

Observations on the placenta of the rabbit : with special reference to the presence of glycogen, fat and iron / by Walter Chipman.

Contributors

Chipman, Walter.

Publication/Creation

[Toronto] : [J. A. Carveth], 1902.

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*Observations on the Placenta
of the Rabbit*

CHIPMAN

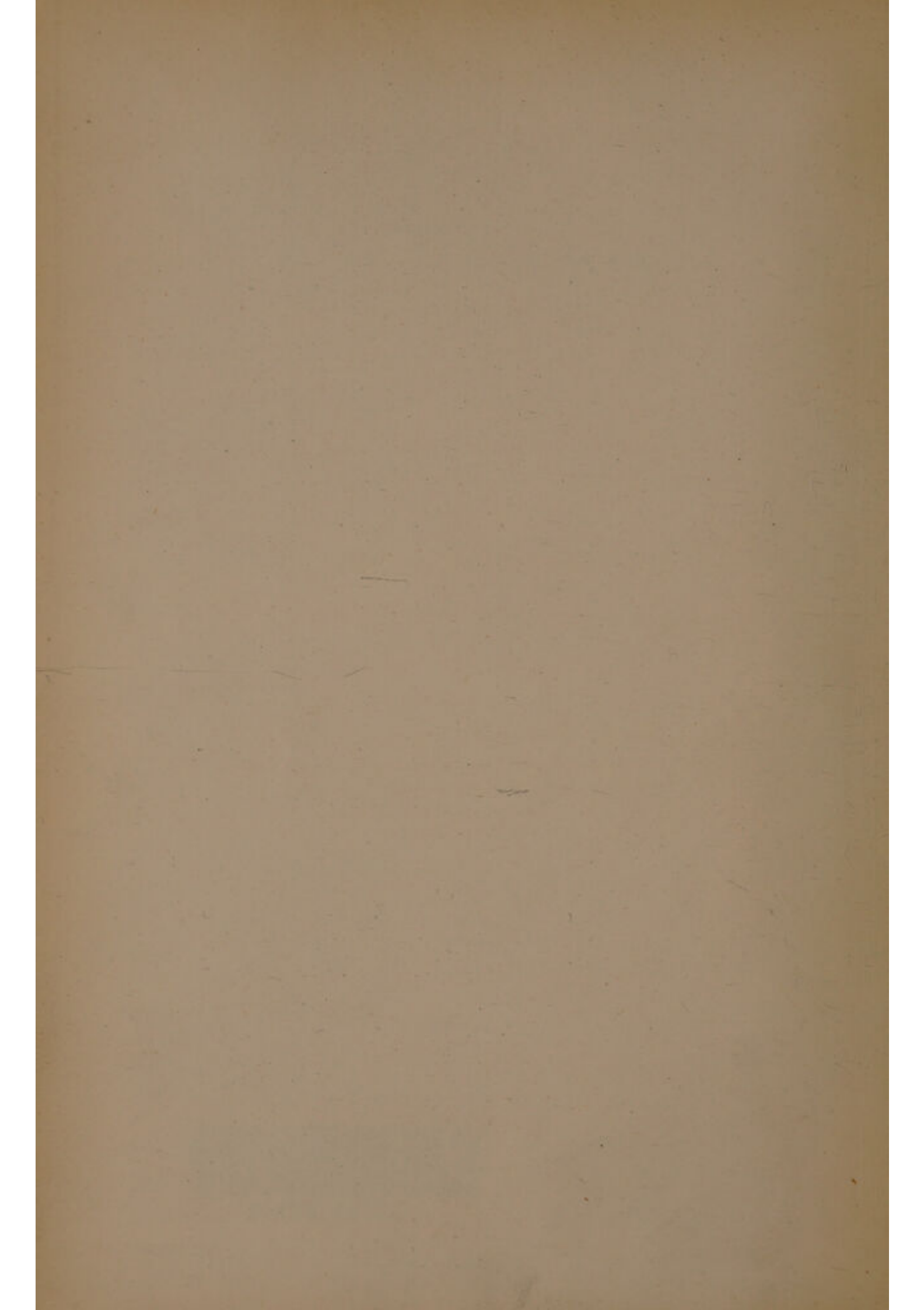


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STUDIES FROM THE ROYAL VICTORIA HOSPITAL,
MONTREAL. Vol. I. No. 4. (GYNAECOLOGY, I.)

OBSERVATIONS
ON THE
PLACENTA OF THE RABBIT,
WITH
SPECIAL REFERENCE TO THE PRESENCE
OF
GLYCOGEN, FAT AND IRON,

BY

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(RESEARCH CONDUCTED IN THE LABORATORY OF THE ROYAL COLLEGE OF PHYSICIANS, EDINBURGH.)

DECEMBER, 1902.

PRINTED BY
J. A. CARVETH & CO.,
TORONTO.

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PART I.

STATEMENT OF MY OWN WORK.

INTRODUCTORY.

WHILE the function of the placenta has long been accepted as a physiological fact, of the actual processes by which that function is initiated and maintained very little is known. The great reciprocity that must exist between the two blood systems, maternal and foetal, in the matter of the nutrition of the foetus, is entertained now in much the same vague and general way as in the day of the Hunters; while our knowledge of the particulars of this reciprocity—its means and its methods—remains almost as conjectural as at that time. Within the last decade, however, the enquiry into the anatomy of the placenta having been in a scientific sense partially satisfied, more attention has been devoted to the

study of its physiology. This study has taken the form of observations, disconnected and casual for the most part, either upon the passage of certain substances, nutritive, inert or toxic, through the placenta from one circulation to the other ; or upon comparative analyses, chemical and physical, of maternal and foetal blood, or of the blood in the afferent and efferent streams in the foetus ; and lastly chemical analyses have been made of the placenta itself, and of the foetus at successive periods of intra-uterine life. The results so far obtained are, in the extreme, meagre and isolated. The great chapter on the physiology of the placenta is yet to be written ; for investigation here is still concerned with the veriest rudimentary details, though a half century has elapsed since the work of Ercolani and Claude Bernard.

The present research was undertaken as a micro-chemical study of the placenta in respect of the substances, Glycogen, Fat and Iron—substances which are concerned more or less directly in all nutrition, and which are comparatively easily detected when present in tissues. The rabbit was chosen because of the ease with which the animals are secured and bred, their short period of gestation and the comparative exactitude of procreation to which their habits lend themselves.

As a preliminary to this study an intimate knowledge of the structure and development of the placenta was essential and this I endeavored to obtain from the numerous monographs and papers which constitute the extensive literature of the subject. I soon realized, however, that the life history of the rabbit's placenta was in many places incomplete, and that some of its most critical incidents were the subject of diverse interpretation and dispute. Accordingly I first devoted myself to an actual investigation of the structure and development of the placenta. Though I have restricted this study largely to a consideration of the points especially important or in dispute, this section—Histology and Histogeny of the Placenta—has grown until it has come to represent the larger part of the present work. Throughout the whole research my constant aim has been solely to record facts as they have been observed, and, especially in the micro-chemical study, where the temptation is peculiarly great, to avoid the presentation of all inferences or conclusions, which from the nature of the work are as yet, of necessity, problematical.

The age series of pregnant uteri which I have obtained extends from the fourth day of gestation to the thirtieth day inclusive, and is the most complete of any series of which I have knowledge. The usual interval in this series is one of two days—48 hours, though I have, however, at several points in the gestation cycle, re-inforced this series by additional specimens with an interval of 12 to 24 hours. My object in so doing is to throw light upon some points in dispute, and to observe more accurately the onset or progress of some process in question. The obtaining of this age-series proved a task of some difficulty—a difficulty noted by such experienced observers as Kölliker, Duval and Minot. As the doe-rabbits were obtained they were kept separately caged until, at the end of ten days, they were proved by palpation to be non-gravid; any found gravid were rejected as worthless. The actual act of insemination was in each case noted, and the rabbit isolated for the given period and then killed. And here at first confusion began. For two rabbits, impregnated within the same hour, and killed after the lapse of a similar time, may, and often do present in their resulting pregnancies an age-interval of 24 to 48 hours. This discrepancy was first recorded by Monsieur Lataste, a French naturalist, who speaks of cases of "retarded gestation" as being common in old rodents. In addition moreover, to this parental idiosyncrasy, there is commonly a difference to be observed in the age of the several gestation sacs of one uterine cornu, some being more advanced than others. Kölliker maintains that this difference follows always a definite order, that the ova that are lodged nearest the cervix, furthest down in the cornu, are the farthest developed. Though I have carefully examined many specimens, I have never been able to satisfy myself that this difference in age corresponded to any regular sequence in position. Difference in age there undoubtedly is, but the less advanced may be placed anywhere in the cornu. Though at first sight the statement of Kölliker seems to express a natural inference, yet when we remember the exceedingly small size of the rabbit's ova, and the generally accepted statement that the 3-9 fertilized ova enter the cornu nearly simultaneously, it by no means follows that the ovum nearest the cervix was the ovum first fertilized. These apparent anomalies cause at first some confusion; but with

experience the observer is enabled through these very age-differences to follow more closely the successive steps in the evolution of the placenta and embryo.

The rabbits were all killed in the same way. Suspended by their heels, a blow behind the ears, with the ulnar side of the hand broke the neck. The abdominal cavity was at once opened—the vessels of the mesometrium tied to ensure a natural injection of the placenta, and the uterus, *en masse*, rapidly removed. The procedure now differed according as the specimens were intended to show histological structure, or to indicate the presence of Fat, of Glycogen, or of Iron. The methods pursued in these instances will be given in detail, each in its separate place.

I have chosen, with few exceptions, to represent my work by means of photographs and microphotographs. In this way only, and possibly at some sacrifice of effect, is an exact representation obtainable. The exceptional instances are where drawings have been used to show some colour reaction. The photographs have been taken with an enlarging-camera, but in every case the same extension has been maintained, so that though the photographs are all enlargements, they yet represent the exact proportional size of the different sections. These photographs are designated in each case and represent a $4\frac{1}{2}$ times enlargement. The low-power and high-power microphotographs are easily distinguished; the low-powers were taken with a No. 3 Leitz Objective and the high-powers with a No. 7 Reichert Objective and a No. 12 (oil immersion).

My investigations have extended over a period of some two years and were carried out in the Laboratory of the Royal College of Physicians, Edinburgh. There the work gained for me the Freeland Barbour Research Fellowship, and, subsequently, embodied in a thesis, was accepted by the University of Edinburgh for the degree of M.D., a gold medal being conferred.*

* The publication of this investigation in their transactions had been vouchsafed by one or more societies in Great Britain, but only on condition that a limited number of the illustrations be reproduced. Considering that the value of the investigation lies largely in the admirable series of microphotographs, illustrating the successive stages in the development of the placenta, and that the cost of reproduction was too considerable for Dr. Chipman, single-handed, to undertake, at the recommendation of the Editorial Committee the Governors of the Hospital have not

I wish to acknowledge my great indebtedness to Dr. Freeland Barbour of the Edinburgh School of Medicine. To him I owe in the first instance the opportunity for prosecuting this present work and from him I received constant inspiration and assistance. To Dr. Noël Paton, the Superintendent of the Laboratory, my best thanks are due. I desire also to thank Professor A. R. Simpson, and Sir William Turner; and Drs. D. Berry Hart, Ballantyne, and Lovell Gulland for valuable direction, criticism and advice.

Toward defraying the cost of the investigation the sum of £5 was granted to me from the Research Fund of the British Medical Association.

In the matter of the publication of this work I gratefully remember the Governors and Medical Board of the Royal Victoria Hospital, Montreal, and especially Mr. Angus, the Hospital's President, and Professor Adami, the Chairman of the Editorial Committee.

SECTION A.

HISTOLOGY AND HISTOGENY OF PLACENTA AND EMBRYO.

The work described under this head is a necessary preliminary to an intelligent study of the micro-chemistry of glycogen, fat and iron. Moreover, an acquaintance with the literature of the structure and development of the rabbit's placenta has revealed points and processes upon which observers are in doubt or are disagreed. Having obtained an age-series of specimens, the most complete of any with which I am acquainted, I have, while following in detail the complete gestation cycle, endeavoured especially to add something to the knowledge of these doubtful or disputed points.

The preparation of the microscopic specimens has been carried out according to the following method: For fixing agent I have chiefly employed the ordinary saturated solution of corrosive sublimate. I have also tried Kleinenberg's picro-sulphuric acid solution, so highly praised by Duval, a

only agreed to apportion to this publication a share of the "Study Fund," but have also individually contributed to defray its very considerable cost, on the ground that under the circumstances of the case, the words, "Works by members of the Staff of the Hospital," may well be permitted to include work by those members undertaken in laboratories elsewhere.

10% solution of formalin, and an osmic acid solution 2%, but in my hands the mercury has given the best results. I have endeavoured as far as possible to preserve the natural relation of parts, and in order to do this have had recourse to various expedients. Up to the fourteenth day, in each case the uterine cornu, with its several gestation sacs, was plunged intact into the corrosive sublimate, where it was left, after being gently straightened, for 12 hours. At the end of this time each gestation sac was isolated with a sharp razor, care being taken to cut wide of, and to exert no pressure upon, the sac. These sacs were again immersed for 12 hours in fresh corrosive. In the larger sacs, namely those of 10, 12 and 14 days, small fenestræ were cut along their ventral aspect to enable the fixing agent more thoroughly to reach the tissues. After the fourteenth day a different plan was followed. The cornu on being removed was at once frozen *in toto* in an ice and salt mixture. When frozen, slabs from $\frac{1}{4}$ to $\frac{1}{3}$ inch in thickness were sawn from the middle zone of placenta and foetus. These slabs were then placed in corrosive sublimate for 24 hours. In this way I have preserved the relations of the foetus *in utero*. After the twenty-second day these slabs, so cut, proved too large for the microtome—a Cambridge rocker—so that from this date onward sections of the placenta alone are given. I may say that freezing in no way injures even the epithelium. The specimens were hardened and embedded in the classic way, save that the length of time in the oven was reduced to 12 hours, as a longer exposure to 50° C. renders the tissues, especially placenta and liver, too brittle to be nicely cut. The blocks have been cut serially, the sections individually examined, and from several hundreds a choice made of some 15 or 20. The time occupied in such selection alone has been great. The slides showing, at the eighth day, the first fixation of the blastoderm to the uterine mucosa, the development of the amnion between the eighth and ninth days, and the first appearance of a foetal liver at the tenth day, represent an examination of some hundreds of sections.

For staining I have used almost exclusively hæmatoxylin and eosin, though in several instances duplicate sections were stained with iron hæmatoxylin and safranin. The older stain is the better, and is the only one from which microphotographs can be well taken.

I have thought it wise to preface this enquiry into the structure and development of the placenta by a short study of the rabbit's genital tract.

In the female rabbit the lumina of the Müllerian ducts remain ununited as far as the vagina, into which they open by separate ora. They thus constitute two distinct cavities. The apposed sides, however, of these two ducts are fused for the distance of $\frac{1}{4}$ to $\frac{1}{2}$ inch at their vaginal ends. In front of this area of fusion the two ducts pursue a separate course, one on either side of the spinal column, till they end in a fimbriated extremity close to the corresponding ovary. Each duct is swung by a ligament and is divided into two portions. The posterior portion, which measures one-third of the entire length, pursues a curved and slightly convoluted course, is of large size, possesses thick walls—the Uterine Cornu. The anterior portion, double the length of the other, is greatly convoluted, of small size, with thin walls—the Oviduct or Tube. The line of division between these two portions is marked by a slight localised thickening in the suspensory ligament—the Round Ligament—and by a sudden and marked diminution in the size of the duct.

A transverse section of the uterine cornu (Fig. 1) shows that it is built up of two layers of non-striped muscular fibre, fairly equal and uniform in thickness; the outer layer is longitudinal, the inner circular. Within is a delicate sub-mucous tissue bearing a ciliated cylindrical epithelium, and constituting the mucosa. This mucosa is arranged in numerous dendritic, leaf-like processes, which project from all sides into the lumen of the cornu, in large degree occluding its actual cavity. This cavity is always eccentrically placed, for the reason that the leaf-like folds of the mucosa are larger and longer on the side of the cornu next the ligament. This cavity is also larger at the tubal end of the cornu than at the vaginal end. The numerous *cul-de-sacs* between the mucosal folds represent the "uterine" glands, and the lining epithelium is evenly ciliated. Between the two muscular layers is the vascular zone, the larger vessels lying nearer the ligament and being longitudinal in direction. There is a covering of peritoneum except at the hilum, where the peritoneum is reflected off the sides in two layers, which, with enclosed areolar tissue, vessels and nerves, go to form the suspensory ligament or "mesometrium."

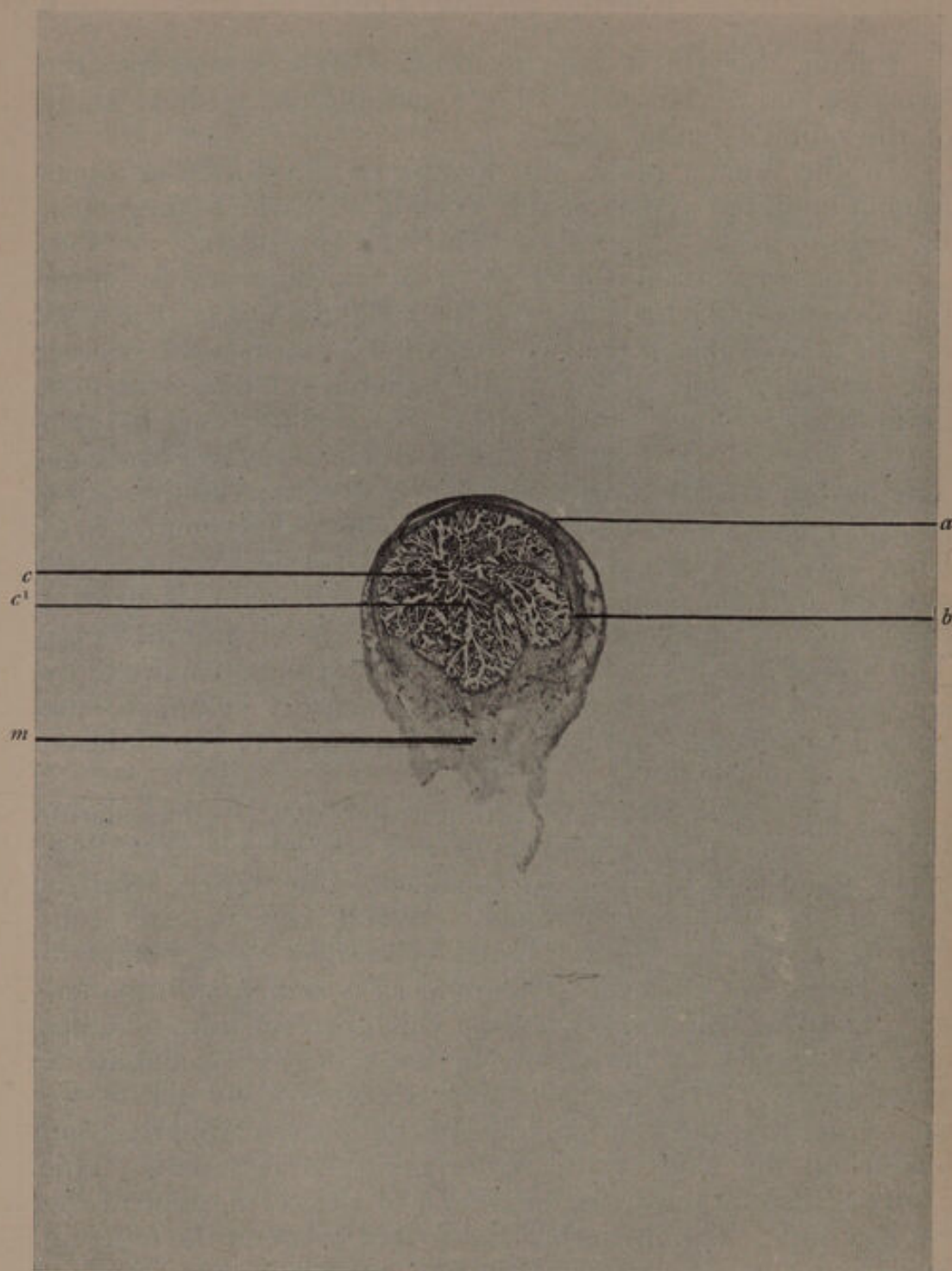


FIG. 1.

Transverse section of empty uterine cornu (nulliparous.)

The muscular walls are thin; there is sharp demarcation between longitudinal and circular muscular layers; the mucosal folds are dendritic and larger next the mesometrium. The cornu is circular in shape.

a, longitudinal muscular layer; *b*, circular muscular layer; *c, c¹*, mucosal folds; *m*, mesometrium. (Photo.)

