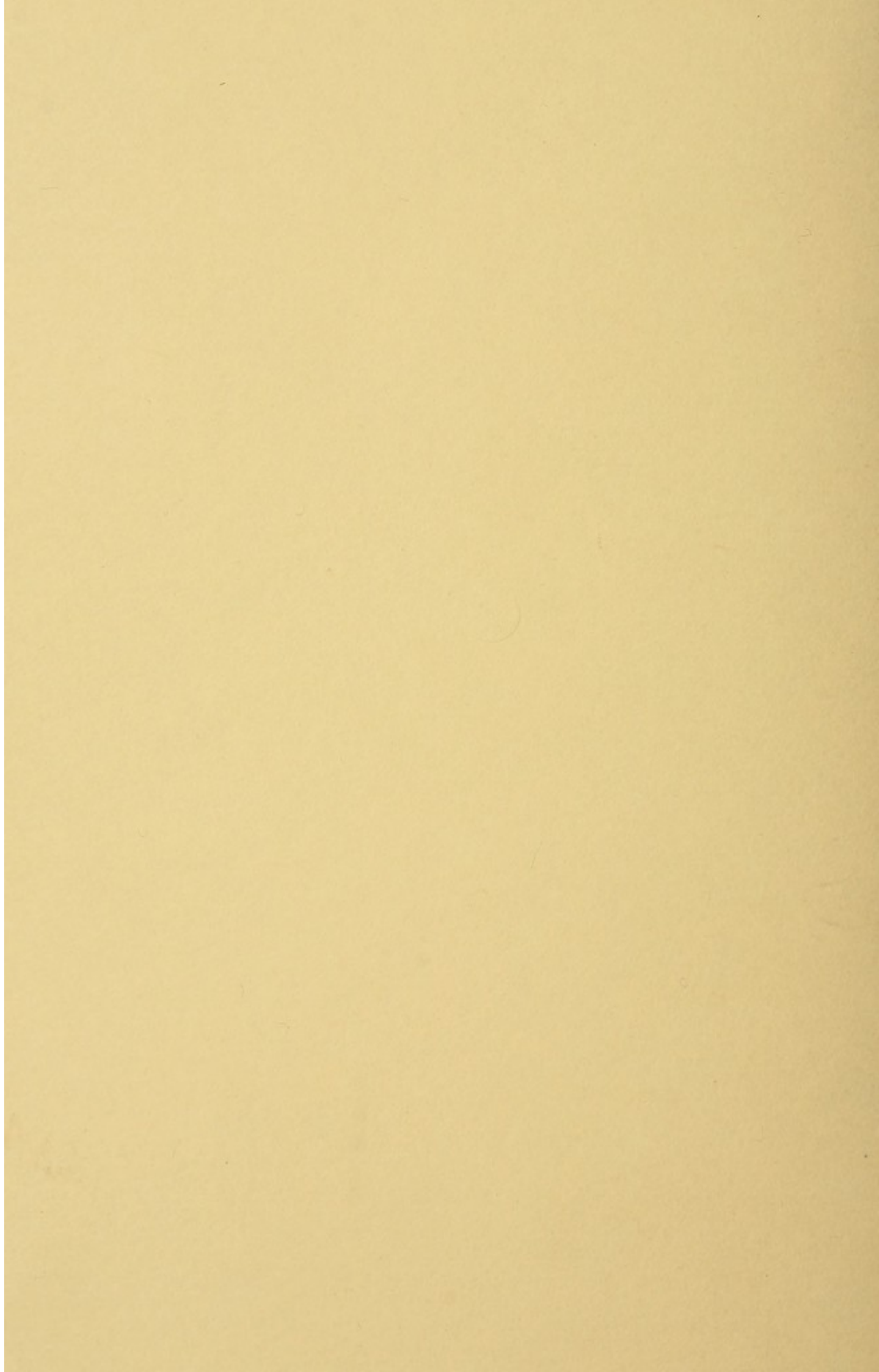
FIG. 1. Placenta of rabbit at eight days, with dilated glands, *gl*, and superjacent foetal ectoderm, *ecto* ( $\times 125$  diams.).

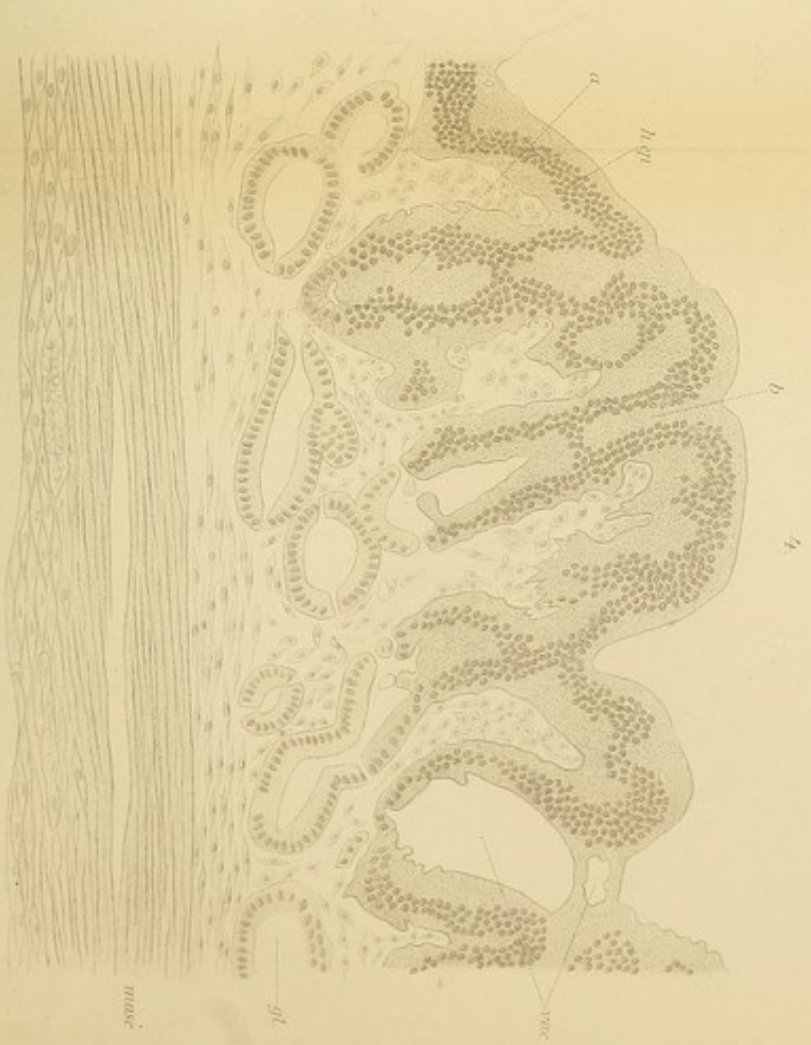
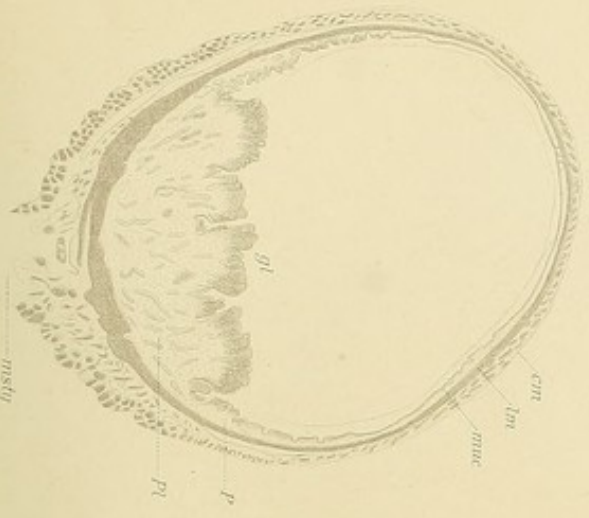
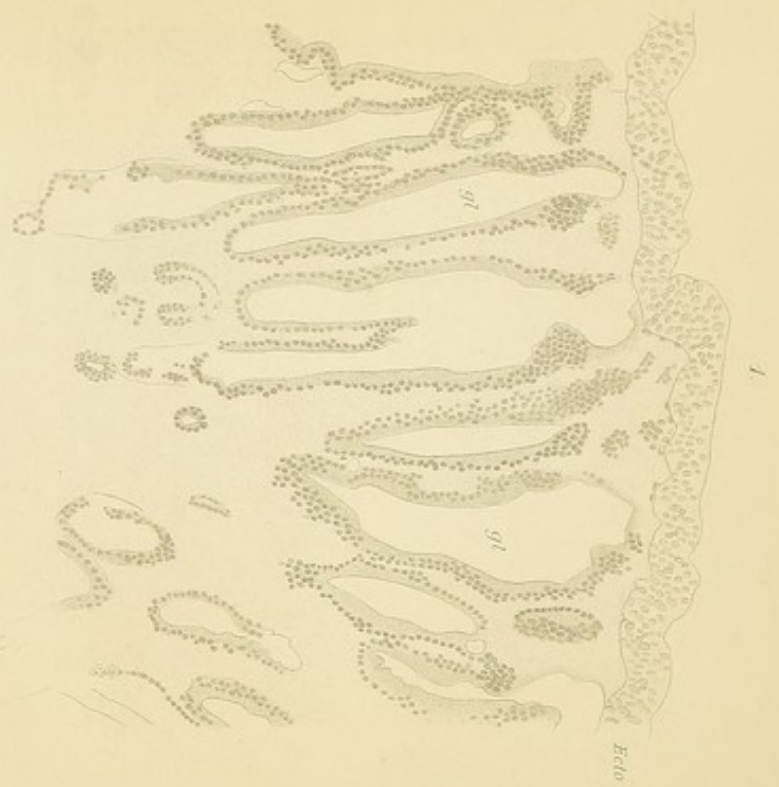
FIG. 2. Rabbit's uterus at nine days, transverse section of a swelling ( $\times 7$  diams.).

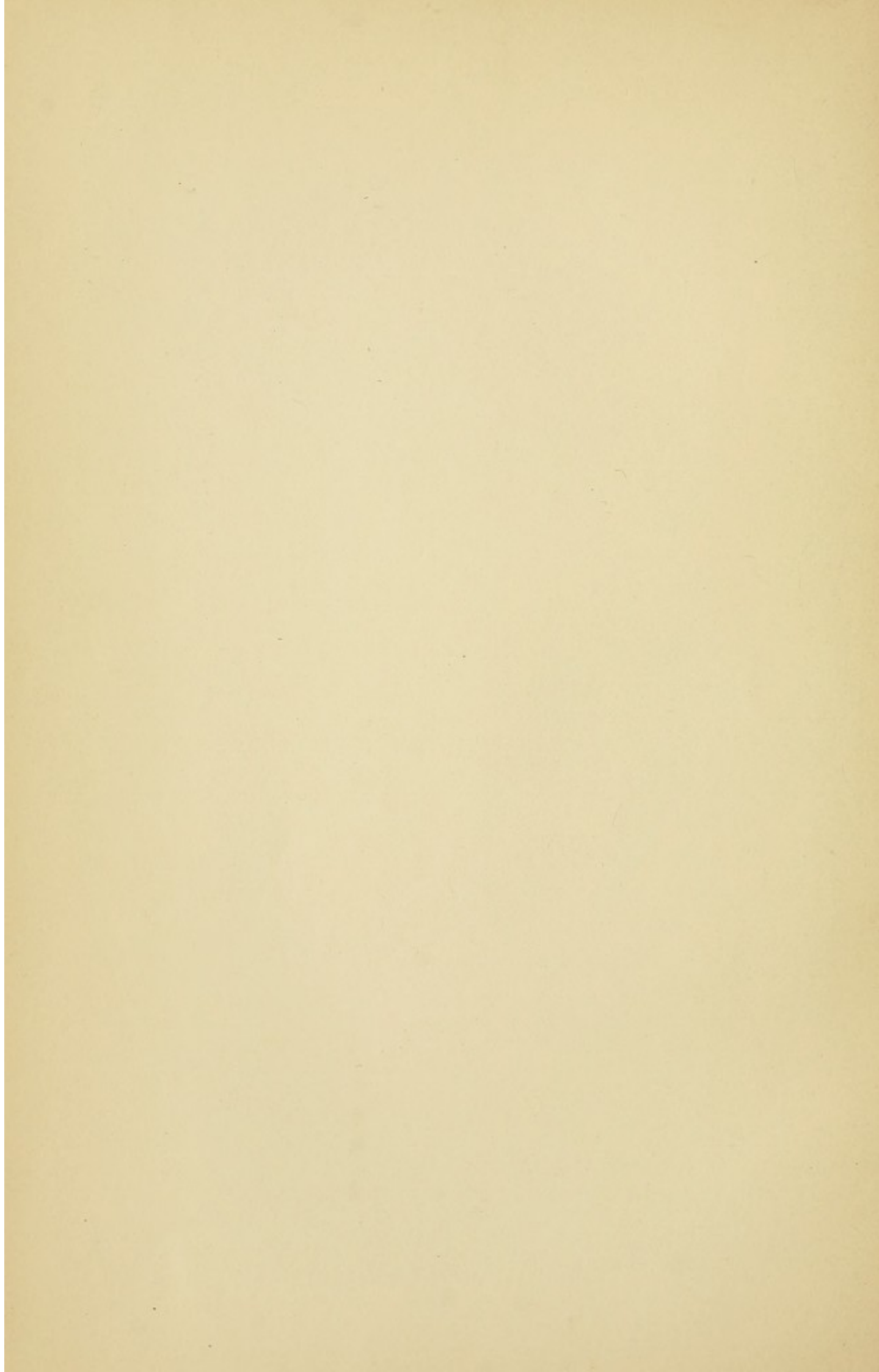
FIG. 3. Portion of the placenta of Fig. 2 ( $\times 445$  diams.), to show the connective tissue, *conn*, the perivascular cells, *per.v*, and the thickened endothelium, *endo*, of the blood capillaries.