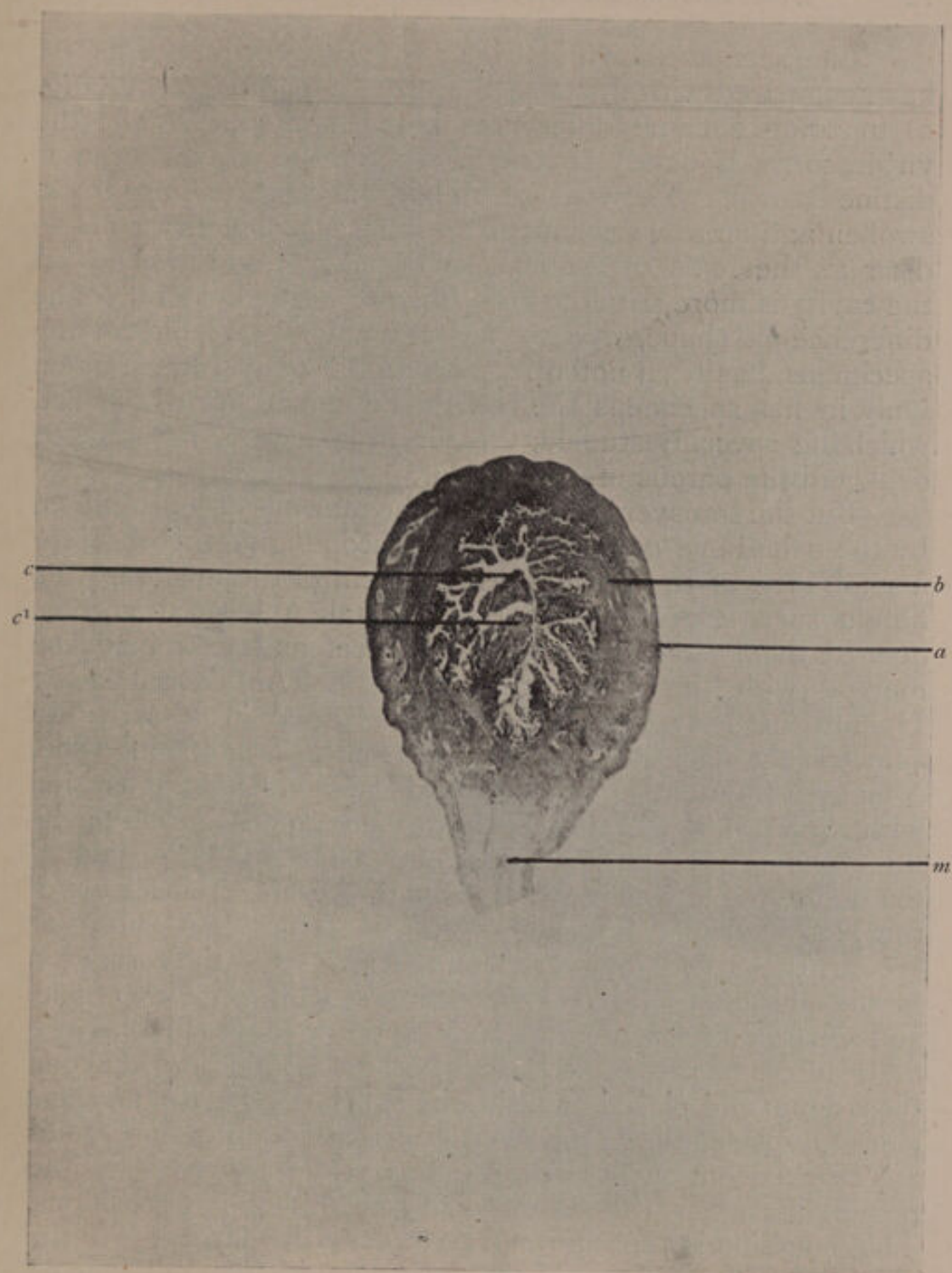


FIG. II.

Transverse section of empty uterine cornu (parous).

The muscular walls are thick and less discrete ; the mucosal folds are club-shaped. The shape of the cornu is oval.

a, longitudinal muscular layer ; *b*, circular muscular layer ; *c, c¹*, mucosal folds ; *m*, mesometrium. (Photo.)

The section shown in Fig. 1 is from a virgin uterus. I have compared with this a section from a parous cornu (Fig. 2) to bring out the differences between them. While the virgin cornu is nearly circular in section, the parous cornu is distinctly oval. The walls of the parous "uterus" are thick, swollen and more vascular, the two muscular layers are not so discrete, the folds of the mucosa are shorter and thicker and the cavity is more patulous; the cilia are not so evident. The difference in shape, due to parity, unmistakeable in all my specimens, has been noted in carnivora also, by Fleischmann. Only in his specimens the converse obtained, for in the cat, which he specially studied, the virgin uterus is pronounced oval and the parous uterus circular.

But the transverse sections of the uterine cornu examined by the naked eye or under the microscope, give the observer a small idea of the general arrangement of the mucosa. To obtain such a general idea I have taken several cornua, opened them along their ventral aspect and examined the mucosa with the naked eye and lens. As described by Hollard in 1863, the mucosa is arranged in a series of symetrically disposed longitudinal folds. Minot, in 1890, computed the number of these folds at six, an enumeration with which I agree, and he has given names to each of the three pairs. The largest pair, situated one on each side of the deep groove which corresponds to the line of insertion of the mesometrium, he calls Placental folds. As will later appear, these two folds are alone concerned in the formation of the placenta. Beyond these largest folds on either side, and separated from them by a shallower groove, lie the two folds intermediate in size, the Peri-placental; and beyond these again and placed opposite the mesometrium, the smallest pair, Ob-placental. Moreover, these six longitudinal folds are marked off by fissures, which cut them transversely into rectangular areas, called by Hollard "coussinets" or cushions. The coussinets thus formed are naturally largest on the placental folds; and two of these placed very generally one on either side of the mesometric groove, hypertrophy at the expense of all the neighbouring mucosa, and come to constitute themselves, as noted by Bischoff, the maternal portion of the placenta. Hence the line of attachment, and bi-lobate shape of the rabbit's placenta. Fig. 3, which gives a very slight enlargement, demonstrates the above facts.

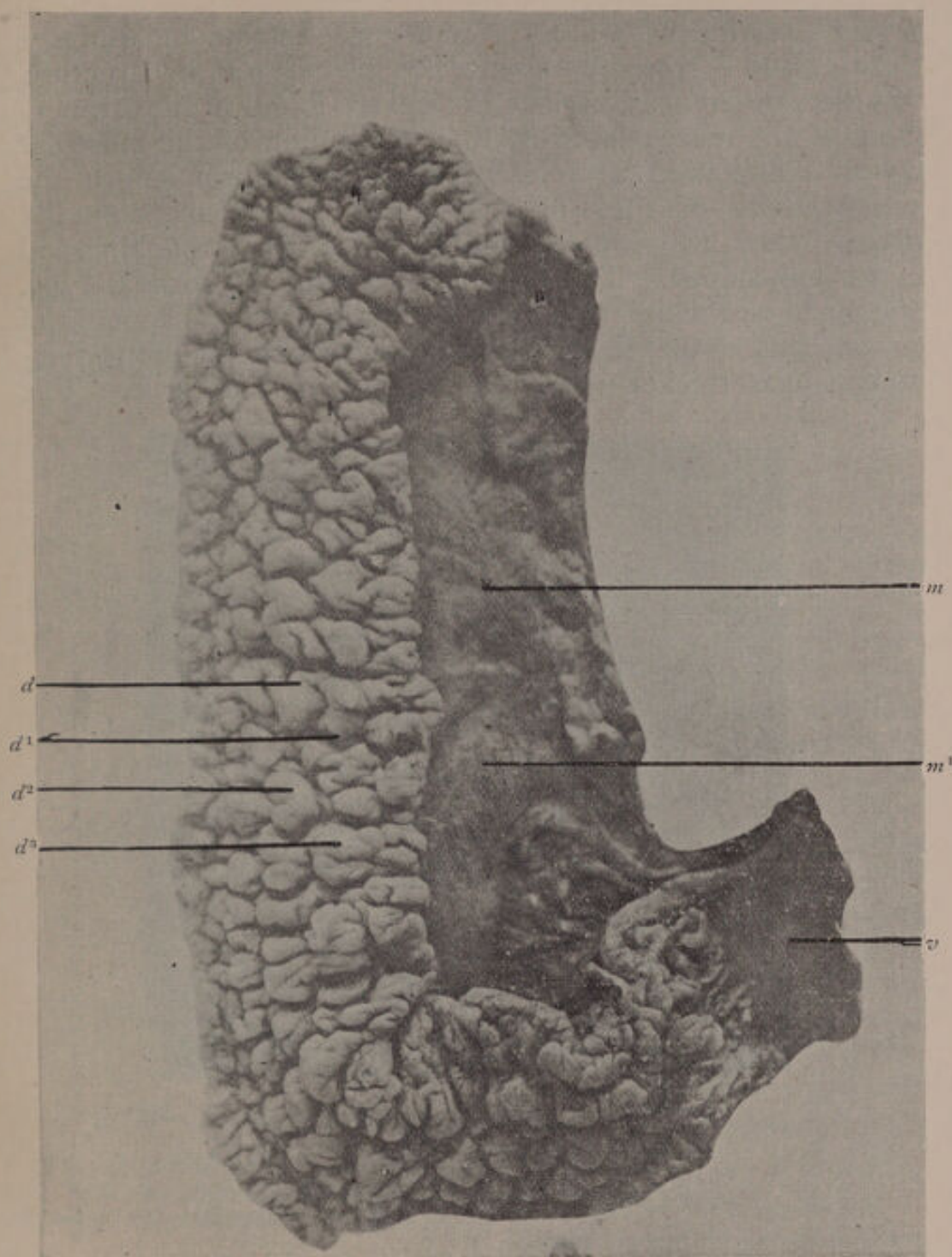


FIG. III.

Uterine cornu laid open along its ventral aspect.

This gives the naked eye appearance of the mucosa and shows its arrangement in longitudinal folds.

m, m¹, mesometrium ; *v*, vagina ; *d, d¹, d², d³*, two mesometric folds of the mucosa. (Photo.)

The oviduct or tube, a transverse section of which is shown (Fig. 4), resembles generally the cornu in its structure. Manifest differences, besides in size, are found in the arrangement of the mucosa, and in the constitution of the muscular layers. The mucosal folds are here of uniform length, the actual cavity of the tube being in consequence centrally placed; they are proportionately shorter, less branching and more club-shaped. The epithelium retains the cornual type, columnar with cilia. While there is but a small amount of sub-mucous tissue, the circular muscular coat is proportionately much thicker than that of the uterine cornu. The

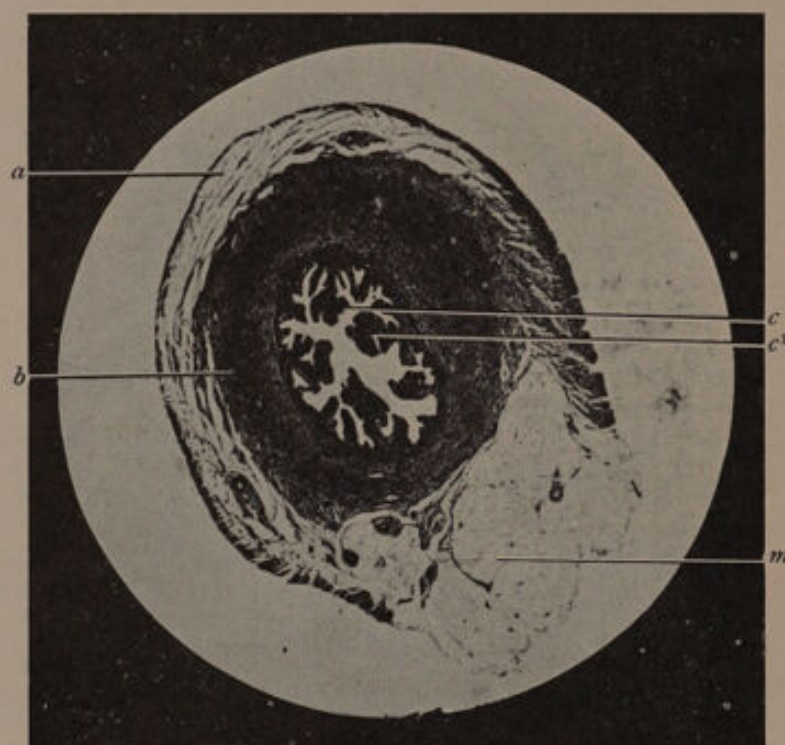


FIG. IV.

Transverse section of oviduct.

a, longitudinal muscular layer; *b*, circular muscular layer; *c, c¹*, mucosal folds; *m*, mesosalpinx.

longitudinal coat, however, shows the most marked differences, it is here stratified, its walls being resolved into various muscular laminæ, separated by a greater or less amount of fibrous tissue.

A longitudinal section passing through the line of demarcation between cornu and tube shows the junction of

their structural peculiarities. As will be seen in the photograph (Fig. 5), this junction is distinct and abrupt. In addition to the change in the arrangement of the mucosa, in the amount of the sub-mucous tissue, and in the disposition of the longitudinal coat, one observes that the circular coat is reinforced at this spot by a localized addition of muscular fibre, resulting in a sphincter-like structure which marks off sharply the lumen of the cornu from that of the tube. The result is a narrow strait, much smaller even than the cavity of the tube, and embraced by a circular muscular wall of considerable thickness.



FIG. V.

Longitudinal section of the junction between cornu and oviduct.

a, longitudinal muscular layer ; *b*, circular muscular layer ; *u*, uterine cornu with its mucosa ; *o*, oviduct with its mucosa ; *s*, sphincter-like thickening of the circular muscular layer.

This examination of the rabbit's genital tract, a necessary preliminary to the study of gestation changes, has directed my attention to two significant anatomical points.

(1) The complete and wide zone of separation which exists between the two muscular layers, the circular and the

longitudinal, of the uterine cornu, a zone composed of blood-vessels and connective tissue. This arrangement, very marked in the virgin cornu is somewhat less evident after parity. Reichert (*Abhandl. der Berl. Akad.* 1861: p. 127) has noted a similar arrangement in the cornu of the guinea-pig, and in consequence has been led to study the peristaltic movements seen in the two layers. He affirms that the two layers do not always act synchronously, and that "while the longitudinal muscular tube is shortened in contraction, the circular layer acts in concert with the glandular stratum as a separate tube, assuming inequalities of surface which are bridged over by the longitudinal coat." From Reichert's descriptions of what he has observed in the guinea-pig, we may infer that in the rabbit also, like peristaltic phenomena occur, which are without doubt associated with the passage down, and regular lodgment in the cornu, of the several ova of a given gestation, and are concerned also in the act of parturition.

(2) The presence of the strong sphincter-like muscular ring at the tubal extremity of the cornu and the attachment at this level of the round ligament. From its disposition this thick circular band must act as a sphincter, and from its location, size, and evident strength must be concerned in parturition. Firmly contracted and anchored by the round ligament, it must constitute itself as a counter pressure to all peristalsis occurring throughout the length of the uterine cornu.

I have begun my age-series at the 4th day after impregnation, when the ovum has been but one day within the cornu. The series advances with a greatest interval of 24 hours until the 10th day, after that the interval is 48 hours. I have directed my attention chiefly to the placental part of the mucosa, the placental folds; the origin and development of the placenta itself in its maternal and foetal portions. The development of the foetus and its membranes has also been followed. In other words I have confined my study to the mesometric pole of the gestation sac; the opposite pole—non-mesometric—presents few points of interest, and has been thoroughly worked out, especially by Duval. My one special reference to this non-mesometric pole is made with regard to the origin of giant cells.

As I have previously intimated, the descriptions seek

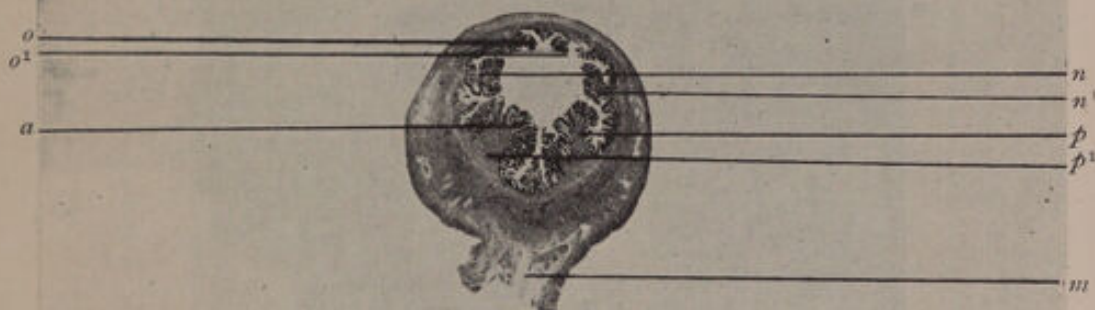


FIG. VI.

(4 days' Gestation.)

Transverse section of a gestation sac of 4 days. The mucosa is now more clearly differentiated into six definite folds. The two folds opposite the mesometrium are the largest and mark the site of placental attachment. The blastodermic vesicle is not preserved.

a, area shown in Fig. 7; *p, p¹*, placental folds; *n, n¹*, peri-placental folds; *o, o¹*, ob-placental folds. (Photo.)

only to emphasize or throw light upon important or disputed points. In these descriptions I shall follow always the same order, in each instance dealing with:—

- (1) Fœtal Tissue—The ovum, embryo or fœtus and fœtal placenta as the age may warrant.
- (2) Maternal Tissue—designated before the 9th day placental mucosa, and after that date maternal placenta.

In every case the gestation sac has been cut at right-

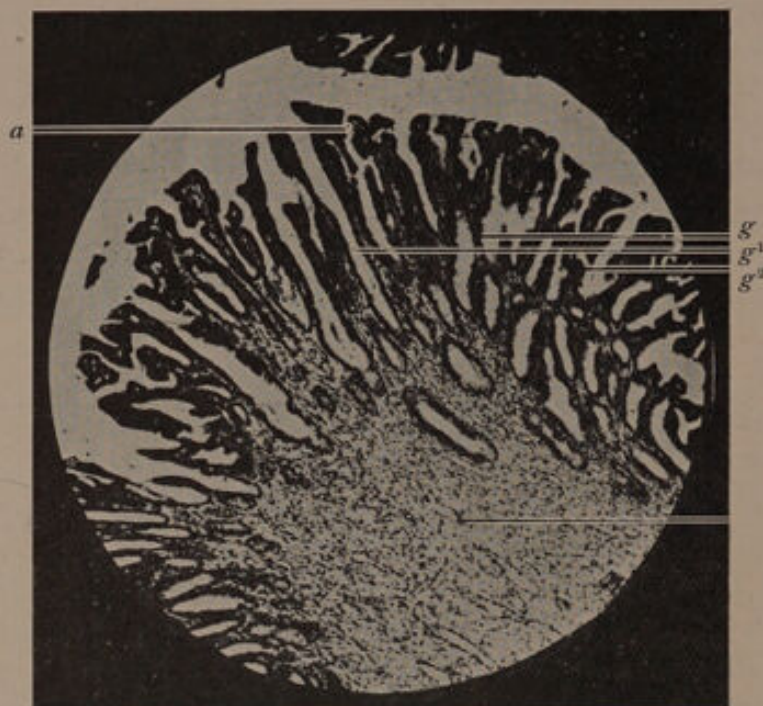


FIG. VII.

(4 days' Gestation.)

Section of the free extremity of a placental fold showing the corium and the tubular character of the glands.

a, area shown in Fig. 8; *c*, corium; *g*, *g*¹, *g*², tubular foldings (glands) of the mucosa over a placental fold.

angles to the long axis of the uterine cornu, and sections representing a central division of the placenta have been selected and photographed.

GESTATION SAC OF 4 DAYS.

The position of the ova is only to be recognised by transmitted light as spherical translucent areas placed at intervals, and toward the

ventral aspect of the uterine cornu. The "uterus" shows no bulging at these points, the ovum has been but one day within it.

(1) Foetal tissue :—ovum

My attempts to preserve the ovum at this stage have been altogether unsuccessful.

(2) Maternal tissue :—placental mucosa.

A transverse section, cutting the uterine cornu through a translucent area shows that the "uterus" has here acquired an actual cavity. This cavity is eccentrically placed, is nearer the ventral wall, is well-defined and circular in shape (Fig. 6). It is lined by the cylindrical epithelium of the mucosa whose folds have been radially shortened, and the cavity of the *sac* so formed. This cylindrical epithelium has lost its cilia, and shows a direct and rapid multiplication of its nuclei with no



FIG. VIII.