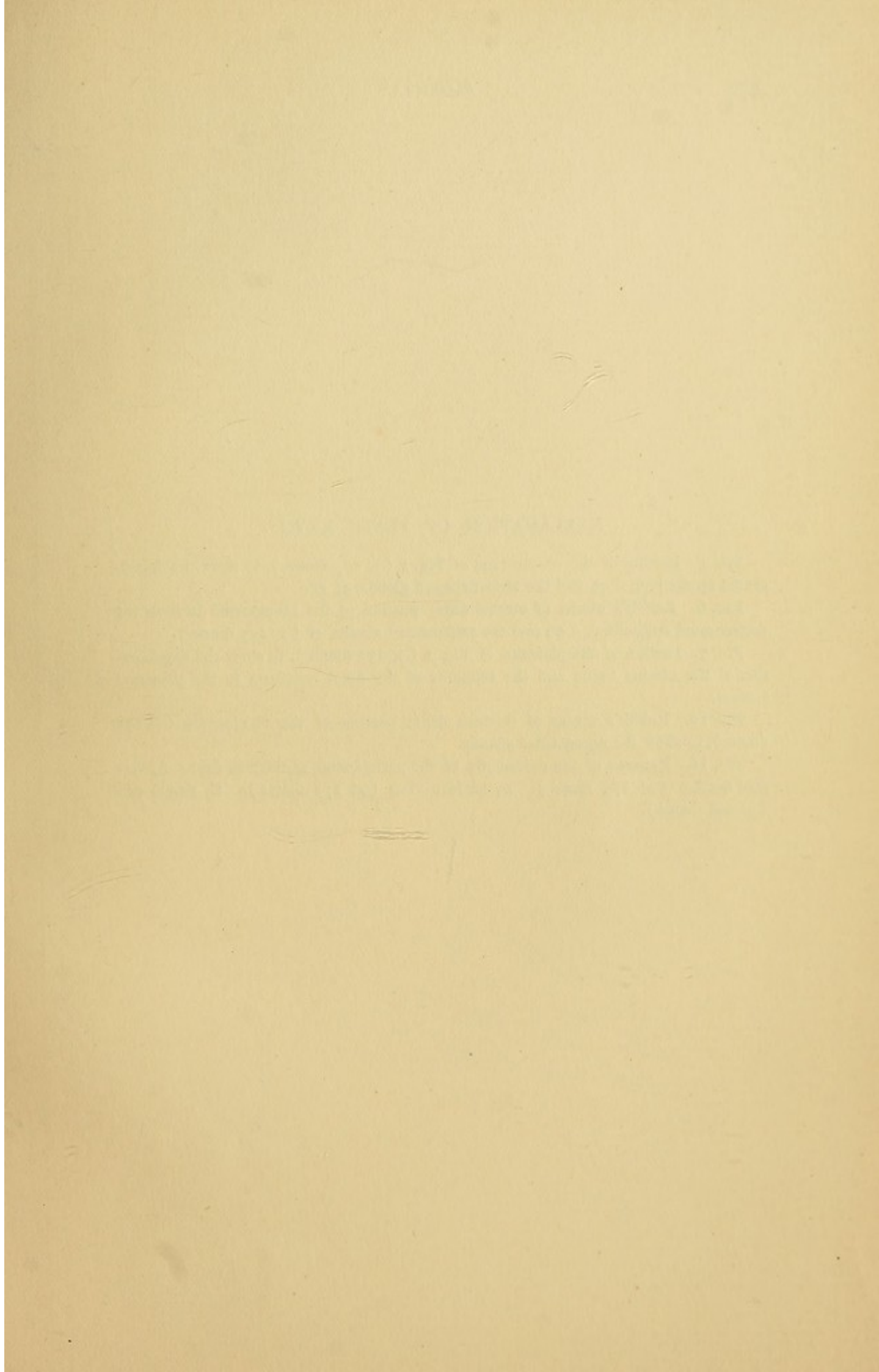
FIG. 4. Portion of the periplacenta of Fig. 2 ( $\times 175$  diams.), to show the degeneration of the epithelium, *h.ep*.











## EXPLANATION OF PLATE XXVII.

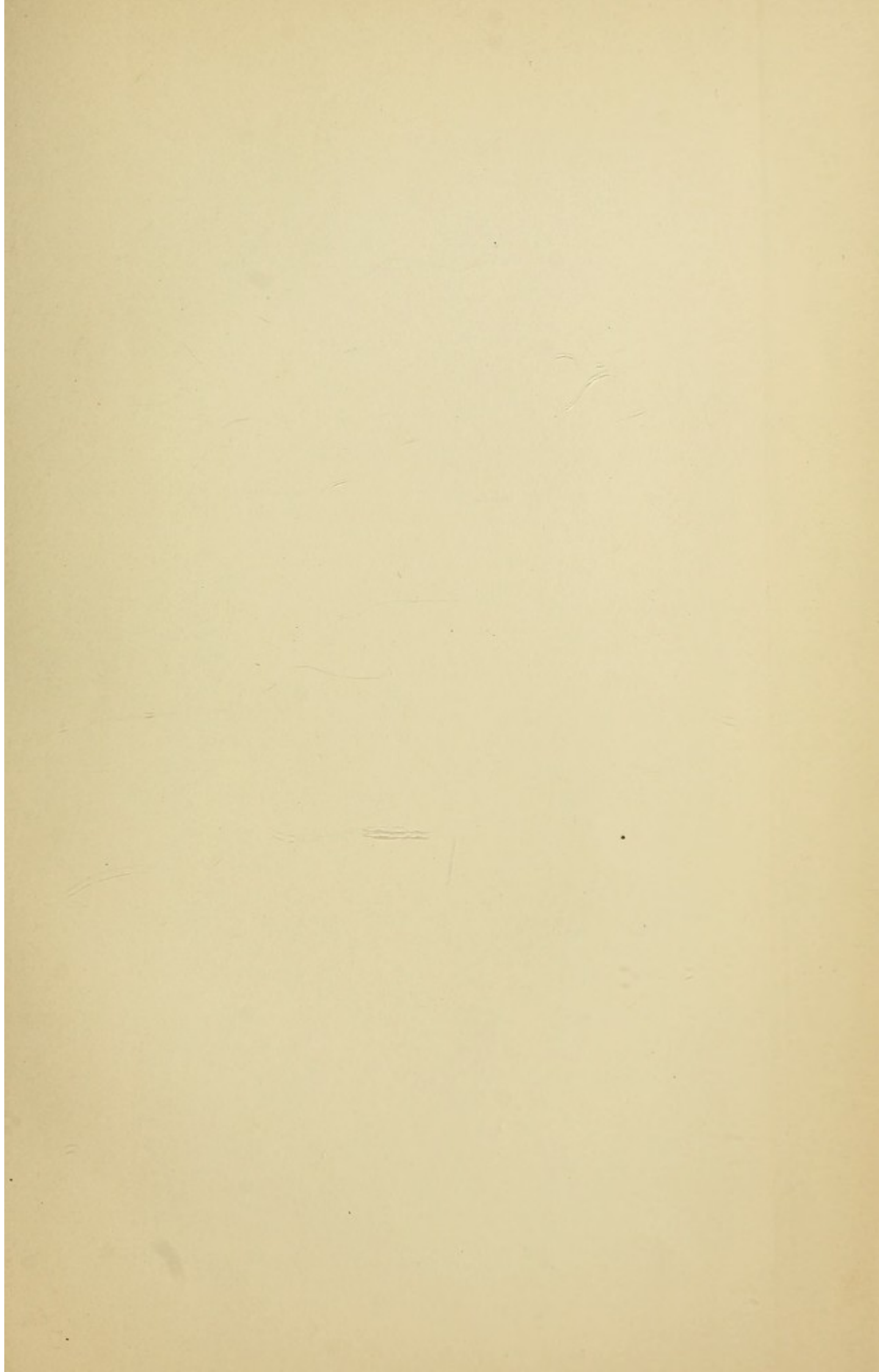
FIG. 5. Portion of the ob-placenta of Fig. 2 ( $\times 175$  diams.), to show the degenerated epithelium, *h.ep*, and the saucer-shaped glands, *gl*, *gl'*.

FIG. 6. Rabbit's uterus of eleven days; portion of the ob-placenta to show the degenerated epithelium, *h.ep*, and the regenerated glands, *gl* ( $\times 175$  diams.).

FIG. 7. Portion of the placenta of Fig. 2 ( $\times 175$  diams.), to show the degeneration of the uterine tissue and the relations of the foetal ectoderm to the placental surface.

FIG. 10. Rabbit's uterus of thirteen days; portion of the ob-placenta ( $\times 175$  diams.), to show the regenerated glands.

FIG. 11. Portions of the epithelium of the periplacenta at thirteen days. A, vertical section ( $\times 175$  diams.). B, surface view ( $\times 175$  diams.). C, single cell ( $\times 445$  diams.).