(4 days' Gestation.)

High-power view of placental glands, showing great multiplication of the nuclei of the epithelial cells.

n, n^1, n^2 , multiplying nuclei—fragmentation.

corresponding growth of cell-protoplasm. In this way it seems that the shortening of the mucosal folds is gradually brought about for the multiplying epithelial cells crowd the superficial *cul-de-sacs*, and so come to press upon and strangulate the vascular axes of the fine terminal folds of the mucosa, and these terminal folds thus deprived of their blood-supply perish and disappear (Fig. 8). All the six folds of the

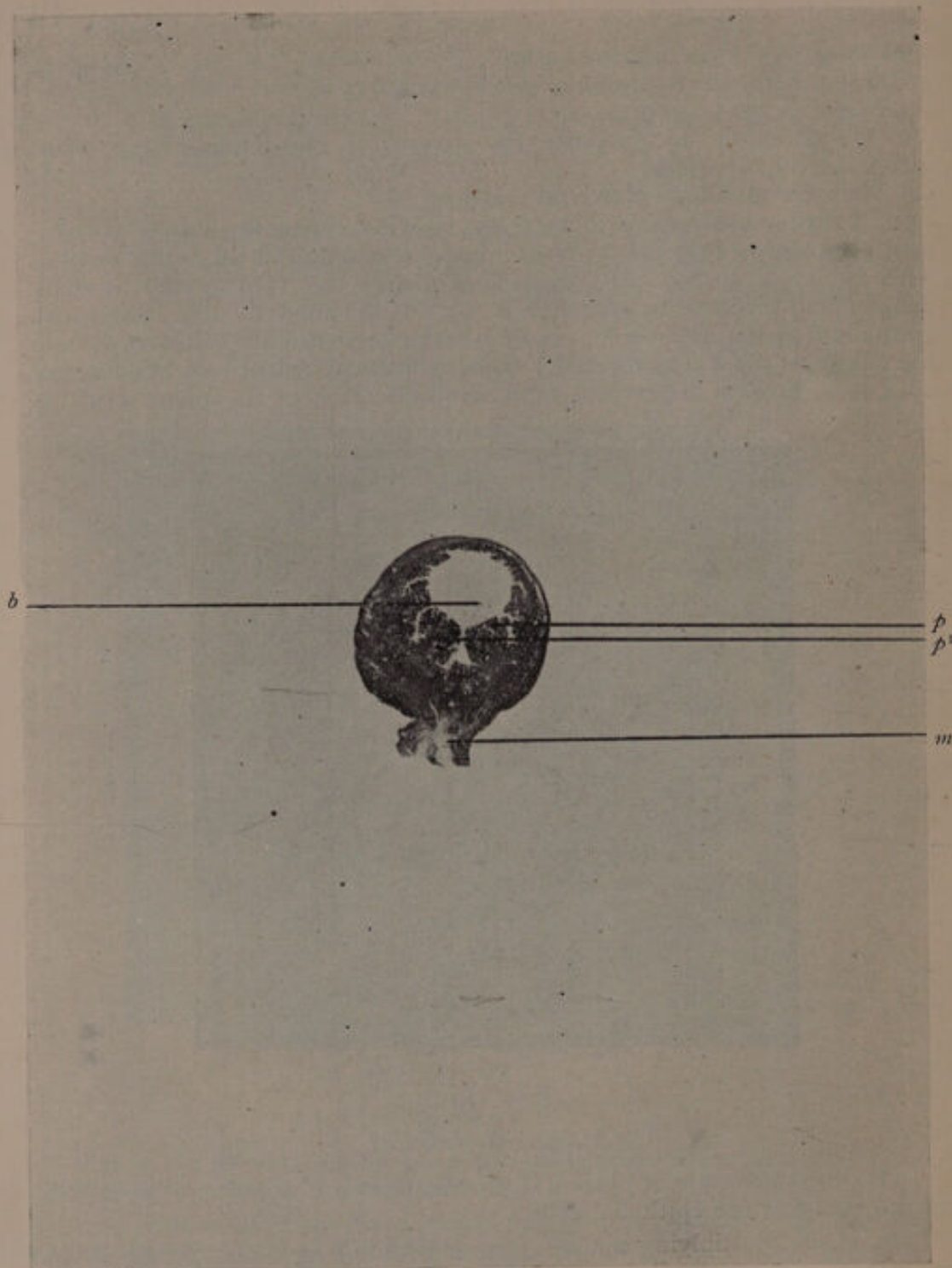


FIG. IX.

(5 days' Gestation.)

Transverse section of a gestation sac of 5 days. The six mucosal folds are still distinct, and within the cavity lies the blastophere.

b, blastophere (indistinct); *m*, mesometrium; *p, p¹*, placental folds.
(Photo.)

uterine mucosa are in this way shortened, but especially the ob-placental folds. The multiplication of the epithelium, most marked upon the surface folds, is not seen in the deeper *cul-de-sacs*.

While the mesometric folds are thus shortened, there is a marked hyperplasia of their sub-mucous tissue, especially in the zone next the musculature (Fig. 7). There is an increase in the number of the star-shaped and fusiform connective tissue cells, a marked addition of inter-cellular substance, and the blood-vessels also become more numerous. In this way these mesometric folds, the *placental folds*, are thickened at their bases. A similar change, though less marked, is seen in the peri-placental folds.

GESTATION SAC OF 5 DAYS (FIG. 9).

The position of the ova is now evidenced by slight swellings seen along the ventral aspect of the uterine cornu.



FIG. X.
(5 days' Gestation.)

Section of a blastosphere of five days. It has been deeply wrinkled by the fixing agent.

a, area shown in Fig. 11.

(1) Foetal tissue :—ovum.

I have not succeeded in preserving the blastodermic vesicle *in situ*, but I have removed several from the uterus, fixed and cut them in the usual way.

Fig. 10 represents a section of a blastosphere. It is scalloped and wrinkled by the action of the fixing agents, but is seen to be composed

of a single layer of fusiform cells, the ectoblast, outside which is a homogenous envelope in which no structure is visible (Fig. 11). This outside envelope is either the Zona Radiata, or a covering derived from the mucoid secretion of the mucosa.

(2) Maternal tissue :—placental mucosa.

The cavity of the gestation sac has increased in size and preserved its regular outline. The lining epithelium exhibits the same appearances as seen on the previous day, the nuclei are rapidly multiplying often with no division of the surrounding protoplasm, and the fine terminal folds of the mucosa atrophy and disappear (Fig. 12).

The mesometric folds are now truncated, while the mucosa of their free extremities is arranged in a series of tubular folds of nearly



FIG. XI.

(5 days' Gestation.)

High-power view of the wall of the blastosphere, the thick external envelope is the Zone Radiata, and within is a single layer of fusiform cells, the Ectoblast.

e, ectoblast ; *z*, zone radiata.

uniform length. The deeper of the *cul-de-sacs* are not affected by this change and are lined by the ordinary cylindrical epithelium.

The hyperplasia of the sub-mucous tissue has further thickened the placental folds.

GESTATION SAC OF 6 DAYS.

The gestation sac is now marked by a well-defined swelling of the uterine cornu.

(1) Fœtal tissue:—ovum.

I have failed to preserve the blastosphere. The cavity of the gestation sac appears empty save for scattered homogeneous masses (mucoid débris) which are stained pink with the eosin.

(2) Maternal tissue:—placental mucosa.

The regular outline of the gestation sac is well preserved.

The placental folds are shorter and thicker, for while the narrow tubular foldings of the mucosa of their free extremities are reduced in



FIG. XII.

(5 days' Gestation.)

Great multiplication of epithelial cells with strangulation of vascular axes and so shortening of the glandular folds.

n, n^1 , multiplying epithelial cells.

length, the hyperplasia of the sub-mucous tissue or corium has continued (Fig. 13).

In this corium the number of the capillaries is greatly increased.

At this time giant cells appear in the ob-placental folds. These cells are of enormous size, with coarsely granular round or oval bodies; the nucleus often has a slight space round it, and shows an indistinct

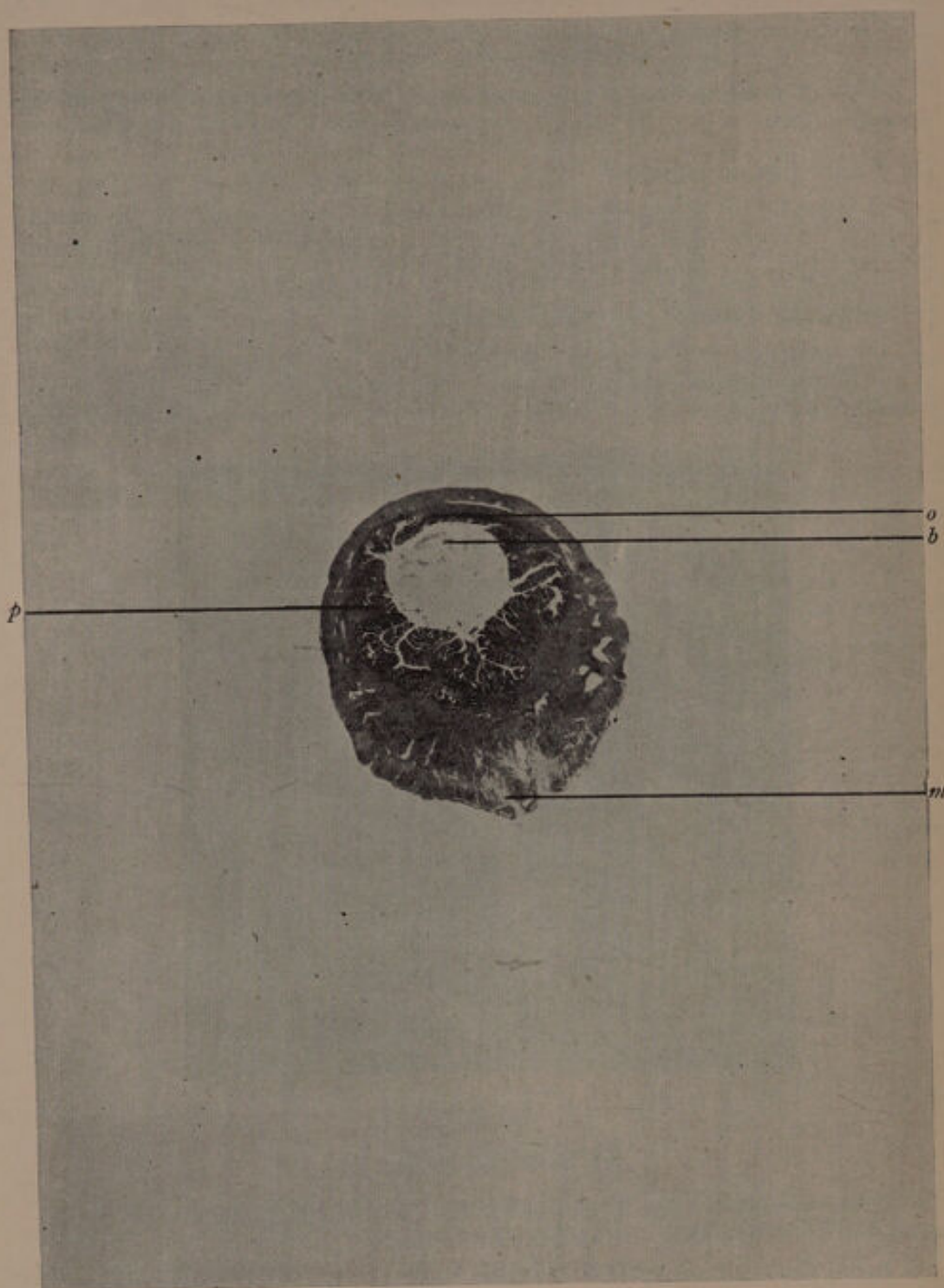


FIG. XIII.

(6 days' Gestation.)

Transverse section of a gestation sac of 6 days.

b, blastophere ; *m*, mesometrium ; *o*, ob-placenta ; *p*, peri-placental folds. (Photo.)

net-work, through which are scattered large fragments of chromatin (Fig. 14). These cells originate from the ordinary epithelial cells, either surface or glandular (Fig. 15), by a process of "degenerative hypertrophy." The nuclei fragment and there is a great growth of cell protoplasm. The smaller of these cells are found near the epithelium, the larger ones deeper, and even among the muscular fibres of the circular coat. I have never found these cells in the placental folds, and have observed that they persist in the ob-placental folds at least until the 14th day of gestation.

GESTATION SAC OF $6\frac{1}{2}$ DAYS (FIG. 16).

(1) Foetal tissue:—ovum.

The blastodermic vesicle is fairly well preserved, though its outline is corrugated. The ectodermal cells are large and cubical, while the

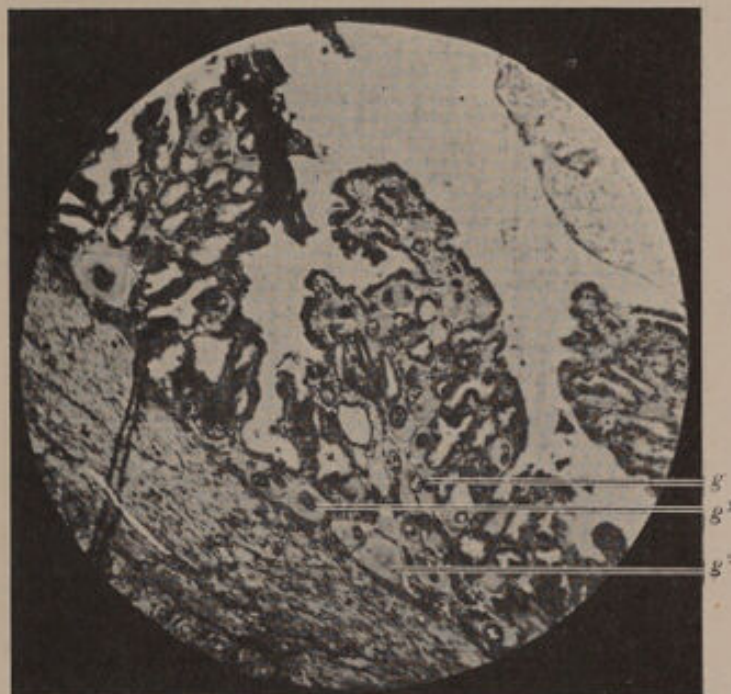


FIG. XIV.

(6 days' Gestation.)

Ob-placental folds showing giant cells.

g, g^1, g^2 , giant cells.

lining endoderm is thin. A primitive streak and groove are visible (Fig. 17).

(2) Maternal tissue:—placental mucosa.

The outline of the gestation sac is no longer regular: the ob-placental folds, as such, have disappeared, and there is marked thinning of the muscular walls of the "uterus."

The mesometric or placental folds have increased in size, and have become more definitely outlined; they now deserve the name "coussinets" which Hollard has given them. These "coussinets" are rendered more conspicuous by the comparative slow increase in the size of the periplacental folds. Their free extremities are much more regular, for the tubular foldings of the mucosa, the placental glands, are shorter and less numerous, and a marked hyperplasia of the corium is evident throughout their entire length (Fig. 18). The covering epithelium no longer shows a rapid multiplication of its nuclei, for each nucleus is now surrounded by a greater or less amount of protoplasm, and cell-outline is very often distinct (Fig. 19). The destructive process by which the placental folds have been shortened is now at an end: henceforward the process is rather a formative one, and already is begun the formation of

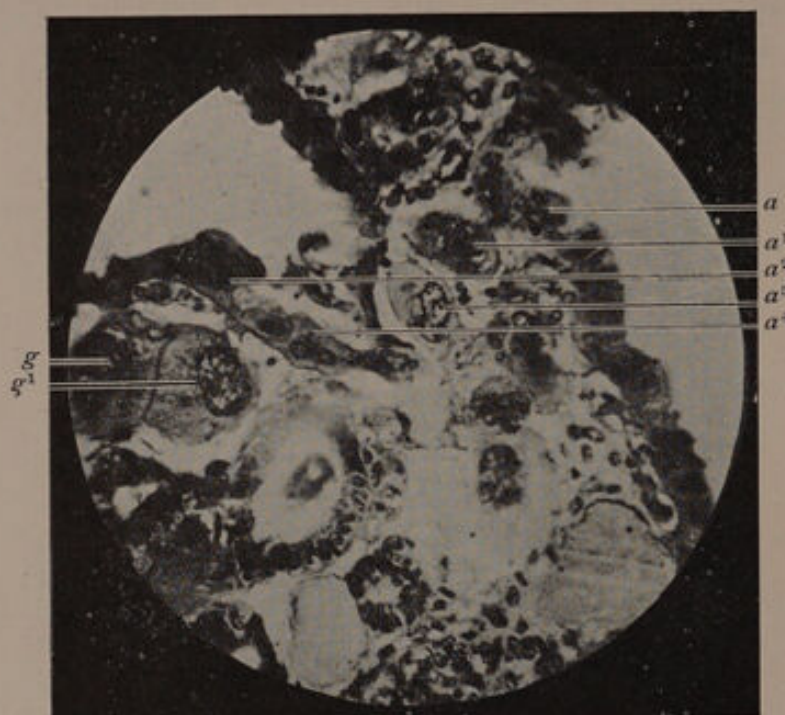


FIG. XV.

(6 days' Gestation.)

Origin and development of giant cells.

g, g^1 , giant cells; a, a^1, a^2, a^3, a^4 , shows development of giant cells from cylindrical epithelial cells.

that more or less regular face, which at the 7th and 8th days the placental folds present to the embryonic ectoderm.

GESTATION SAC OF 7 DAYS (FIG. 20).

(1) Foetal Tissue :—ovum.

The embryonal area (blastodisque of van Beneden) is now outlined (Fig. 21). It is directed toward the placental cotyledons. Cut trans-

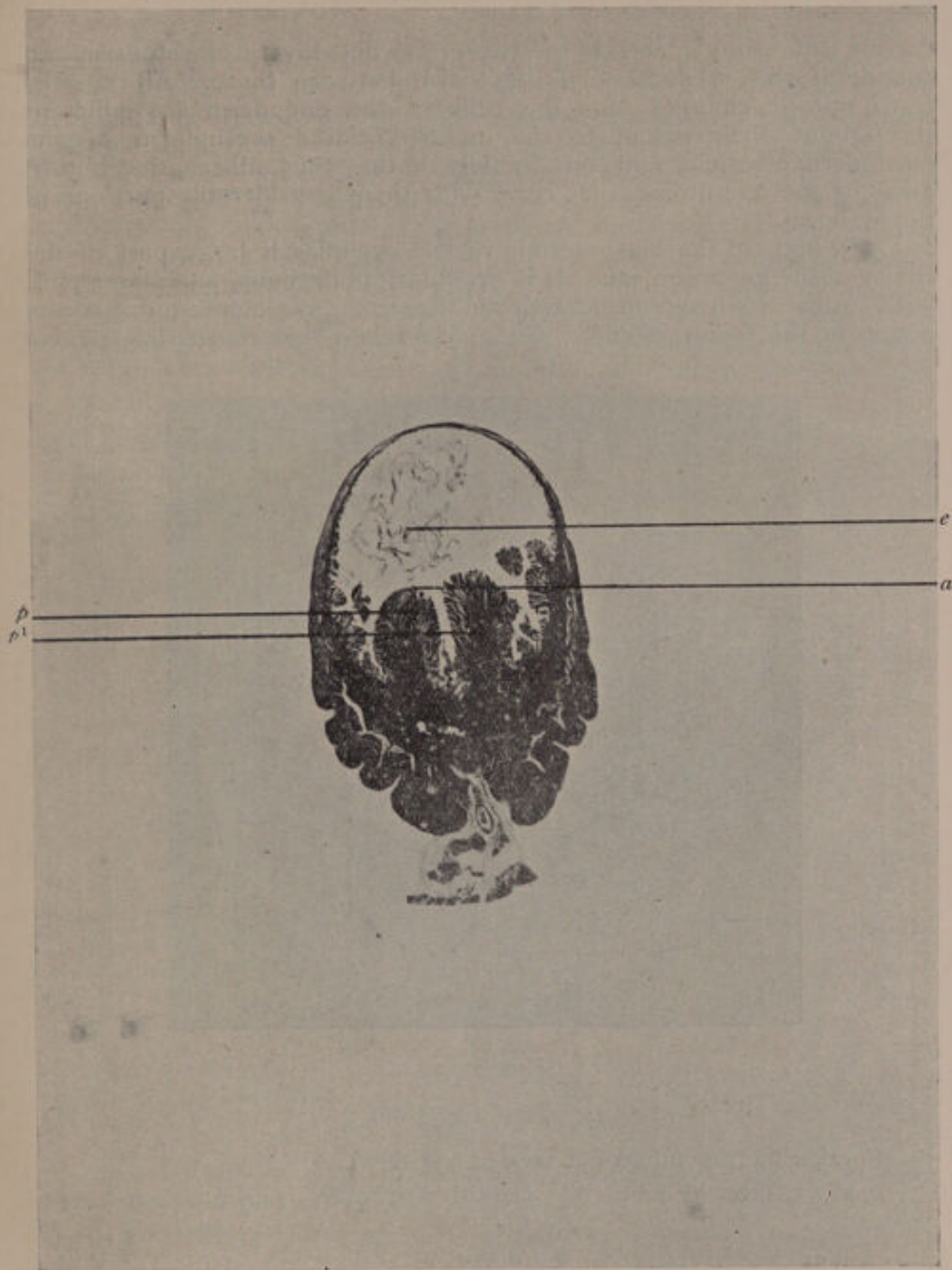


FIG. XVI.