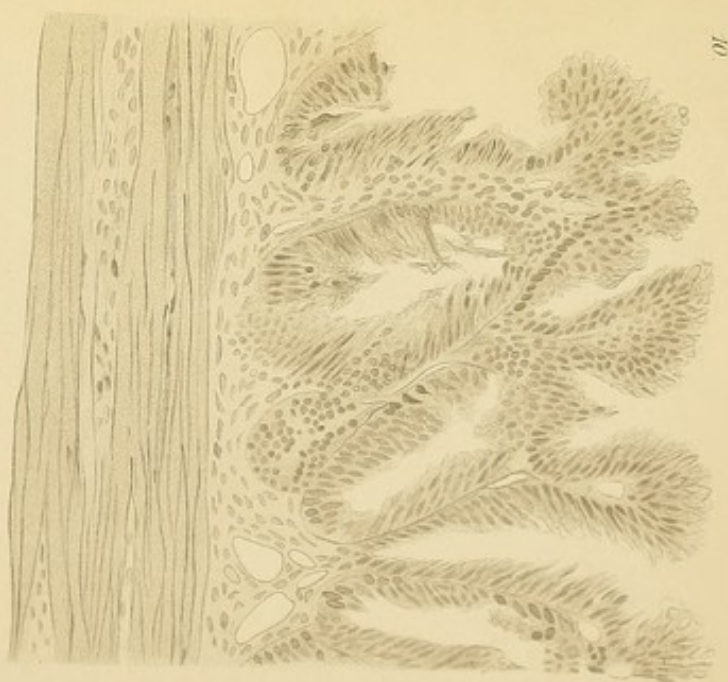








5



10



A

B

C

Z

A

H

B

C

HCP

hcp

G

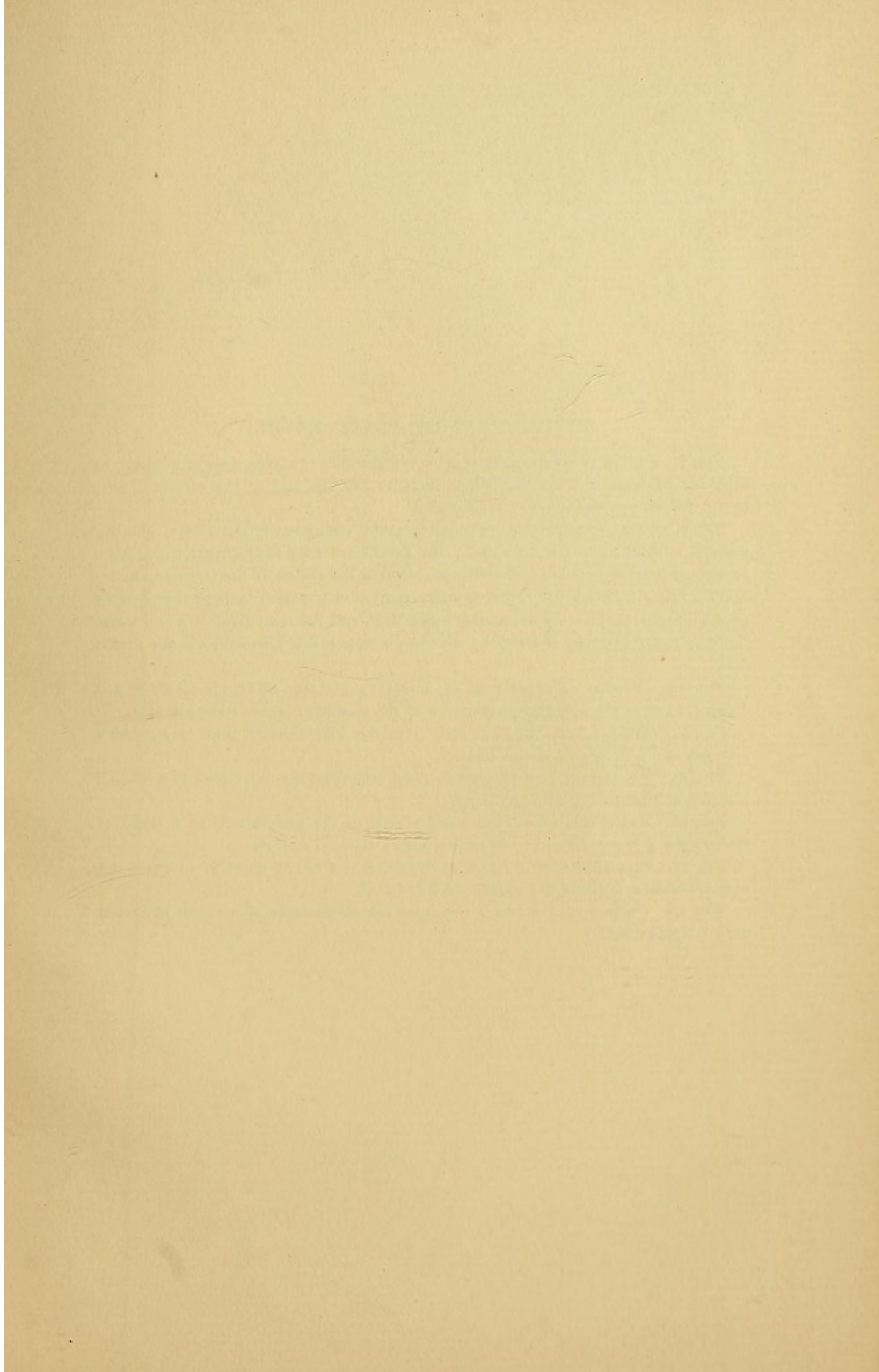
hcp

gl

cornu

muscle





## EXPLANATION OF PLATE XXVIII.

FIG. 8. Portion of a vertical section of the placenta at eleven days of a rabbit, to show the relations of the mesothelium, *msth*, to the top, and of the ectoderm, *ecto*, to the side of the placenta ( $\times 175$  diams.).

FIG. 9. Complete transverse section of a rabbit's uterus at thirteen days, with the embryo, *emb*, in place ( $\times 7$  diams.); the details are only approximately accurate; *x*, mass of perivascular decidual cells, developed in the region of the ob-placenta.

FIG. 12. Rabbit's uterus at fifteen days; portion of a section through the placenta ( $\times 90$  diams.), to show the degenerated glands, *gl*, and the mesoderm, *mes*, and mesothelium, *msth*, covering the surface of the placenta; the blood-vessels are drawn dark.

FIG. 13. Portion of upper part of a rabbit's placenta at fifteen days ( $\times 340$  diams.), to show the histological structure of the glandular layer of the placenta.

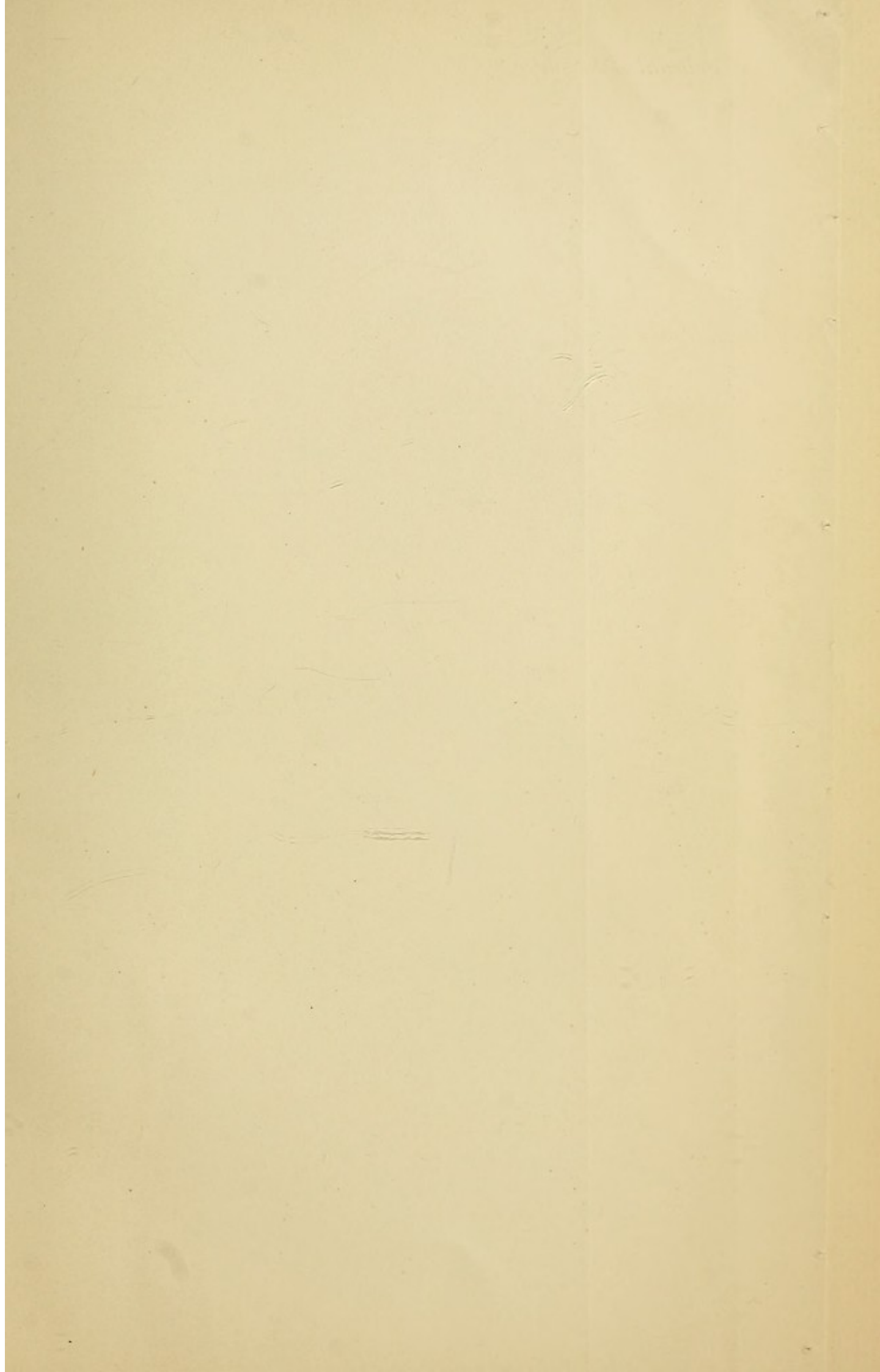
FIG. 14. Multinucleate decidual cells from the subglandular zone of a rabbit's placenta at fifteen days ( $\times 540$  diams.).