($6\frac{1}{2}$ days' Gestation.)

Transverse section of a gestation sac of $6\frac{1}{2}$ days. The placental folds are conspicuous and the muscular walls of the non-mesometric half of the uterus are greatly thinned.

a, area shown in Fig. 18; *e*, embryo; *p, p¹*, placental folds "Cousinets."

versely it presents in section the two primordial layers of ectoderm and endoderm with a nucleus of mesoderm between these. All the cells show mitotic changes, and the cells of the endoderm are adherent throughout their extent to the undifferentiated protoplasm of the blastodermic vesicle, and so intimately do they thus adhere, that if torn away by the microtome, they carry with them considerable portions of the material.

The body of the blastodermic vesicle occupies a large part of the cavity of the gestation sac. It is granular, amorphous, and stains pink with eosin. Its irregular contour and fissured character are due to the action of the fixing agents. So marked is often the shrinkage, no



FIG. XVII.

($6\frac{1}{2}$ days' Gestation.)

Section of the embryonal area at $6\frac{1}{2}$ days.

a, a^1, a^2 , mucoid debris ; g , primitive groove ; s , primitive streak.

matter what fixing agent is employed, that Minot records a failure to preserve in any degree the contour of the blastodermic vesicle in his specimens of six and seven days.

(2) Maternal tissue :—placental mucosa.

The site of the future placenta is more clearly defined. The two "coussinets" now fairly deserve the name of "cotyledons" which Duval has given them, though these cotyledons have increased in

prominence not so much by their own growth as from the fact of the further resorption and shrinkage of the remaining portion of the mucosa. Between them is now a well-marked intercotyledonary groove. The epithelium (Fig. 22) covering the free surface of the cotyledons is thickened, the cells are greatly increased in size, due to a growth of cell protoplasm, cell outline is in places becoming indistinct: cells tend to fuse together, the nuclei are increased in number, and are in groups in the deeper parts of each cell. These nuclei do not stain evenly, they have clear centres, with the colouring matter fragmented and scattered about their periphery. The above changes, "a hyaline degeneration," are more marked upon the exposed surface of the cotyledons: within the glands, on the other hand, they are much

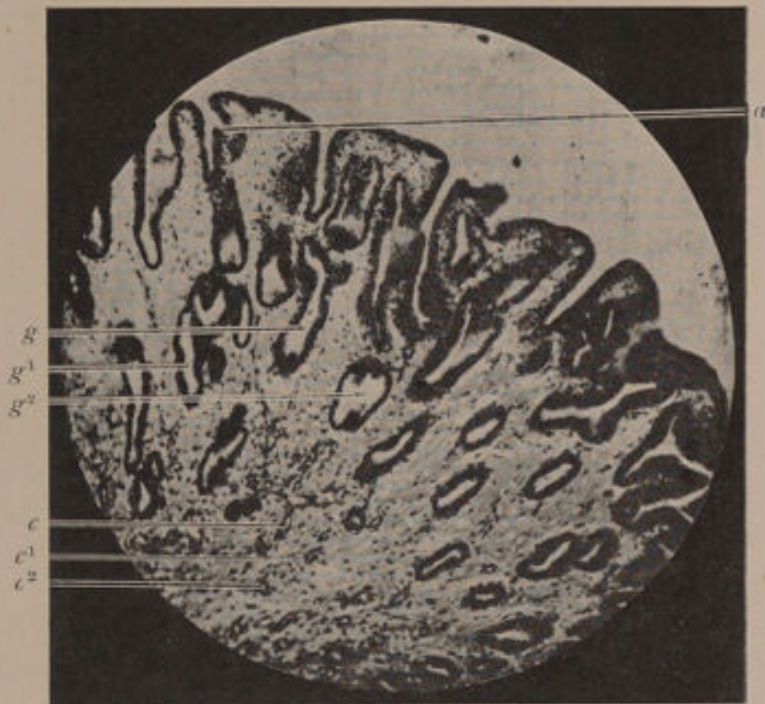


FIG. XVIII.

(6½ days' Gestation.)

Free surface of placental fold. The glandular foldings are short; there is marked hyperplasia of the corium.

a, area shown is Fig. 19; *c, c¹, c²*, capillaries; *g, g¹, g²*, glands.

less evident. For here the cells are not so large, and they also possess for the most part a single evenly-stained nucleus and a distinct cell wall.

The glands themselves are somewhat dilated, and of nearly uniform depth.

As in the earlier stages the main body of the cotyledons is composed of connective tissue cells with large oval nuclei and long interlacing processes. Blood-vessels are numerous and large. Immediately next

the musculature they have a longitudinal direction, but for the most part they run radially in the plane of the section. These vessels have no muscular wall or adventitia, are of the nature of capillaries—a condition which has also been observed in the placenta of the guinea-pig by Leighton. Near the free surface of the cotyledons these capillaries, though large in size, retain their simple endothelial wall; in the deeper zones there is found pressed against such a simple wall an acquired adventitia formed of one or two layers of large cells (Fig. 23). These layers of cells (perivascular sheaths of Masquelin and Swaen) are derived from the neighbouring connective tissue cells; one can follow their development, and they represent the first appearance of the decidual cell. These cells are large, spherical, with a single round or oval nucleus.



FIG. XIX.

(6½ days' Gestation.)

Shows the thickening of the epithelium, surface and glandular, of the placental lobe.

g^1, g^2 , glandular epithelium; s , surface epithelium (multiplying).

GESTATION SAC OF 8 DAYS (FIG. 24).

(1) Foetal tissue:—embryo and adnexa.

This section is of special importance as it represents the first organic contact of the embryonic and maternal tissues which go afterwards to form the placenta. My own sections give the only representation of this early contact that I have been able to find. It will be

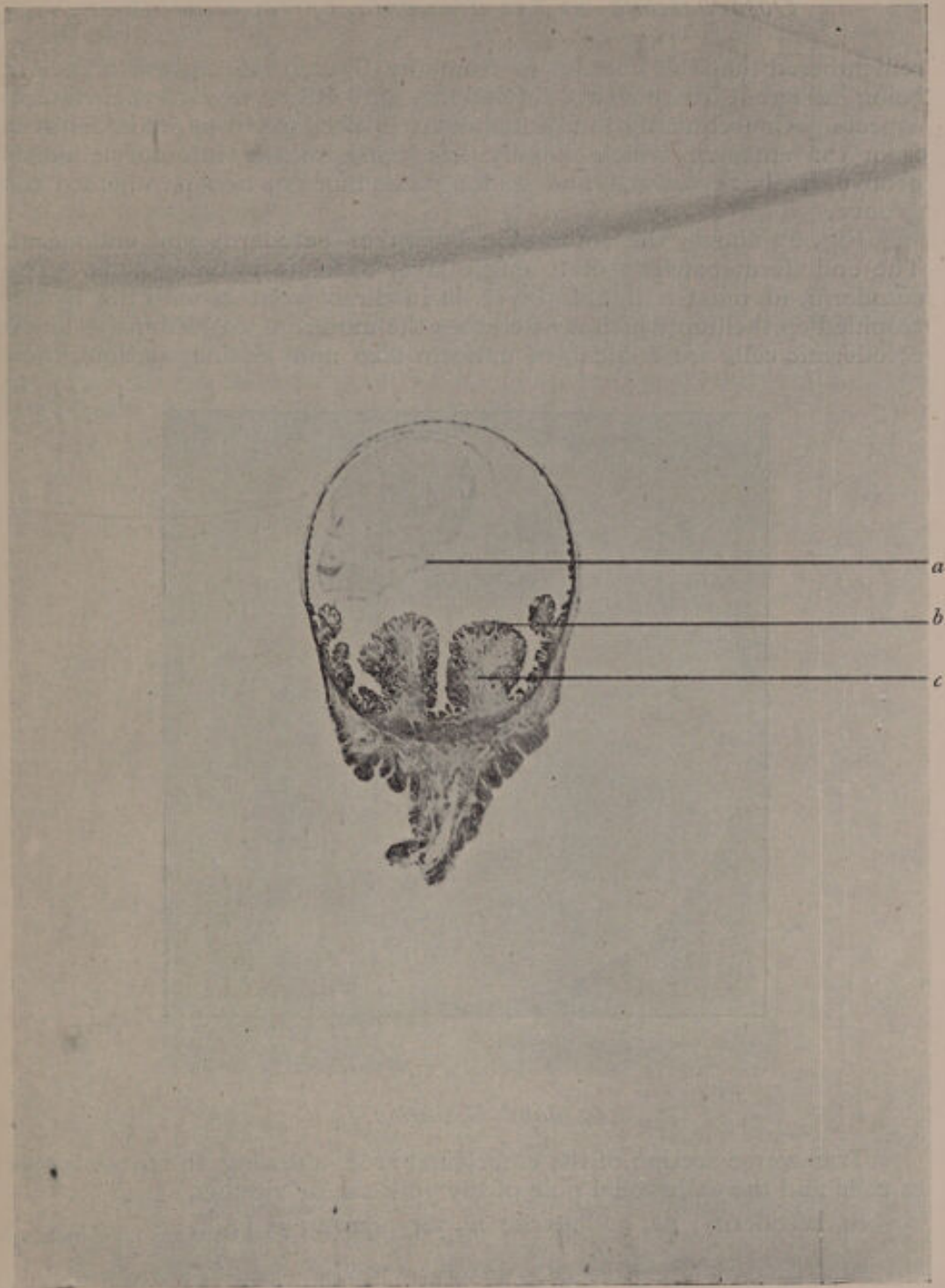


FIG. XX.

(7 days' Gestation.)

Transverse section of a gestation sac of 7 days. The placental folds (coussinets) are large, the muscular walls of the sac are thin and the embryo is outlined.

a, area shown in Fig. 21 ; *b*, area shown in Fig. 22 ; *c*, area shown in Fig. 23. (Photo.)

remembered that this contact is from the first bi-lateral, the ectoderm being adherent to the two cotyledons, and rather toward their lateral aspects. Consequently this attachment is first made at some distance from the embryo, which usually lies opposite the intercotyledonary groove, its back toward, and its long axis more or less parallel to the groove.

Fig. 25 shows the embryonic layers of ectoderm and endoderm. The endoderm consists of a single layer of fusiform lining cells. The ectoderm, at most a double layer, is in direct contact with the hypertrophied epithelium which now clothes the maternal cotyledons. These ectodermic cells are cubical, of uniform size and distinct outline, their

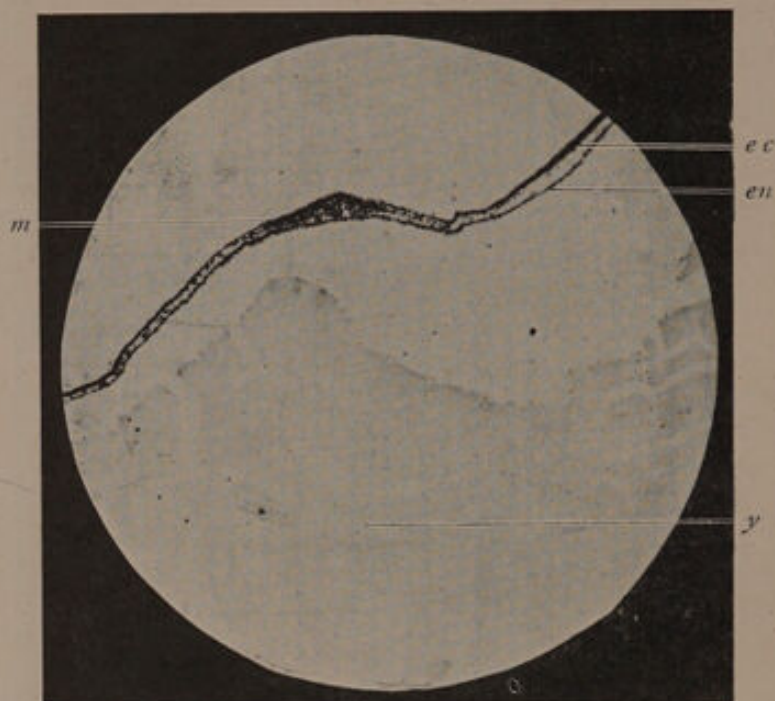


FIG. XXI.

(7 days' Gestation.)

Transverse section of the embryonal area, showing the three layers of cells and the embryonal pole of the yolk-sac or vitellus.

ec, ectoderm; *en*, endoderm; *m*, mesoderm; *y*, yolk.

protoplasm is coarsely reticular, their nuclei are large, uniformly and deeply stained, with here and there Karyokinetic changes (Fig. 27). These extremely active cells are laid directly upon the maternal epithelium which is now fused into a thick, amorphous, protoplasmic layer. Thus the contact is that of two more or less plane surfaces, albeit the small irregularities in the outline of the reticulated embryonic cell impinge and impress upon the structureless and less viable maternal covering. In this way it seems to me the contact is made. This con-

tact is enforced and its area extended solely at the expense of the maternal layer; for while the ectoderm will extend and thicken its area of attachment, the degenerated epithelial layer will lose in corresponding degree. In other words the active embryonic cells appear to corrode and penetrate the less viable maternal tissue, the which may possibly serve as a pabulum.

Minot in his paper *Uterus and Embryo*, and in respect of this question, affirms that his studies afford no explanation.

He surmises, however, that the attachment of the ectoderm to the maternal epithelium may be due to a simple agglutination or to a process of mutual growth "as a graft unites with a bough." But as Minot here regards the thickening of the ectoderm as degenerative also, these hypotheses in view of later facts are proved gratuitous.

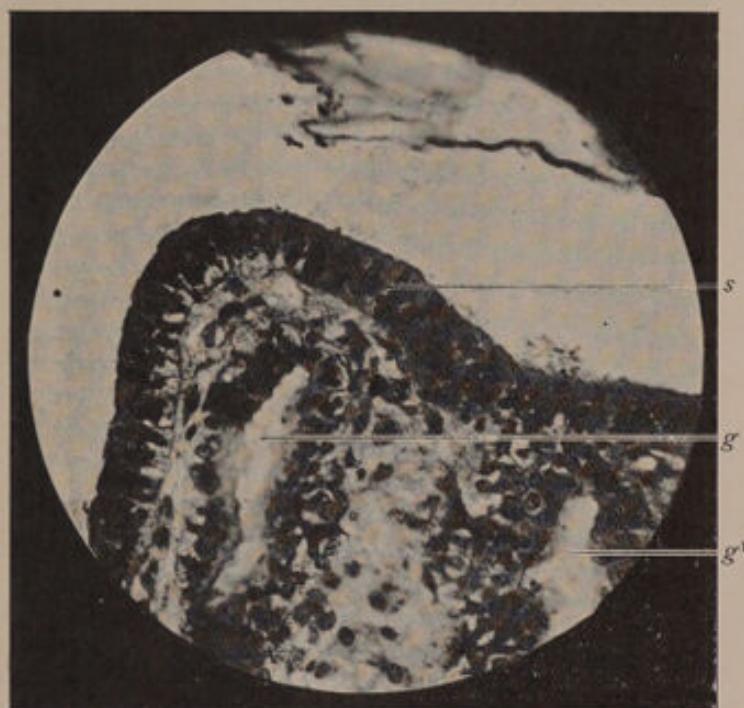


FIG. XXII.

(7 days' Gestation.)

Surface epithelium of placental lobe, showing direct division of nuclei and increase of cell protoplasm.

g, g¹, glands cut obliquely; *s*, surface epithelium (thickening.)

(2) Maternal tissue:—placental mucosa.

The two cotyledons have not greatly increased in size. The most marked change is seen in the epithelial covering. This layer throughout its extent (Fig. 26), but especially over the more exposed areas, shows a continuation of the change already begun at the 7th day. Now all cell-outline is lost, the cell protoplasm has increased in amount and appears as a continuous and amorphous stratum, in the deeper areas of

which lie the nuclei, greatly increased in number, irregularly grouped and yet occupying this definite deeper zone. This protoplasmic layer stains faintly and in places is vacuolated; in many instances the gland openings, to a variable depth, are blocked by their swollen epithelium, and so this amorphous stratum comes to present an unbroken face to the embryo. This degenerative change extends down the glands into all save the deepest *cul-de-sacs*. The nature of this change is regarded by Minot as "a hyaline degeneration with hyperplasia of the degenerating elements" witnessed by growth of the protoplasm, and the proliferation of the nuclei. The same observer tenders the hypothesis "that the degeneration consists in direct change of the protoplasmic reticulum into hyaline substance."

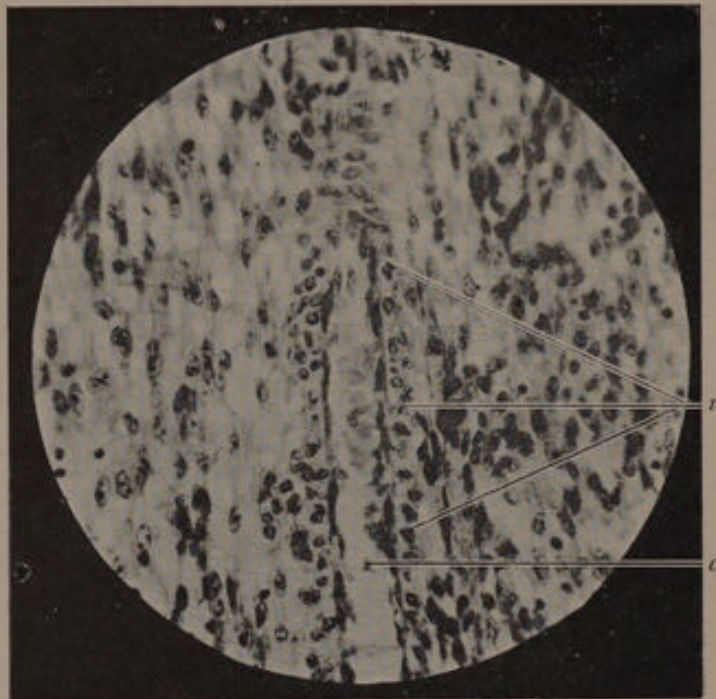


FIG. XXIII.

(7 days' Gestation.)

Capillary of placental lobe cut longitudinally. The first appearance of the decidual cell, the perivascular uninucleate decidual cell, and its early arrangement into a perivascular sheath.

c, capillary; *u*, perivascular uninucleate decidual cell.

The addition of perivascular cells is more marked and extends to capillaries nearer the free surface of the cotyledons.

One of the sacs of this 8 days' gestation revealed a development some 6 or 8 hours in advance of all the others. Sections of this sac show a great increase in the area of ectodermal attachment. The ectoderm is here three or four layers in thickness, and the maternal epithelium beneath it is considerably thinned (Fig. 28).

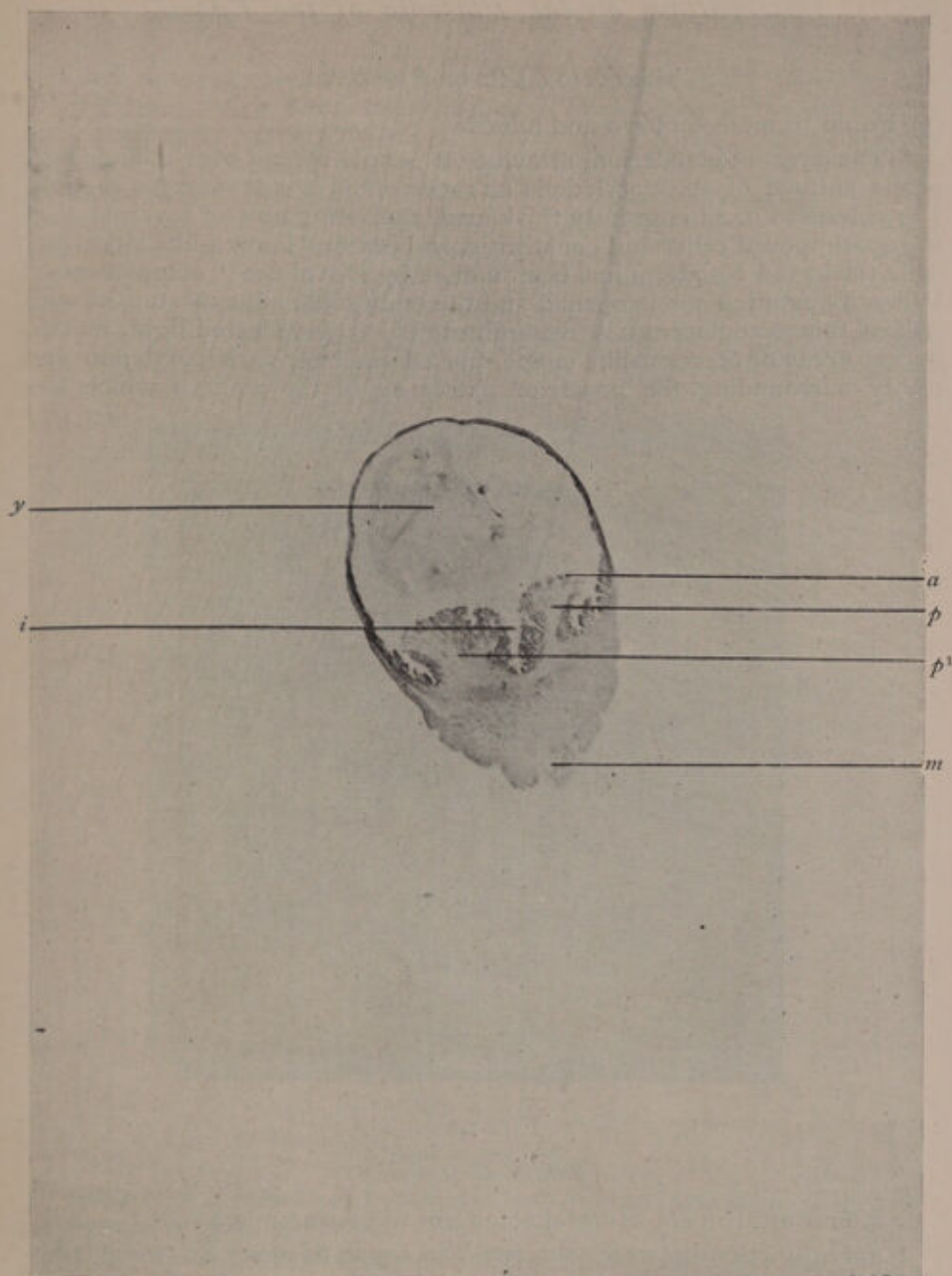


FIG. XXIV.

(8 days' Gestation.)

Transverse section of gestation sac of 8 days. The embryo and its first attachment to the uterine mucosa appears only indistinctly with this power.

a, area shown in Fig. 25 ; *i*, intercotyledonary groove ; *m*, mesometrium ; *p*, *p*¹, placental folds or cotyledons ; *y*, yolk.

GESTATION SAC OF $8\frac{1}{2}$ DAYS.

(1) Fœtal tissue:—embryo and adnexa.

The area of ectodermal attachment is now spread over a large part of the surface of the cotyledons as represented in a transverse section. The ectoderm itself is greatly thickened, consisting now of several layers of superimposed cells, and constituting a bi-lateral lamina-like structure. This thickened ectoderm has been named by Duval the "ectoplacenta." When a gestation sac is opened and the embryonic adnexa studied with a lens this ectoplacenta is recognized, even by reflected light, as two darker areas of crescent-like shape, placed one over each cotyledon and partly surrounding the posterior extremity of the embryo which lies

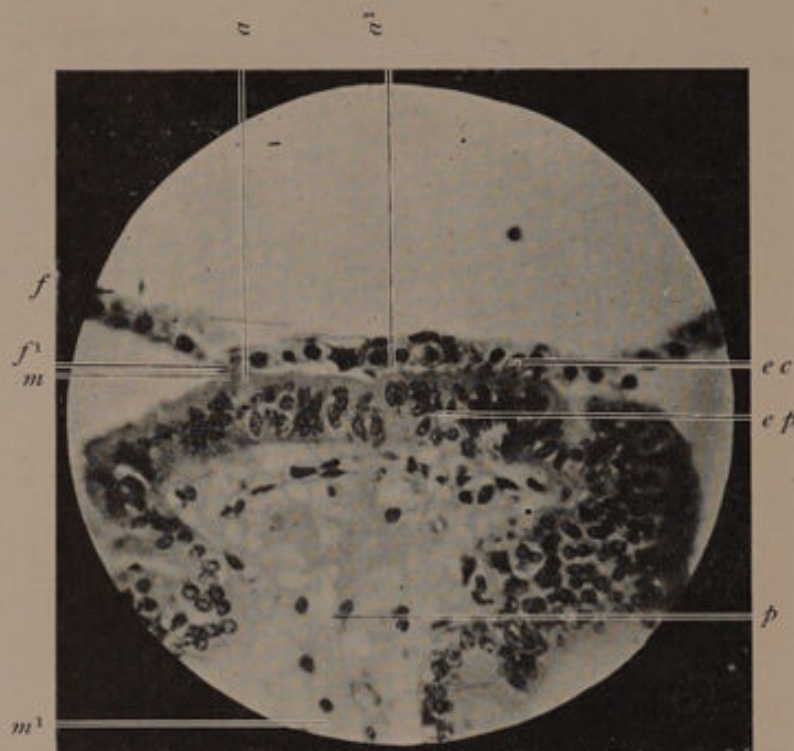


FIG. XXV.

(8 days' Gestation.)

A first attachment of fœtal ectoderm to uterine mucosa.

a, a¹, junction between maternal and fœtal tissues; *ec*, fœtal ectoderm; *ep*, epithelium covering placental lobe; *p*, placental lobe; *f, f¹*, fœtal tissue; *m, m¹*, maternal tissue.

between them. These two crescents represent the area of ectodermal attachment, and have together a shape not unlike a horse-shoe, and consequently have been named by van Beneden, who first described them "fer à cheval placentaire."

In section and under the microscope this ectoplacenta is now seen deeply soldered to the degenerated maternal epithelium, the greater part

of which has disappeared from beneath it. Fig. 30 shows its lateral line of attachment to the uterine epithelium. The junction of the two tissues is seen and their further application the one to the other. The embryonic cells are of uniform size with dark evenly-stained nuclei, and are multiplying rapidly. The surface of the uterine epithelium to which they are attached, presents under a high power a bitten or corroded appearance. This epithelium is rapidly disappearing; already in many places it is represented only by a thin hyaline band, separating the aggressive embryonic cells from the delicate connective tissue of the cotyledons. It will be remembered that at the 8th day the mouths of the uterine glands were already blocked by their hypertrophied cells, and that the thickened

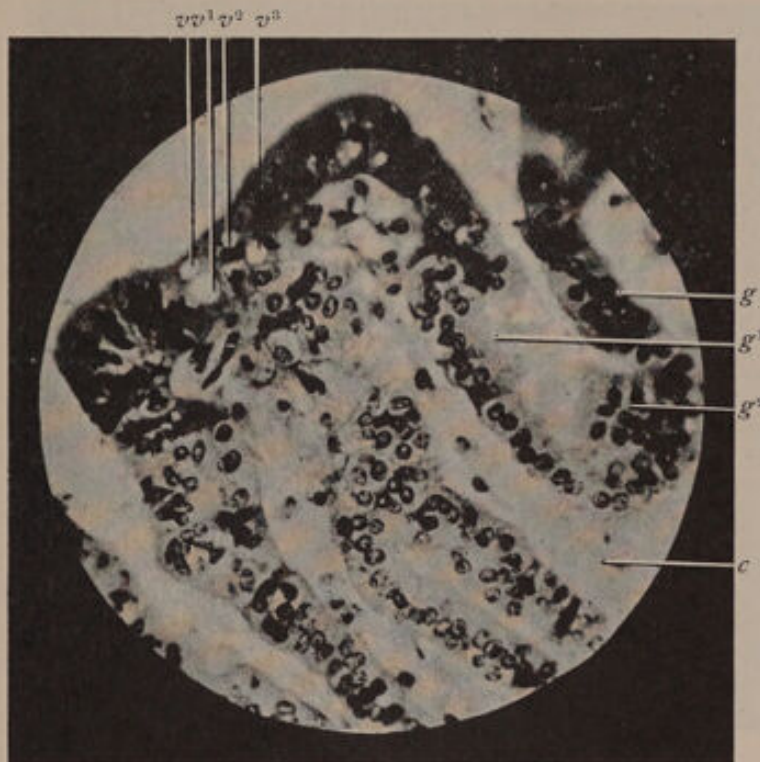


FIG. XXVI.

(8 days' Gestation.)

Shows great thickening of epithelium, surface and glandular, over free surface of placental lobes. Vacuoli appear.

c , corium ; g, g^1, g^2 , hyperplasia of glandular epithelium ; v, v^1, v^2, v^3 , vacuoli.

epithelium of the cotyledons presented an almost unbroken face to the approaching ectoderm. Along this unbroken face the thickened ectoderm—the ectoplacenta—has been laid. Nevertheless the line of union is already markedly undulating, the ectoplacenta dipping much deeper at some places than at others. As is shown in Fig. 31, at this date these incursions obtain only at the blocked mouths of the glands. It is as if

the epithelial barrier presents at these areas a weaker resistance, a supposition supported by the facts that the maternal cells here are farthest from their blood-supply and that vacuoli occur first and in largest number at these places. These incursions mark the first appearance of the "foetal villi."

The sinus terminalis is also seen in Fig. 30. This vessel is filled with nucleated foetal blood, and marks the peripheral limit of the vascularization of the umbilical vesicle.

From this section it is clear that the embryo is attached to the maternal placental surface by the ectoderm alone, the other layers are

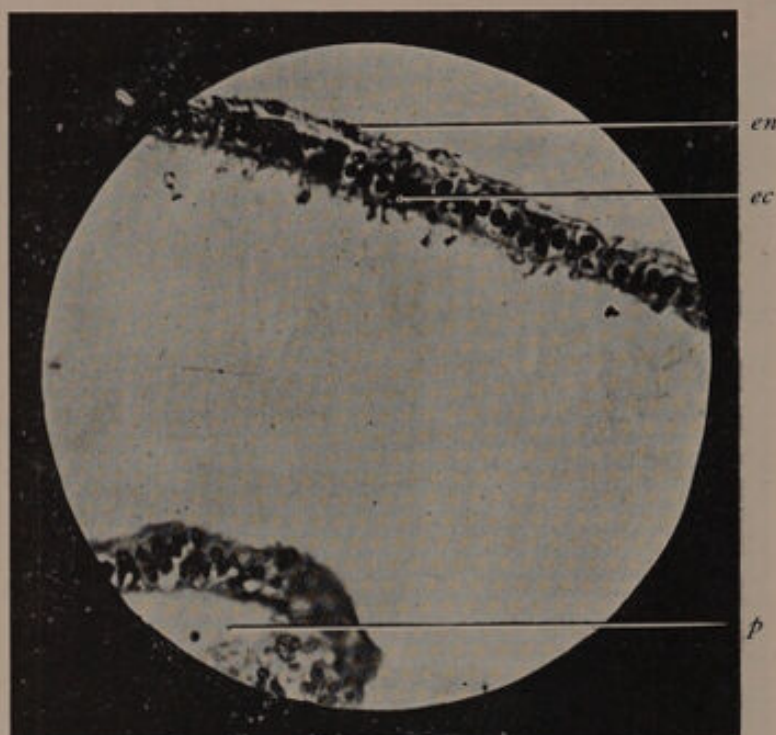


FIG. XXVII.

(8 days' Gestation.)

Section of foetal ectoderm and endoderm slightly nearer the embryonal area than that shown in Fig. 25.

ec, foetal ectoderm ; *en*, foetal endoderm ; *p*, placental lobe.

not concerned in this attachment. In (Fig. 29) the embryo will be observed cut transversely and with a completed amniotic sac.

(2) Maternal tissue :—placental mucosa.

The degenerated epithelial covering, though greatly thinned is still intact ; the ectoplacenta is nowhere in actual contact with the maternal connective tissue and its included vessels. The glands, save in rare instances, are represented now by solid branching columns of degenerated

epithelium. The most important changes however, in the cotyledons are associated with the vessels. The perivascular decidual sheaths noted at the 7th day, and increased in thickness and extent at the 8th, are now found round all save the most superficial capillaries. To these most superficial capillaries decidual sheaths never come to be applied, and they retain for the present their simple endothelial wall. The sheaths of the deeper capillaries are composed of a single or double row of cells, while in the deepest regions the process is much more advanced, so many rows being here aggregated round each vessel, that neighbouring sheaths are beginning to impinge upon one another, in other words, the deeper

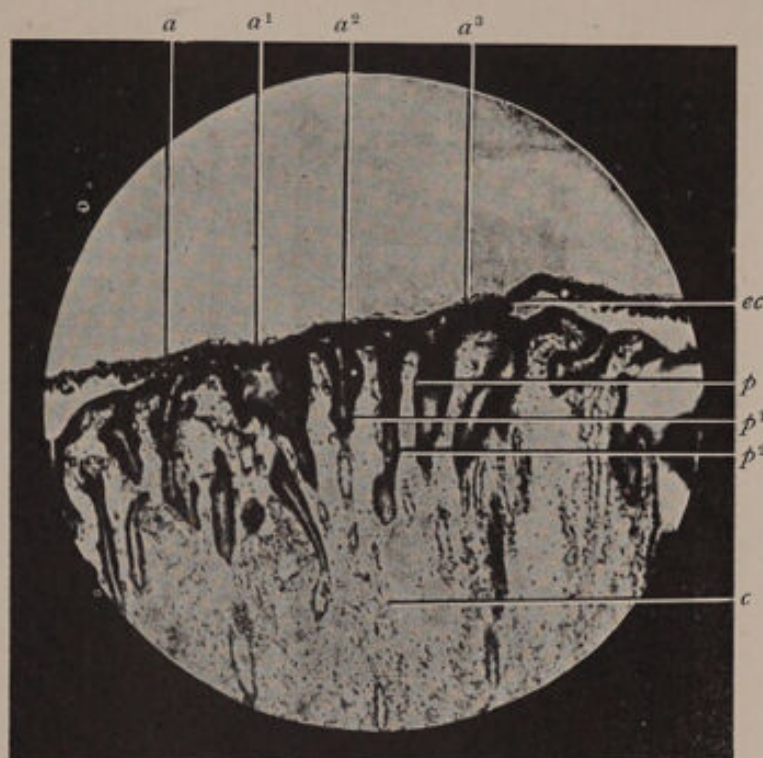


FIG. XXVIII.

(8 days' Gestation.)

Attachment of ectoderm to placental cotyledon, 12 hours later than that shown in Fig. 25. The uterine glands are in many places solid.

a, a^1, a^2, a^3 , line of attachment of foetal ectoderm; ec , ectoderm; p, p^1, p^2 , placental glands; c , corium of foetal lobe.

areas of the cotyledons are coming to be chiefly composed of decidual cells (Figs. 32 and 33.) These cells retain as yet their original characters; they are large, round or oval with a single round nucleus and a considerable amount of cell protoplasm. The character of the deeper vessels so surrounded is completely changed, they are no longer vessels but rather sinus-like spaces with large and irregularly shaped cavities. This change must owe its occurrence to the peripheral growth and traction of these perivascular cells. These sinus-like spaces retain their endo-

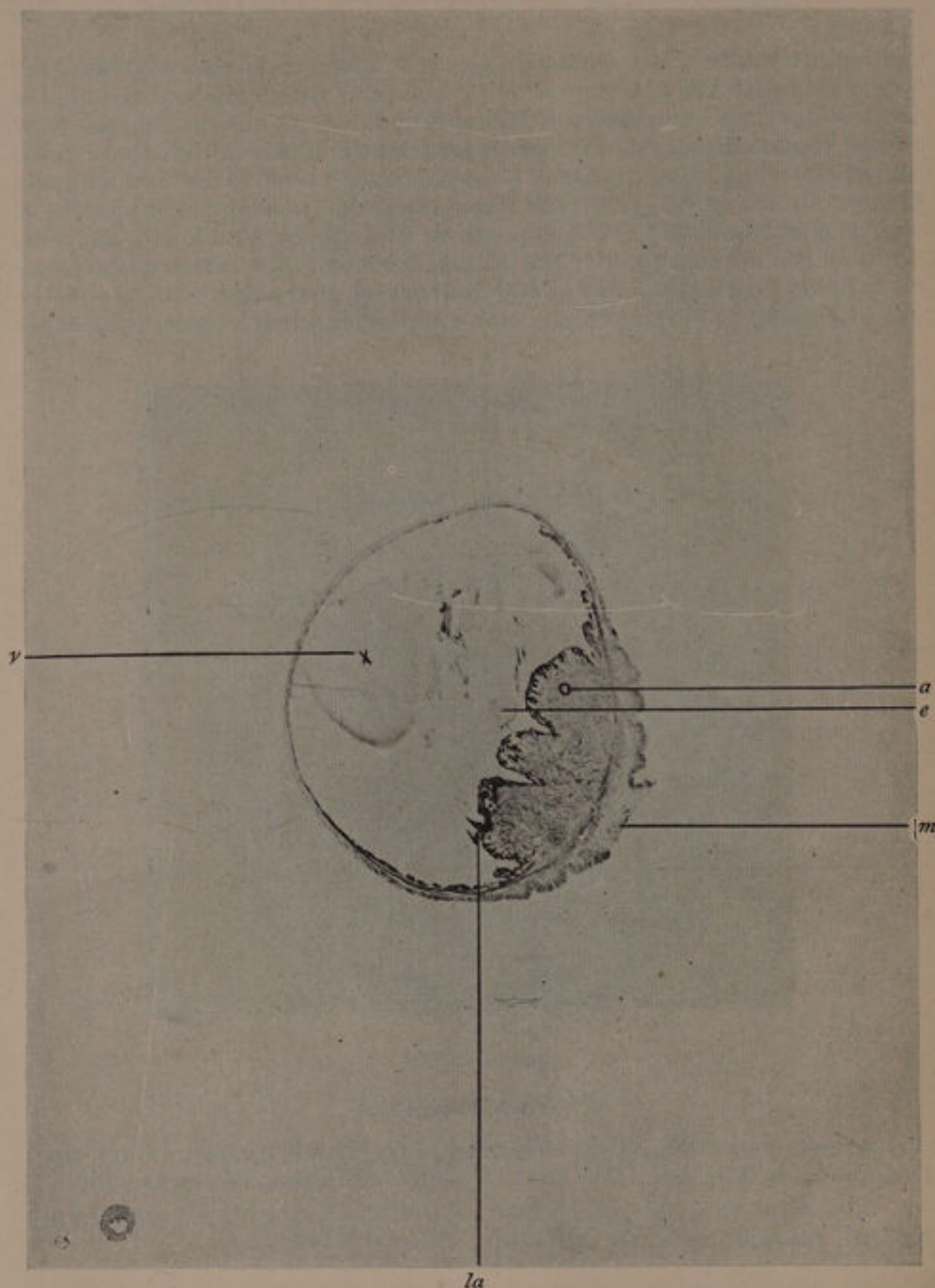


FIG. XXIX.

(8½ days' Gestation.)

Transverse section of gestation sac of 8½ days. The line of attachment of the embryonal ectoderm is seen on the lower cotyledon. The embryo is cut transversely.

a, area shewn in Fig. 32; *m*, mesometrium; *y*, yolk; *la*, line of lateral attachment of the ectoderm, see also Fig. 30. (Photo.)

thelial lining, though the individual cells of this lining are in some places swollen, with large oval nucleui, while in other places they are greatly attenuated with rod-like nucleui.