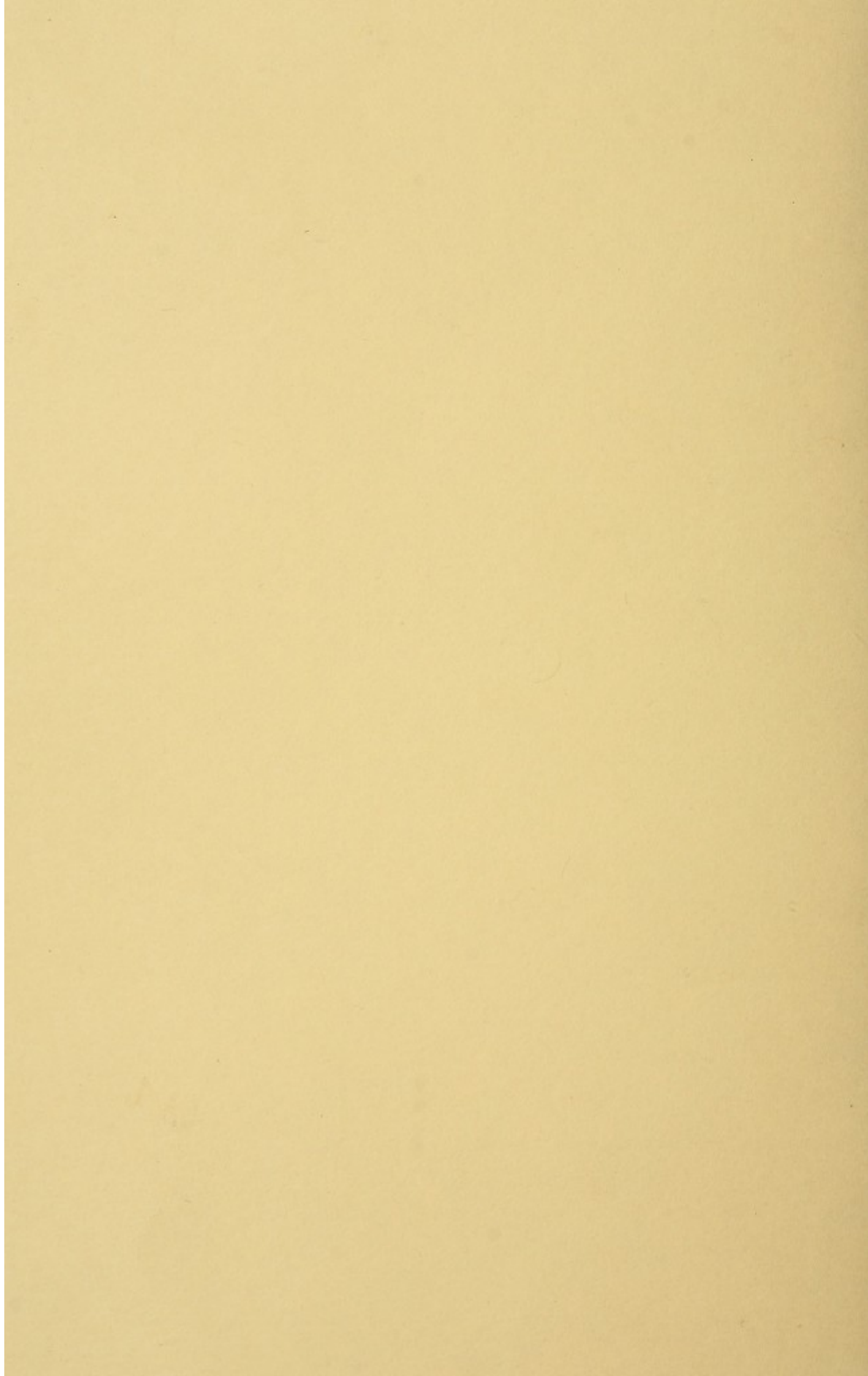
FIG. 15. Uninucleate perivascular decidual cells from the outer zone of a rabbit's placenta at fifteen days ( $\times 540$  diams.).

FIG. 16. Endothelium from the blood-vessels of the periplacenta of a rabbit at fifteen days ( $\times 240$  diams.). A, surface view; B, C, in section.

FIG. 17. Ob-placenta of a rabbit at fifteen days ( $\times 125$  diams.), to show the monster cells, *a*, *b*, *c*, and the uterine epithelium, *ep*.