At this stage— $8\frac{1}{2}$ days—I have endeavored to show by a series of microphotographs the origin and development of the true amniotic sac (Figs. 34, 35, 36, 37, 38, 39). The several sections from which these microphotographs are taken represent a selection from a serial cutting of the entire length of the embryo. The embryo has been cut transversely and the series runs from before backward, and the microphotographs follow the same order. The constitution of the amniotic wall is plainly shown—ectoderm and mesoderm—and also is it evident that the

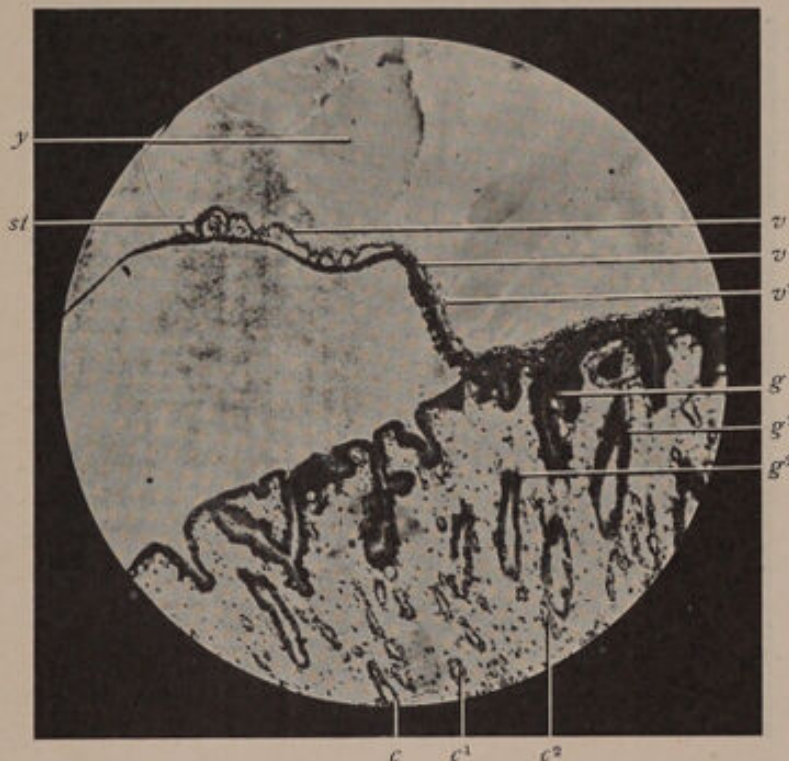


FIG. XXX.

($8\frac{1}{2}$ days' Gestation.)

Line of attachment of embryonal ectoderm to epithelium of placental cotyledon ; vascular wall of yolk-sac and sinus terminalis.

c, c^1, c^2 , capillaries ; g, g^1, g^2 , glands ; v, v^1, v^2 , vascular wall of yolk-sac ; st , sinus terminalis ; y , yolk.

side-folds, at least with relation to the middle regions of the embryo, take a full share in the formation of the sac. Professor Milnes Marshall states in his *Vertebrate Embryology* that in the rabbit the tail-fold takes by far the largest share in the formation of the amnion. My specimens scarcely bear out this assertion. Of the microphotographs Fig. 34 is from a section passing through the middle region of the embryo,

the side-folds are scarcely raised. While Fig. 39 is from a section nearer the tail end where the roof is complete. At this date, therefore, only the tail end is roofed in; it will be remembered that the whole body of the embryo is not so covered until the 10th day.

GESTATION SAC OF 9 DAYS.—(FIG. 40.)

(1) Foetal tissue :—embryo and adnexa.

The ectoplacenta has increased in thickness, and has almost reached its maximum superficial area. It consists of many layers of cells which are still uniform in appearance and still show active mitotic changes.

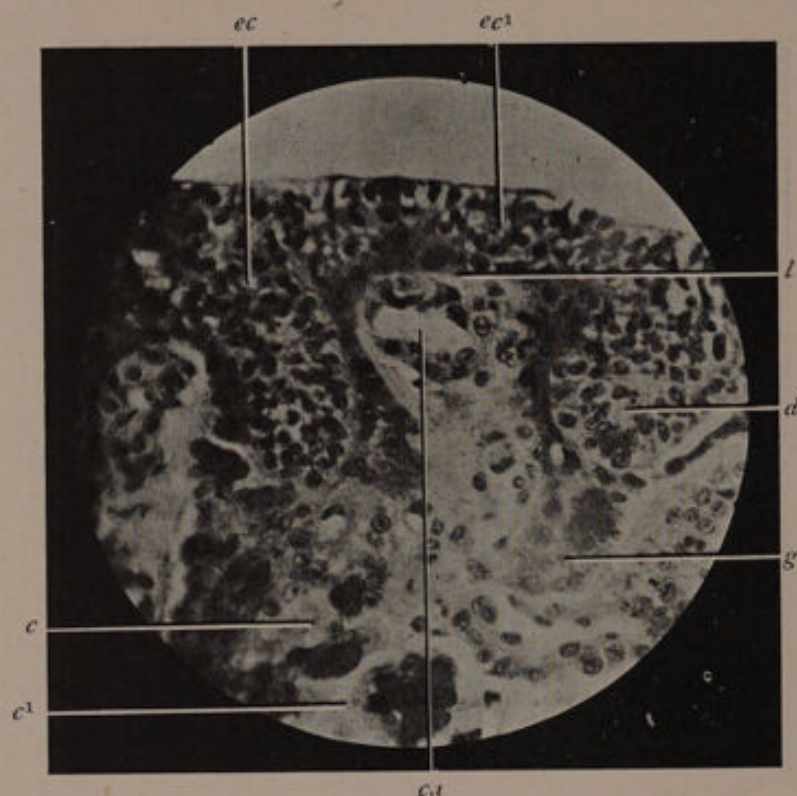


FIG. XXXI.

(8½ days' Gestation.)

Thickened ectoderm, ectoplacenta, attached to placental lobe and dipping more deeply at the position of the glands.

ec, ec¹, foetal ectoderm; *l*, line of attachment of ectoderm; *d*, foetal entoderm dipping into placental gland; *g*, terminal cul-de-sac of placental gland; *ca*, capillary; *c, c¹*, corium.

The most advanced of these cells, those farthest from the thin layer of mesoderm which lines the foetal face of the ectoplacenta, are now in direct contact with the connective tissue of the cotyledons, *for the intervening uterine epithelium has completely disappeared*. The disappearance of this epithelial covering is shown in a microphotograph. (Fig. 41).

The line of fusion of the maternal and embryonic tissues is now still more irregular. The incursions of the ectoplacenta into the gland-mouths have extended more deeply and are more villous-like. In addition new incursions, bud-like in-growths from the ectoplacenta, push their way into the bared connective tissue face of the cotyledons. These later ingrowths select for their invasion the near neighbourhood of a superficial capillary. (Fig. 42). They push in until they reach the endothelium of the capillary, then gradually work round this wall until they completely circumvent the vessel (Fig. 43) which, albeit retaining its endothelial wall, now lies in the midst of tissue of foetal origin. If

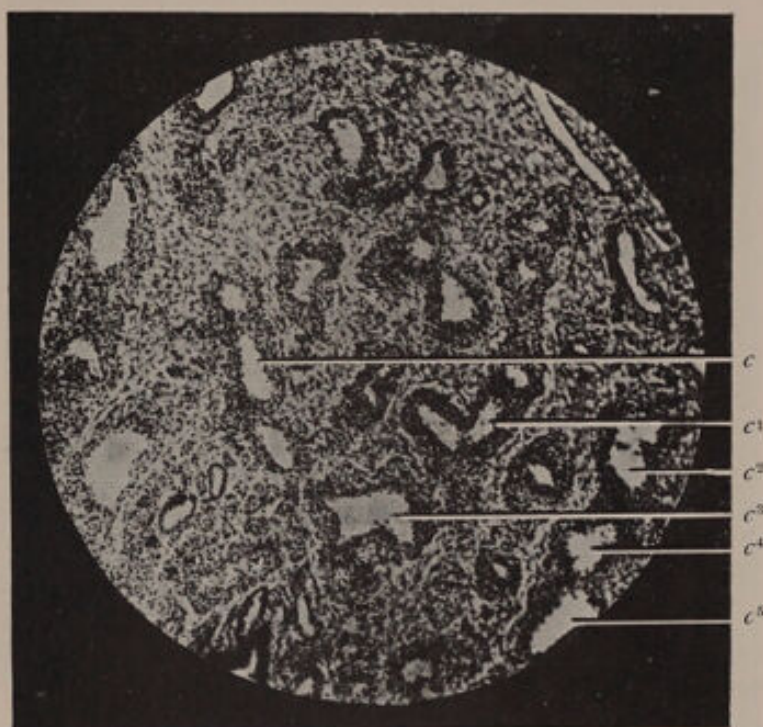


FIG. XXXII.

(8½ days' Gestation.)

Deeper capillaries of placental lobe, already sinus-like and surrounded by sheaths of uninucleate-decidual cells.

c, c¹, c², c³, c⁴, c⁵, capillary-sinuses with perivascular sheaths.

the vessel be cut in its long axis this process of invasion is more distinctly shown.

In this way arises a second variety of "foetal villi." The foetal face of the ectoplacenta is now clothed by a complete *mesodermic* lining.

(2) Maternal tissue :—placental mucosa.

As we have seen, the uterine epithelium has now disappeared and the ectoplacenta is in direct contact with the exposed connective tissue of the cotyledons. This superficial connective tissue has retained its

original adenoid character. But this tissue, during the past 12 hours, has greatly increased in amount until it now comes to constitute a zone—a zone where the great number of the cells are fusiform or radiate connective tissue cells—and where about the vessels there are but thin perivascular sheaths, one or at most two rows of uninucleate decidual cells. The main growth of this zone, which is distinctly shown in the microphotograph (Fig. 44) is due to an increase in the inter-cellular substance which has become oedematous, and through which are scattered many leucocytes. This zone, retiform tissue with lymph coagulum and numerous leucocytes, is identical in structure with a corresponding zone in the placenta of *Perameles* as described by Hill.



FIG. XXXIII.

(8½ days' Gestation.)

High-power view of capillary sinus. The perivascular sheath is plainly visible and the lining endothelium is thickened.

c, corium; *e, e¹*, endothelium; *p, p¹, p²*, perivascular sheaths of uninucleate decidual cells; *s*, capillary-sinus.

I have observed that the formation of this zone always dates from the disappearance of the epithelial covering and the first contact of the underlying maternal corium with the advancing foetal ectoderm. Thus in its birth, and equally also in its constitution, it answers exactly to a reactionary zone—reactionary to the advance of the ectoplacenta. This reaction of the maternal placenta to the "parasitic" foetal placenta was

first suggested by Sir William Turner in the course of his extensive researches. The idea has since been particularized by Hubrecht, Berry Hart and Fothergill, though not in the case of the rabbit. This reactionary zone is called by Duval "*région intermédiaire*" intermediary between the ectoplacenta and the deep region of the maternal placenta—the "*région des sinus utérins*" as Duval names it. Hereafter these two areas become more distinct and persist to the end of gestation. In their nomenclature I shall follow Duval.

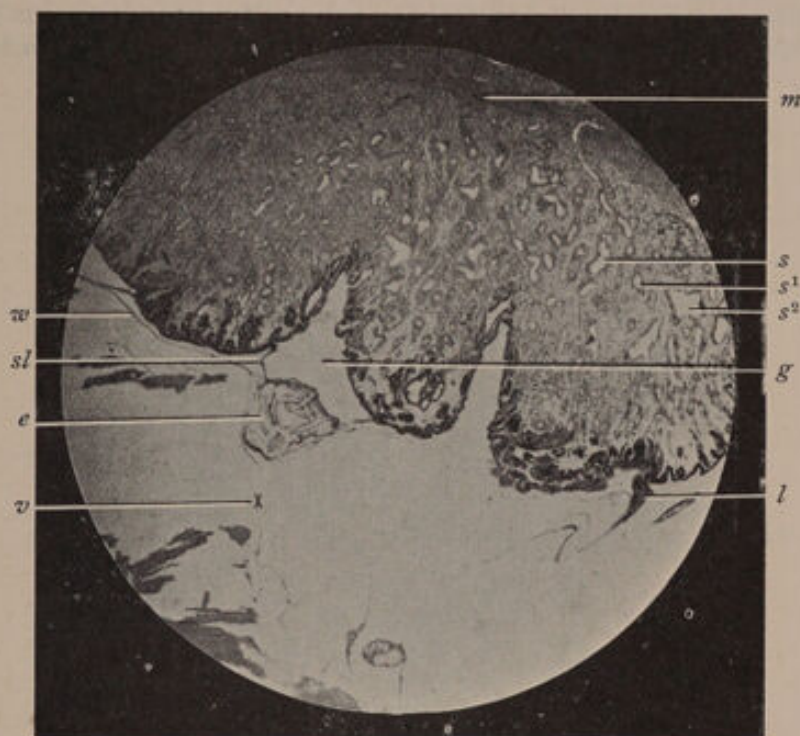


FIG. XXXIV.

(8½ days' Gestation.)

Development of the side-folds of the amniotic sac. Shows the suspensory laminae, composed of ectoderm and mesoderm, beginning to grow upwards over the back of the embryo. The area of chorionic attachment and the vascular wall of the yolk-sac are seen and also the placental cotyledons.

s, s¹, s², Capillary-sinuses; *g*, intercotyledonary groove; *l*, lateral line of attachment of ectoplacenta; *m*, muscular wall of cornu; *v*, cavity of vitellus; *e*, embryo; *sl*, suspensory laminae; *w*, vascular wall of yolk-sac.

This intermediary region is to become the region of the multinucleate decidual cell, and already there are evidences of such histological change. These multinucleate cells play an important role in the further modification of the maternal placenta, and their origin and development is in consequence a matter of some moment. Minot writing in 1889

says "the development of these cells would doubtless repay more accurate investigation."

The illustrative microphotograph (Fig. 45) is from one of a number of specimens which show the actual process. As I have previously indicated the capillaries of the intermediary region are surrounded by one, or at most two, layers of uninucleate decidual cells. The foetal ectoderm is everywhere advancing upon these; already it has reached many of them. These uninucleate cells nearest the ectoderm now undergo a change. The cell increases in size, becomes vesicular, and divides once or twice by direct division; the cell-outline remains distinct. There thus results a large multinucleate cell, with clear content, and



FIG. XXXV.

(8½ days' Gestation.)

Development of the side-folds of the amniotic sac. The suspensory laminae are here more vertical (c.f. Fig. 34).

sl, sl¹, suspensory laminae; *m*, mesenteron.

sharply-defined cell wall—the *multinucleate decidual cell*. These cells increase rapidly in number and in size, and they soon become detached from the perivascular sheaths of their origin, and come to occupy the surrounding oedematous and sparsely-celled corium. This change begins near the foetal ectoderm, and rapidly extends throughout the whole depth of the intermediary region. Thus the *multinucleate decidual cell* arises directly from the *perivascular uninucleate decidual cell*.

This intermediary region or reactionary zone is marked off from the larger and deeper area of the placenta—the region of the uterine sinuses—by the presence at nearly regular intervals of solid masses of amorphous epithelium. These masses which now serve as boundary-posts represent the degenerated epithelium of the deepest *cul-de-sacs* of the uterine glands; they are darkly stained, sewn with irregular nuclear fragments, and appear as islands, for their solid epithelial stalks, which at $8\frac{1}{2}$ days represented the gland-channels, have now disappeared. These islands are rapidly disintegrating. Their fragmented nuclei, in groups of various sizes, become disassociated from the main mass, and often, still included within a portion of the degenerate protoplasm, they



FIG. XXXVI.

($8\frac{1}{2}$ days' Gestation.)

Development of side-folds of amniotic sac. The suspensory laminae—the side-folds—here approach each other (c.f. Fig. 35).

a, a¹, amniotic folds; e, embryo.

come to constitute themselves a sort of multinucleate cell in the midst of the neighbouring corium. I submit a microphotograph (Fig. 46) of several such isolated groups. It will at once be noted that these groups have no cell wall; their surrounding protoplasm ends raggedly. They soon entirely disappear.

In the region of the uterine sinuses the perivascular decidual cells are still more numerous, clothing more thickly the sides of the sinus-like spaces. But there is now a change in the character of these cells.

They too have become vesicular, and consequently appear as if filled with a clear fluid, while their granular protoplasm is heaped up into a mere peri-nuclear zone. The lining endothelium of the sinus-like spaces is still intact.

I have added here a microphotograph (Fig. 47) showing a section of the upper or vascular wall of the yolk-sac. This wall is composed of endoderm and mesoderm, and within it run numerous small vessels filled with foetal blood. The sinus terminalis on either side, marks the extent of this vascular wall—the *vascular area* of the umbilical vesicle. This vascular area beyond the cavity of the external coelome represents the *yolk-sac placenta* of the rabbit. The vitelline circulation has now

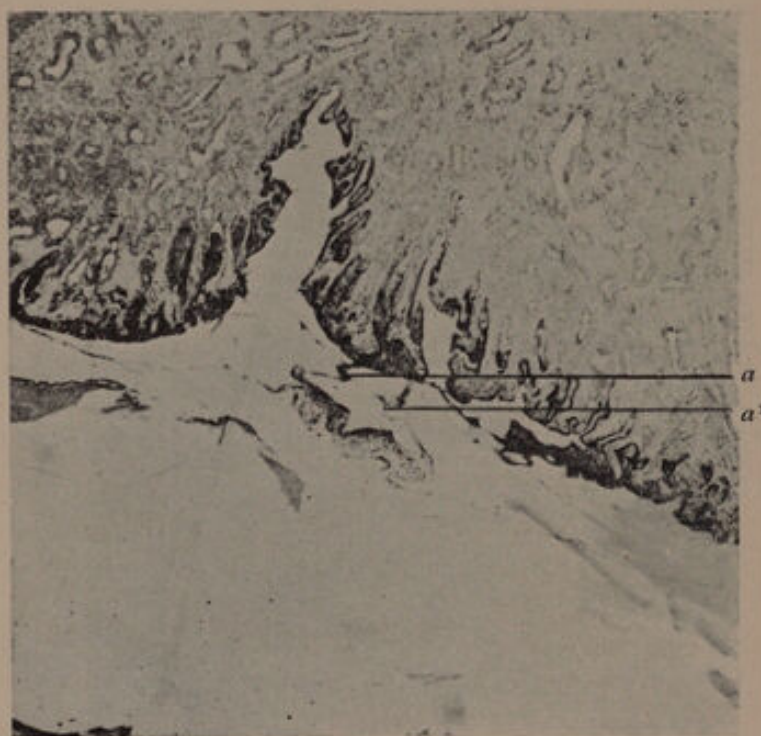


FIG. XXXVII.

(8½ days' Gestation.)

Development of side-folds of amniotic sac. The side-folds of the amnion approach each other more closely (c.f. Figs. 34, 35 and 36) over the back of the embryo.

a, a¹, amniotic folds.

reached its greatest functional activity, for at the 10th day the allantoic circulation is established. The same microphotograph (Fig. 47) shows the embryo cut longitudinally and largely roofed in by the amniotic sac. Growing out into the external coelome from its posterior extremity, and following round this, to be continued upon the wall of the amnion, is a considerable mass of mesoblastic cells. This mass represents the

growing allantois. The amnion is not completely formed, that is, is not wholly separated from the "serous envelope." The allantois then, by merely following along upon the mesoblastic surface of the amnion, will find itself directed to the chorion. Such a procedure, the beginning of which we see in Fig. 47, would correspond exactly to the assumptions emitted by Hertwig in regard to the mode of development of the human allantois. I draw attention to this point, for the reason that in respect of the development of the allantois in rodents, the older view of Kölliker almost universally obtains.

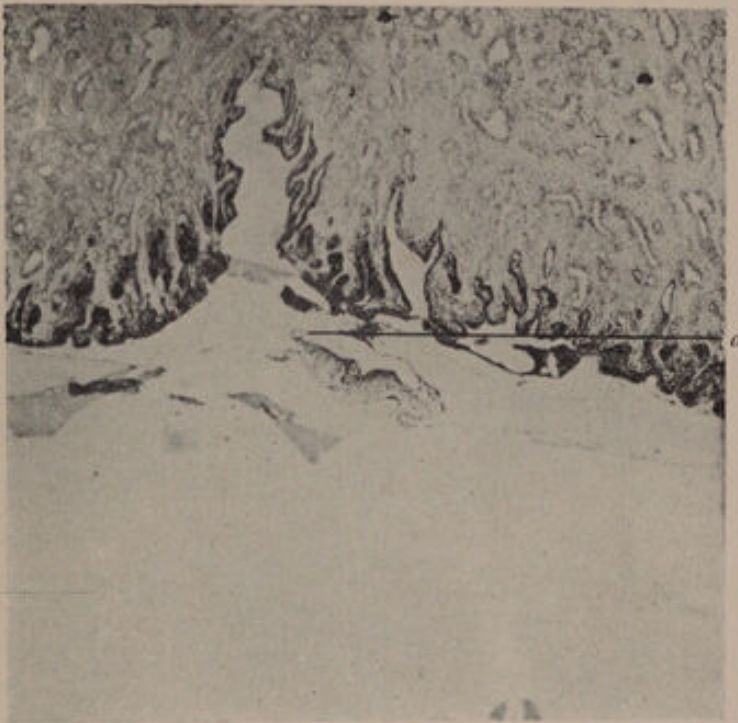


FIG. XXXVIII.

(8½ days' Gestation.)

Development of side-folds of amniotic sac. The side-folds have fused (c.f. Figs. 34, 35, 36 and 37).

a, fusion of opposite side-folds of amnion.

GESTATION SAC OF 10 DAYS (FIG. 48).

(1) Fœtus and fœtal placenta.

The fœtus lies as is usual opposite the intercotyledonary groove, but in this instance its ventral aspect is directed toward the placenta. The allantois shows itself united with the mesoderm of the ectoplacental laminæ, on either side of the intercotyledonary groove. Included within the allantois are numerous small fœtal vessels filled with nucleated fœtal blood, which thereby reach and vascularise the mesodermic layer of the ectoplacenta. These facts are shown in the

microphotograph (Fig. 50) where also it is evident that this vascularisation begins near the foetus—near the intercotyledonary groove—and extends gradually outward on either side.

The foetal liver makes its appearance at the 10th day as a solid outgrowth from the "mesenteron." All the succeeding sections of the foetus have been chosen to show the liver, as it is especially with this organ that the subsequent micro-chemical study is concerned.

The ectoplacenta is now divisible into two layers, the plasmodial layer—the "symplaste" of Laulanie, the "plasmodiblaste" of van Beneden, "la couche plasmodiale," of Duval—with cells fused, cell-

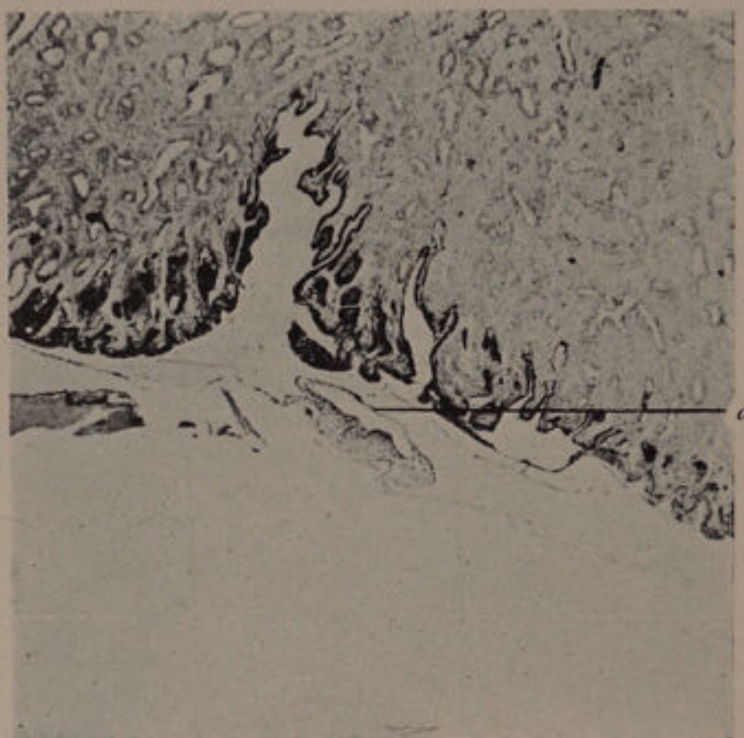


FIG. xxxix.

(8½ days' Gestation.)

Development of side-folds of amniotic sac. The amniotic sac is here complete (c.f. Figs. 34, 35, 36, 37 and 38).

a, amniotic sac complete.

outline lost, nuclei small and irregularly grouped—lies next the maternal tissue; the cellular layer—the "cytoblaste" of van Beneden, "la couche cellulaire," of Duval, with cells of uniform size, cell-outline distinct, nuclei large and belonging each to its own cell, is superficial to the other, that is, is nearer the mesoderm. This division of the ectoplacenta into these two layers, formerly a point of great dispute, is much more evident at the 12th and 14th days. It is of comparatively little importance, as ultimately the whole of the ectodermal cells undergo



FIG. XL.
(9 days' Gestation.)

Transverse section of a gestation sac of 9 days. The embryo is cut longitudinally and the limits of the attachment of the ectoplacenta are seen. The two placental cotyledons appear symmetrical and between them is a well-defined intercotyledonary groove.

a, a¹, limit of attachment of ectoplacenta; *y*, yolk; *e*, embryo; *g*, intercotyledonary groove; *m*, mesometrium. (Photo.)

this plasmodial change and the cellular layer as such, disappears. While the ectoplacenta has increased greatly in thickness its general disposition is now much more irregular. It is now markedly folded, and the concavities of these large folds look alternately, now to the foetal mesoderm and now to the maternal tissue. These foldings are derived :—on the maternal aspect from the more rapid advance of the ectoplacenta into the maternal tissue at certain points :—and on the foetal aspect they are due to the ingrowth at successive intervals of the mesoderm. Thus succeeding concavities of this double folding look,

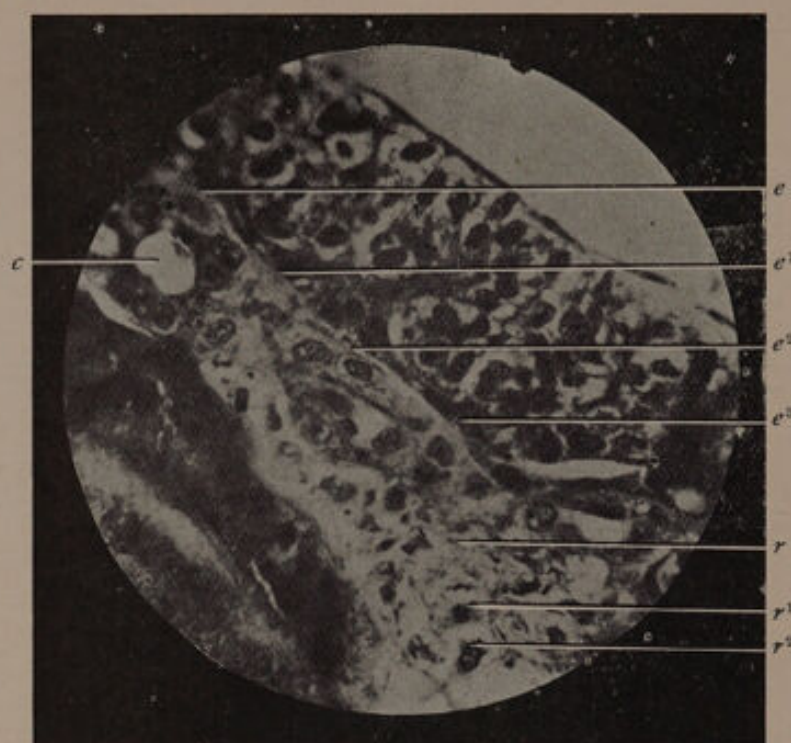


FIG. XLI.

(9 days' Gestation.)

Line of attachment of the ectoderm. The uterine epithelium has completely disappeared.

c, superficial capillary with perivascular sheath of a single row of uninucleate decidual cells; *e*, *e*¹, *e*², *e*³, line of attachment of foetal ectoderm to the corium of the placental cotyledons, uterine epithelium has disappeared; *r*, *r*¹, *r*², intermediary region of maternal cotyledon.

the one toward the foetal mesoderm, the other toward maternal placenta (Fig. 51). I have shown that the foetal ectoderm, the ectoplacenta, begins to invade the maternal tissue through the agency of villous-like ingrowths, and that these ingrowths penetrate first into the blocked gland-mouths at 8½ days, and at 9 days they push in also in close proximity to some superficial capillary. Thus these villi enter

in two situations—along the glands and along the vessels. Those that enter the gland-mouths find their line of direction speedily obliterated, for the solid stalk-like gland-channels disappear immediately upon the determination, at the 9th day, of our reactionary zone—the intermediary region. The degenerate epithelium of these gland-channels is absorbed by the reactionary tissue with which they become surrounded, and which in its turn is replaced at the 10th day, by multinucleate decidual cells. Thus in the rabbit the uterine glands are only temporary guides to the invasion of the foetal ectoderm. The further direction of these

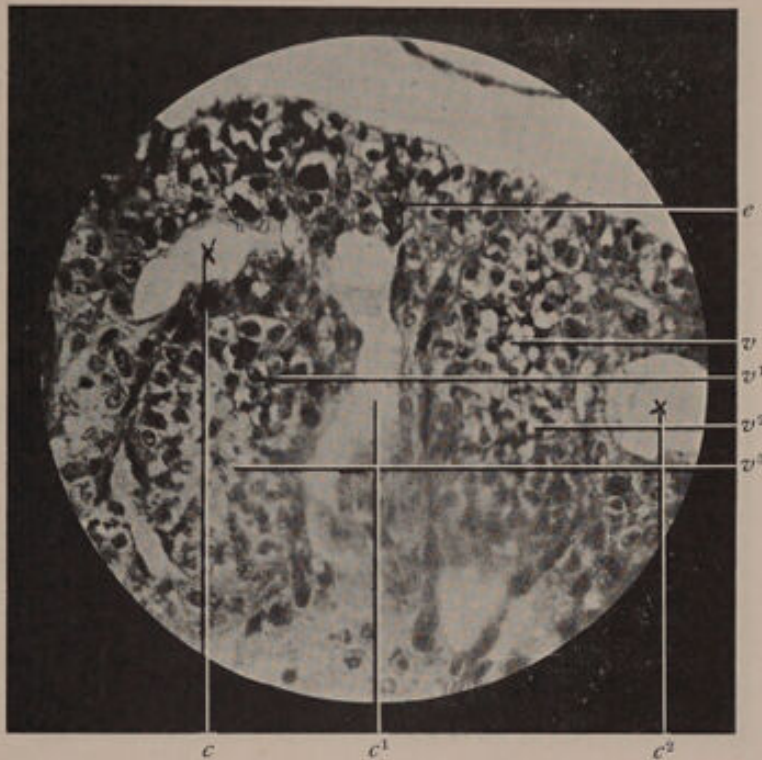


FIG. XLII.

(9 days' Gestation.)

Invasion of ectoderm along the superficial capillaries of maternal cotyledons.

c, c^1, c^2 , superficial maternal capillaries partly surrounded by foetal ectoderm, their endothelium has in part disappeared; e , foetal ectoderm, ectoplacenta; v, v^1, v^2 , "villi" of ectoderm following in upon and surrounding maternal capillaries.

"glandular villi" is determined by the blood-vessels in their immediate vicinity. *The permanent guides to the invasion of the foetal tissue are the maternal vascular channels.*

In a microphotograph (Fig. 42) at the 9th day I showed the origin and behaviour of these "vascular villi," how they reach in towards the superficial capillaries, follow round their endothelial wall, and so come

to include within themselves the capillary spaces. The present sections show a further advance in this process. Many maternal capillaries are now completely surrounded by the foetal tissue and lie deeply within it. Such capillary spaces have lost even their endothelial wall, and the maternal blood which they contain is walled in only by the surrounding foetal ectoderm. Reference to a microphotograph (Fig. 52) of such maternal blood-spaces shows conclusively the nature of their walls. Where a somewhat longitudinal course of the maternal capillary is exhibited, the ingrowth of a "villus" along its walls illustrates the pro-

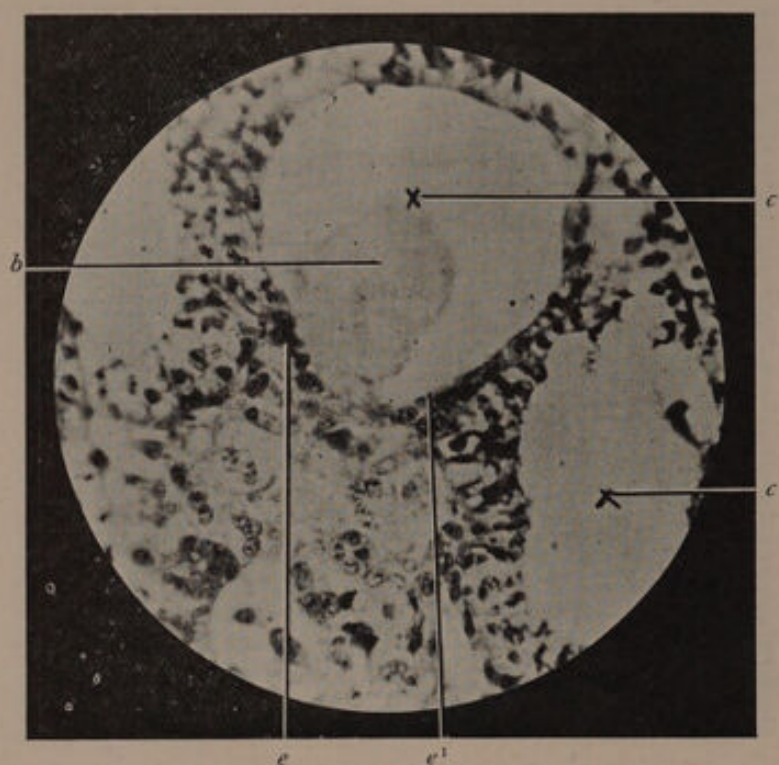


FIG. XLIII.

(9 days' Gestation.)

Superficial maternal capillary almost completely surrounded by the foetal ectoderm. The lining endothelium has disappeared save from one point at its deeper margin.

c, maternal capillary almost completely surrounded by foetal ectoderm; *c¹*, limits of preserved endothelium; *b*, blood-clot, maternal blood.

cess more clearly. The "villus" reaches the distal or superficial end of the capillary and surrounds it in the usual way: it then advances along either side of the vessel, gradually *swallowing* the vessel. Before this advance the uninucleate cells of the vessel's decidual sheath become multinucleate, vesicular, and detached the one from the other; and the endothelium disappears to be replaced by the foetal tissue. In such an

instance the vessel, while filled throughout with maternal blood, possesses a wall composed, in its distal part, of foetal cells, and in its proximal part of maternal endothelium. The junction of these two tissues along the wall of a capillary is shown in a microphotograph (Fig. 53).

From the foregoing it will be manifest that the foetal "villi" never penetrate the wall of a maternal vessel, always does the "villus" come to surround and include the maternal vessel.

The lumina of the maternal vessels when surrounded by foetal tissue, and when robbed of their endothelial wall, lose at once their original

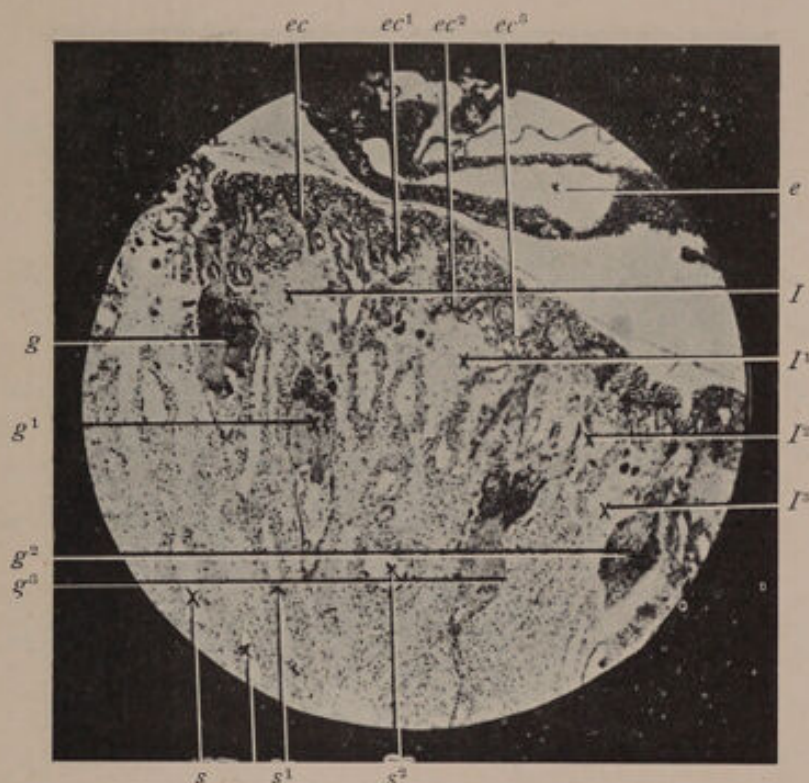


FIG. XLIV.

(9 days' Gestation.)

First appearance of the intermediate (reactionary) zone. A longitudinal section of the embryo, the line of attachment of the ectoplacenta, superficial sinus-capillaries and solid glandular cul-de-sacs are shown.

e, embryo; *ec*, *ec¹*, *ec²*, *ec³*, ectoplacenta; *g*, *g¹*, *g²*, *g³*, glandular cul-de-sacs completely filled by the hyperplasia of their lining cells; *I*, *I¹*, *I²*, *I³*, Intermediary zone of maternal placenta.

size and shape; they become distorted into large irregularly-shaped cavities. (See Fig. 52.)

I introduce here a microphotograph (Fig. 54) of a more central portion of the ectoplacenta in order to show its general arrangement in a stage slightly more advanced, and in order to deal here once for all with the so-called "villi." The ectoplacenta as here shown is thicker

and its foldings are much more elaborated. The striking feature is its comparatively uniform thickness, and that its line of application to the maternal tissues is not very deeply irregular. Although at repeated intervals the ingrowth of the foetal tissue is somewhat further advanced, there is little to represent the lengthy finger-like process of the conventional "villus." These foetal ingrowths pursue maternal vessels, as I have shown, are evidently determined by the increased nutritive supply at these points, and are followed closely in their advance by the main mass of the ectoplacenta. Moreover, they contain maternal blood-

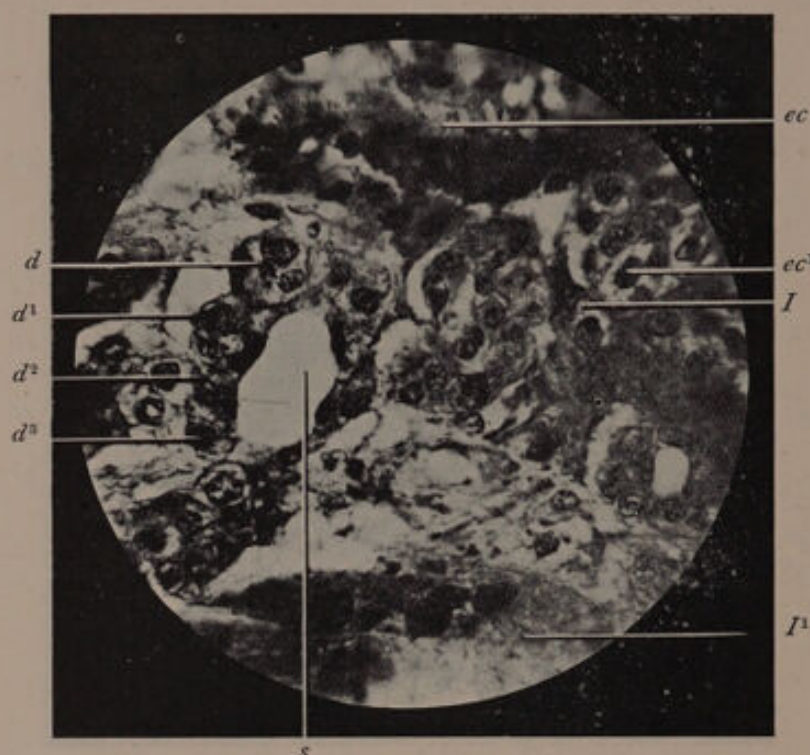


FIG. XLV.

(9 days' Gestation.)

Origin of multinucleate decidual cells. These arise from the uninucleate decidual cells.

d, d^1, d^2, d^3 , origin of multinucleate decidual cell from a perivascular uninucleate decidual cell; ec, ec^1 , ectoplacenta; I, I^1 , intermediary zone of maternal placenta; s , sinus-capillary with perivascular sheath.

cavities, and where a capillary is shown longitudinally, they present an open extremity to the maternal tissue, and the maternal blood-cavity occupies their axes. It is with such definition that the term "villi" is herein used. (See Figs. 55 and 56.)