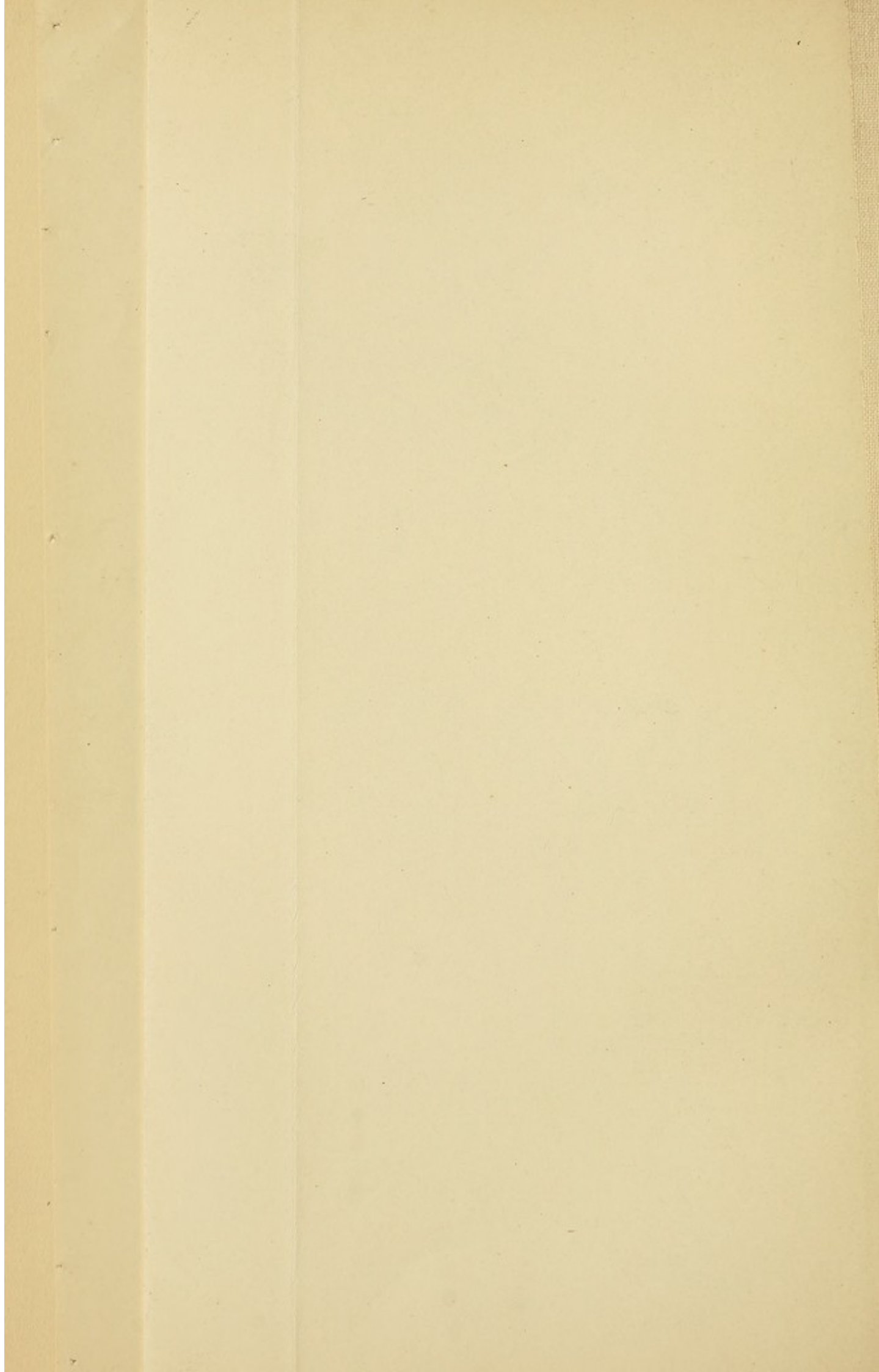
FIG. 18. Nucleus of a monster cell from the ob-placenta of a rabbit at fifteen days ( $\times 445$  diams.).

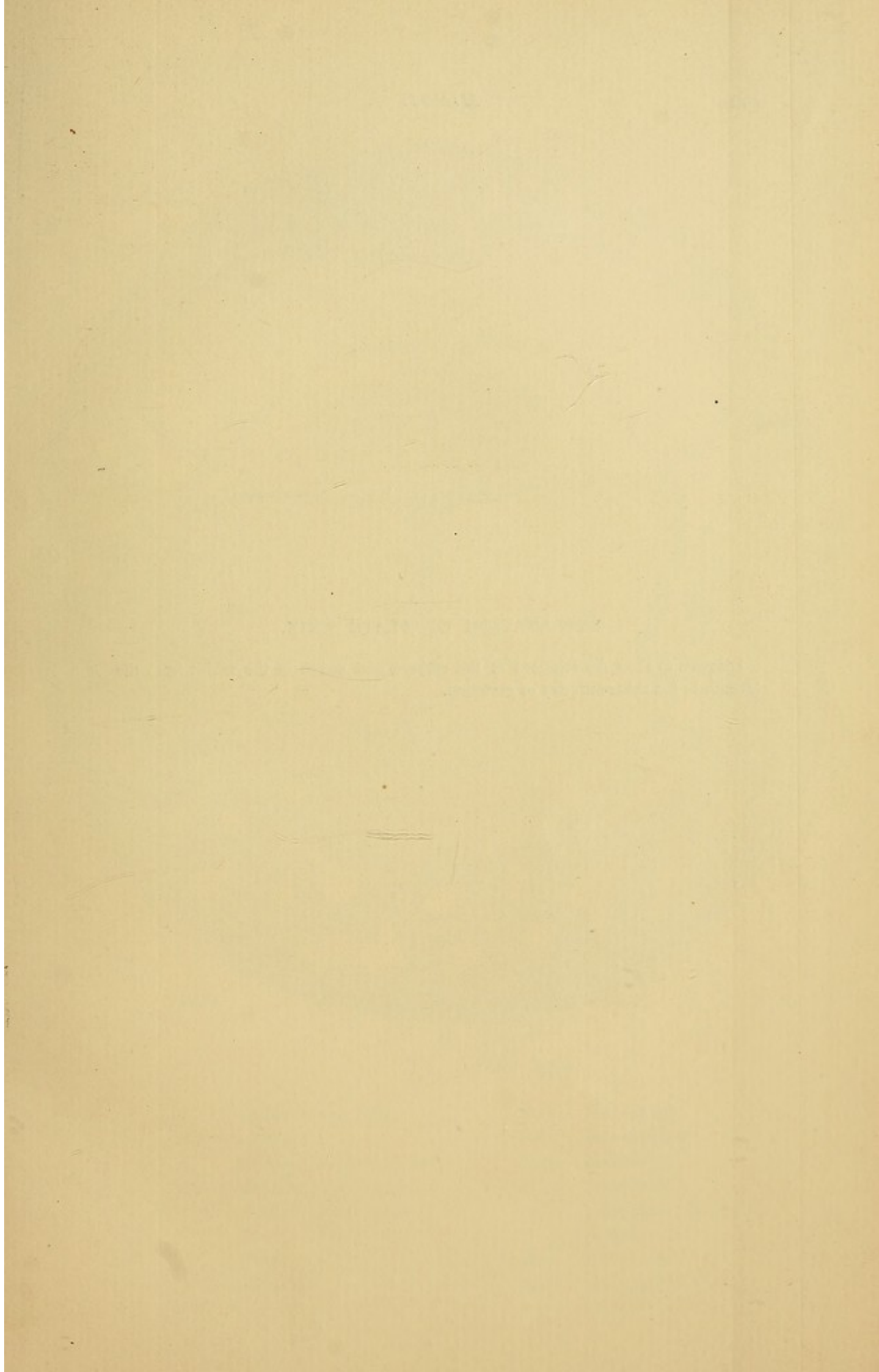






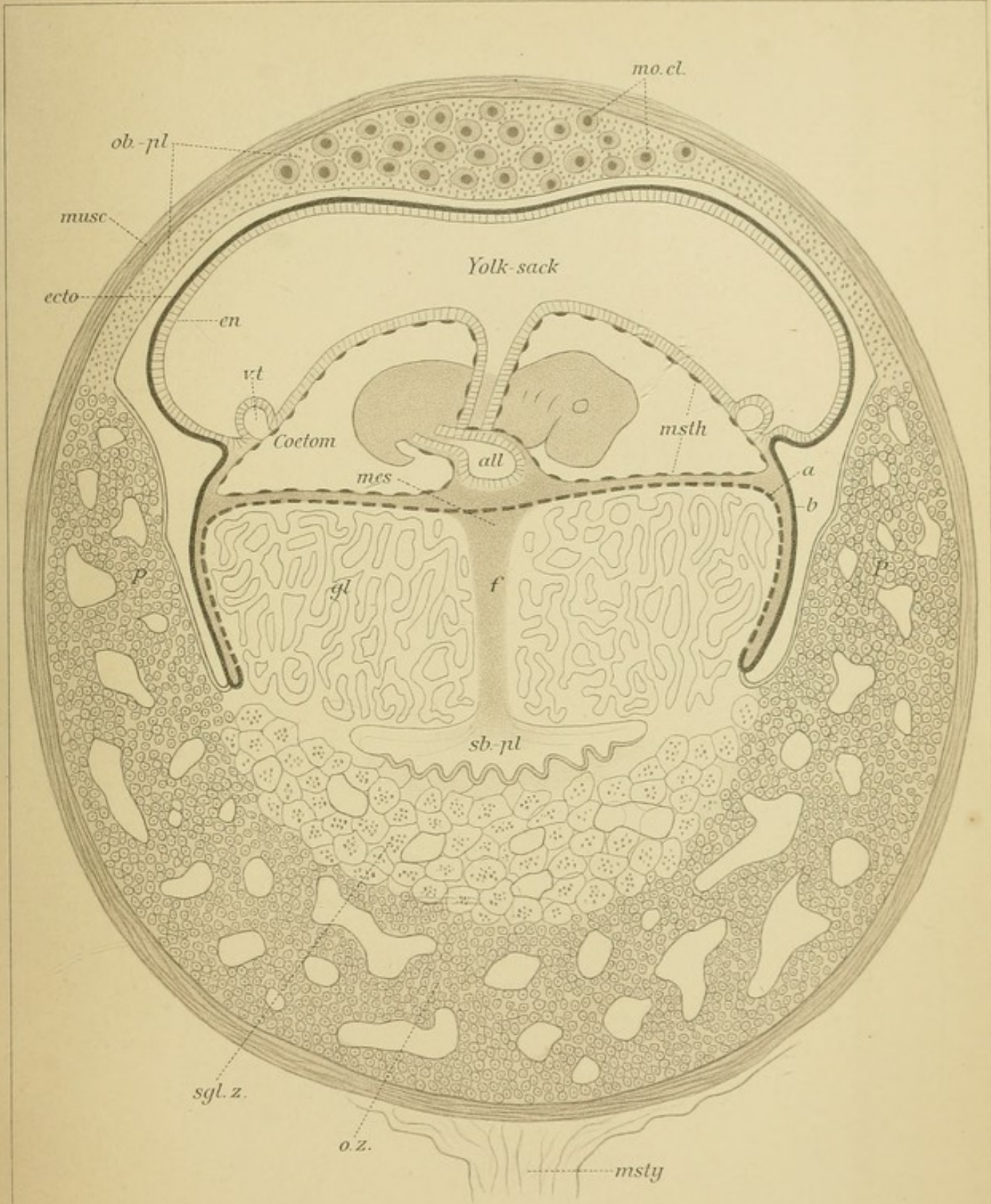






## EXPLANATION OF PLATE XXIX.

Diagram to show the relations of the embryo and uterus in the rabbit from the eleventh to the thirteenth day of gestation.



- |             |                                     |               |                               |
|-------------|-------------------------------------|---------------|-------------------------------|
| <i>a</i>    | <i>ectoderm, lost part</i>          | <i>musc.</i>  | <i>muscularis</i>             |
| <i>all</i>  | <i>allantois</i>                    | <i>msth.</i>  | <i>mesothelium</i>            |
| <i>b</i>    | <i>ectoderm at side of placenta</i> | <i>msty</i>   | <i>mesentery</i>              |
| <i>ecto</i> | <i>ectoderm of yolk-sack.</i>       | <i>ob.pl</i>  | <i>ob placenta</i>            |
| <i>en</i>   | <i>entoderm of yolk-sack</i>        | <i>o.z.</i>   | <i>outer zone of placenta</i> |
| <i>f</i>    | <i>fissure between lobes.</i>       | <i>P.</i>     | <i>periplacenta</i>           |
| <i>gl.</i>  | <i>glands.</i>                      | <i>sb.pl</i>  | <i>sub-placenta</i>           |
| <i>mes</i>  | <i>mesoderm.</i>                    | <i>sgl.z.</i> | <i>sub-glandular zone</i>     |
| <i>mod.</i> | <i>mouster cells.</i>               | <i>vt.</i>    | <i>vena terminalis.</i>       |