I have previously stated and shown that the maternal blood-spaces in the foetal placenta represent merely surrounded and included maternal capillaries, deprived of their endothelium, or, in other words, that the

foetal tissue simply *swallows* the maternal capillary space. But it is at once manifest from the microphotographs (Figs. 55 and 56) that the maternal capillary space must undergo a considerable change in size and shape during this *swallowing* process; for while the blood-channels of the uterine corium are simply large-sized capillaries, the maternal blood-spaces of the foetal placenta are cavities of much larger size and irregular shape. The explanation of this anomaly is found in the following further details of the ingrowth of the foetal ectoderm. The intermediary region of the maternal placenta immediately underlies the

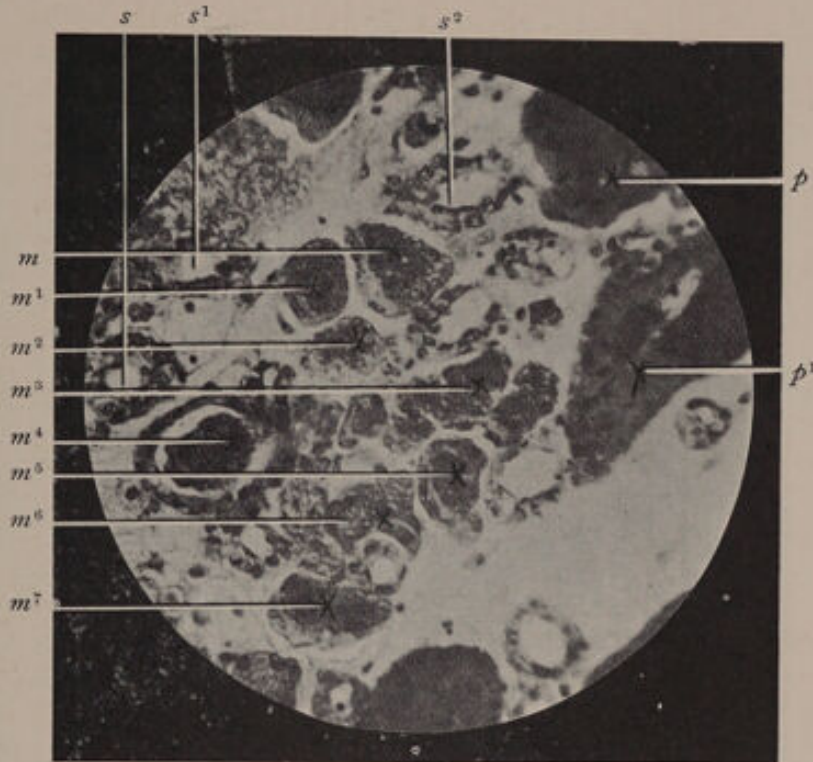


FIG. XLVI.

(9 days' Gestation.)

Fate of solid plugs of glandular epithelium. Shows such a plug fragmented into a number of multinucleate masses which are becoming scattered in the surrounding corium.

$m, m^1, m^2, m^3, m^4, m^5, m^6, m^7$, multinucleate epithelial masses arising from the fragmentation of the solid glandular plugs of epithelium; p, p^1 , plugs of glandular epithelium; s, s^1, s^2 , sinus capillaries.

foetal placenta. At this date it is composed of large multi-nucleate decidual cells, formed at the expense of the peri-vascular sheaths of the vessels. In consequence the vessels have no supporting sheaths, but lie in the midst of a region uniformly cellular. Moreover, the endothelium of these capillaries is swollen, vitreous and degenerated in appearance. A full description of this region will be found in its proper place under the maternal placenta.

Now it is upon such tissue as this and along such weakened vessels that the foetal ectoderm advances. Here and there, usually immediately in front of the advancing ectoderm, the degenerated endothelium gives way and hæmorrhages occur among the multinucleate decidual cells. The result is that the foetal tissue is at these places confronted with large and irregularly-shaped blood-cavities, whose walls are composed partly of vessel endothelium, and partly by the multinucleate cells of the vicinity, compressed by the hæmorrhage into a sort of ragged wall. My sections show that the foetal ectoderm acts in respect of these irregular blood-

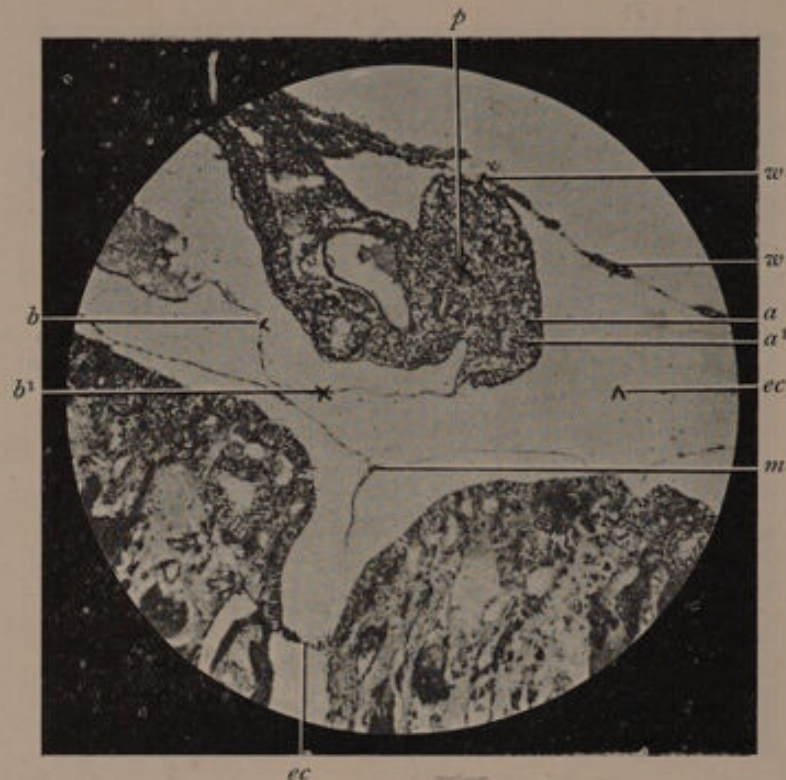


FIG. XLVII.

(9 days' Gestation.)

Development of allantois, which is following the mesodermic surface of the amnion. The intercotyledonary groove is bridged by the foetal ectoderm.

b, b¹, amnion; *m*, mesoderm; *ec*, external coelome; *a, a¹*, allantois; *w, w¹*, vascular wall of yolk-sac; *p*, posterior end of embryo.

cavities exactly in the same way as towards the maternal capillaries—it surrounds them.

I have chosen two microphotographs to illustrate this. Microphotograph (Fig. 57) shows a maternal capillary partly surrounded by the ectoderm. Its endothelial wall has snapped in two places. There results a large irregularly shaped cavity around which the foetal cells have continued to advance.

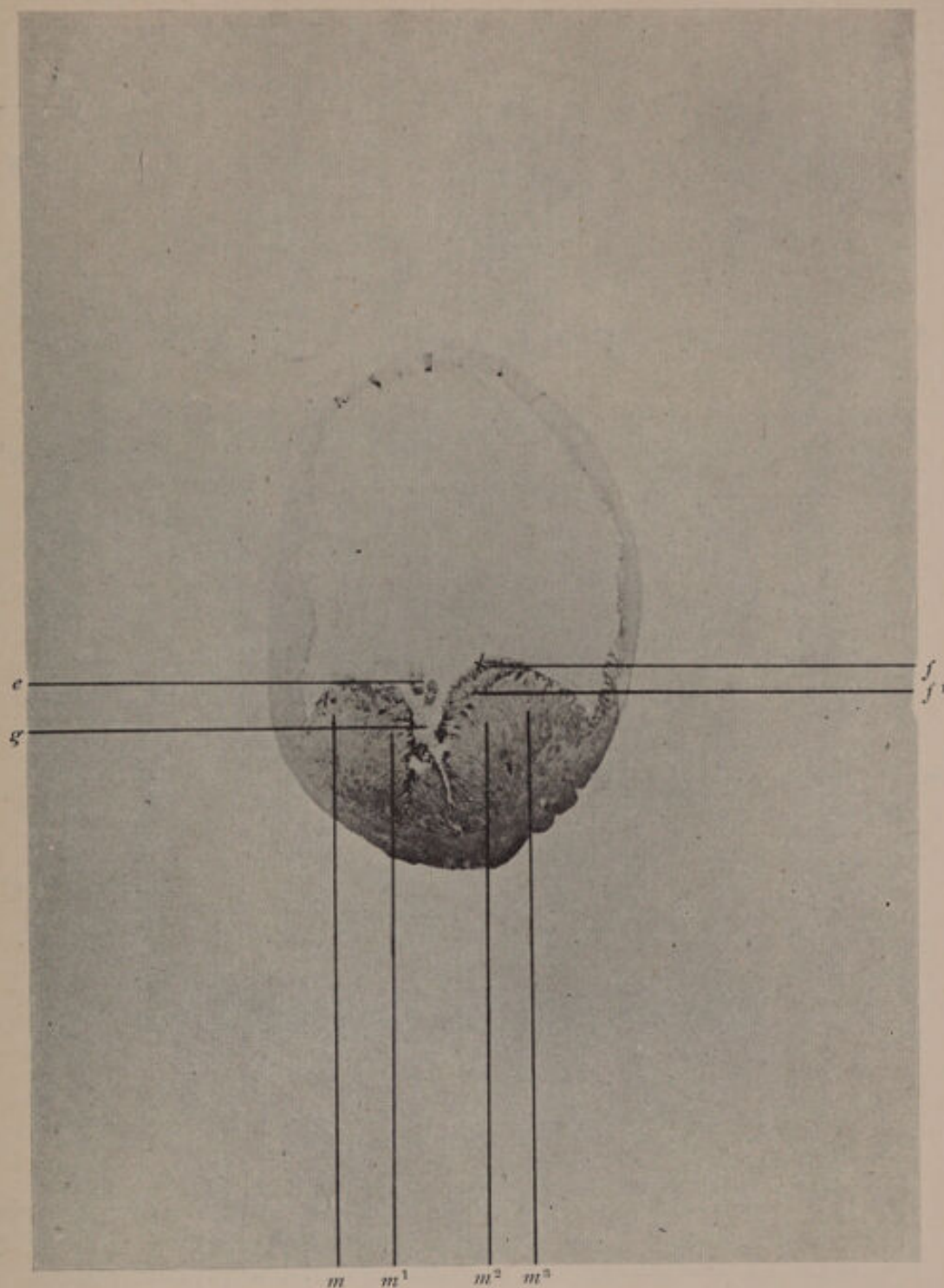


FIG. XLVIII.

(10 days' Gestation.)

Transverse section of gestation sac of 10 days. The foetal portion of the placenta is here recognisable.

e, embryo; *ff¹*, foetal portion of placenta; *g*, intermediary groove; *m, m¹, m², m³*, Maternal portion of placenta. (Photo.)

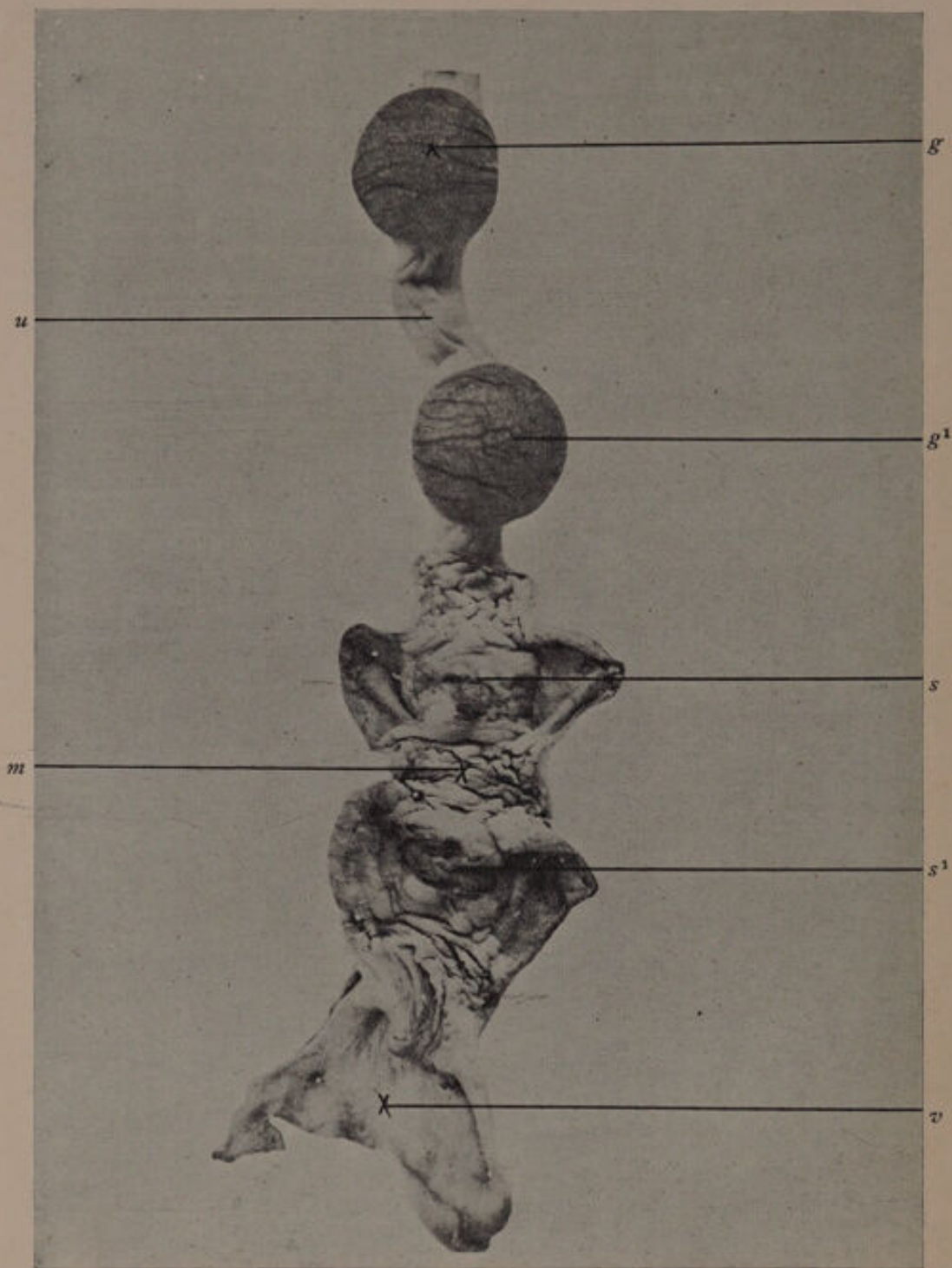


FIG. XLIX.

(10 days' Gestation.)

Uterine cornu removed en masse, the two lower gestation sacs have been opened along their ventral aspect.

g, g¹, gestation sacs intact; *s, s¹*, gestation sacs laid open; *v*, vagina; *m*, mucosa between two gestation sacs; *u*, uterine cornu between two gestation sacs. (Photo.)

Microphotograph (Fig. 58) illustrates a more accentuated phase of the same process. Three capillaries have ruptured and their fragmented endothelium is seen lying in the midst of a hæmorrhagic cavity. But at the same time this whole cavity is seen outflanked on its two sides by the foetal cells.

I have followed carefully all the stages, and I find that the above is the process by which the large maternal blood-cavities within the foetal placenta are to be accounted for. The ectoderm behaves towards these cavities exactly as towards the capillaries.

I can find no instance where an ectoplacental loop extends out

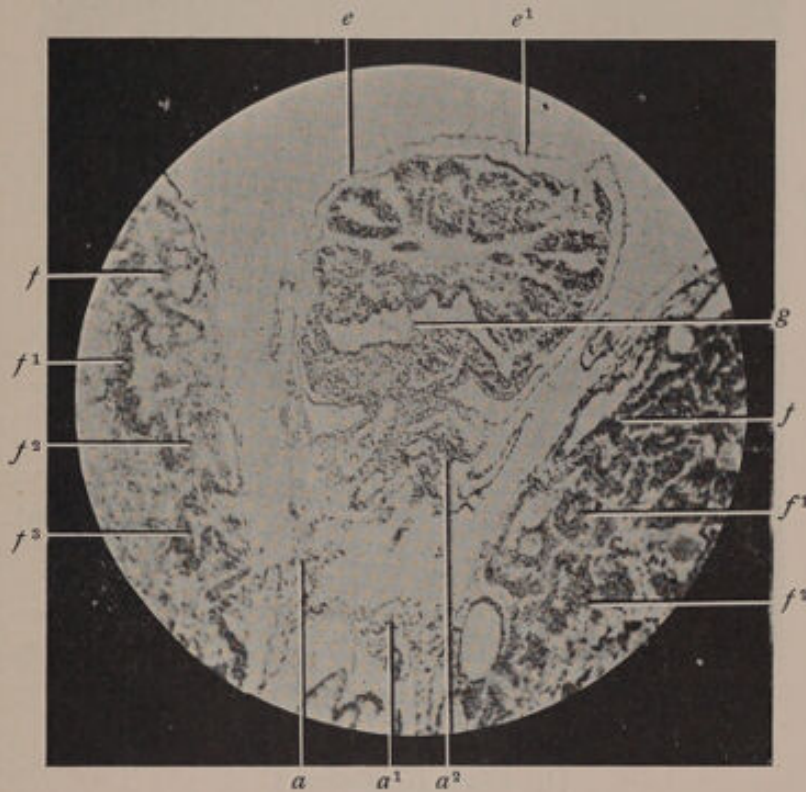


FIG. 58.

(10 days' Gestation.)

The embryo cut transversely lies opposite the intercotyledonary groove. The allantois with its vessels has reached the ectoplacenta on either side.

a, a¹, a², allantois with its vessels; *e, e¹*, embryo; *g*, gut; *f, f¹, f²*, and *f, f¹, f², f³*, foetal portions of placenta (ectoplacenta).

directly into the blood cavity; the foetal tissue never crosses such a cavity, it always goes round it.

The undulating foetal surface of the ectoplacenta, at the 9th day was lined with several layers of mesodermic cells, these cells being specially numerous in the concavities of the undulations. This mesoderm is now greatly increased in thickness and has also become

vascularized by the allantoic vessels (Fig. 51). Starting at these concavities where it is specially active it has come to infold or invade the ectodermal laminæ—the ectoplacenta, dividing these by such partitioning ingrowths into definite areas. These areas are so marked off, that there are included in each large maternal blood-spaces filled with maternal blood. These spaces, as I have shown, are simply *swallowed* maternal blood-spaces, and are walled solely by ectodermic foetal cells. The

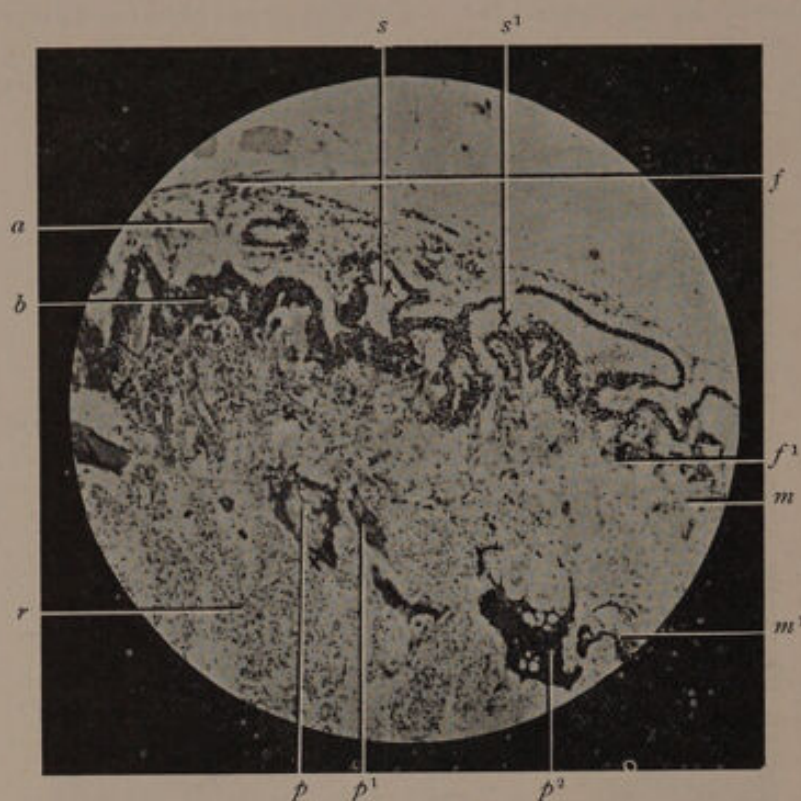


FIG. LI.

(10 days' Gestation.)

Low-power view of foetal placenta. The ectoplacenta is now folded, its superficial surface is clothed by vascular mesoderm. The intermediary region of maternal placenta, the remains of the glandular plugs, and the superficial portion of the region of uterine sinuses.

a, foetal mesoderm; *b*, foetal ectoderm; *f, f¹*, foetal portion of placenta; *m, m¹*, maternal portion of placenta (intermediary region); *r*, region of uterine sinuses; *p, p¹, p²*, glandular plugs of epithelium; *s, s¹*, maternal sinuses-capillaries completely surrounded by foetal cells and containing maternal blood.

mesodermic ingrowths bound on either side these areas or *columns*, which are of varying size. Foetal vessels with nucleated foetal blood accompany these mesodermic ingrowths. In this way the two blood systems—maternal and foetal—make their first approach, and in this way also the ectoplacenta, even as it invades maternal tissue, is likewise

itself invaded by its own mesoderm. The ectoplacenta as a mere lamina of thickened ectoderm ceases to exist, and in its place there now obtain the foundations of a more complicated structure composed of both ectoderm and mesoderm, and within which is contained maternal and foetal blood—the *foetal portion of the placenta*.

(2) Maternal placenta.

With the establishment of the allantoic circulation the placental mucosa now deserves the designation—the *maternal portion of the*

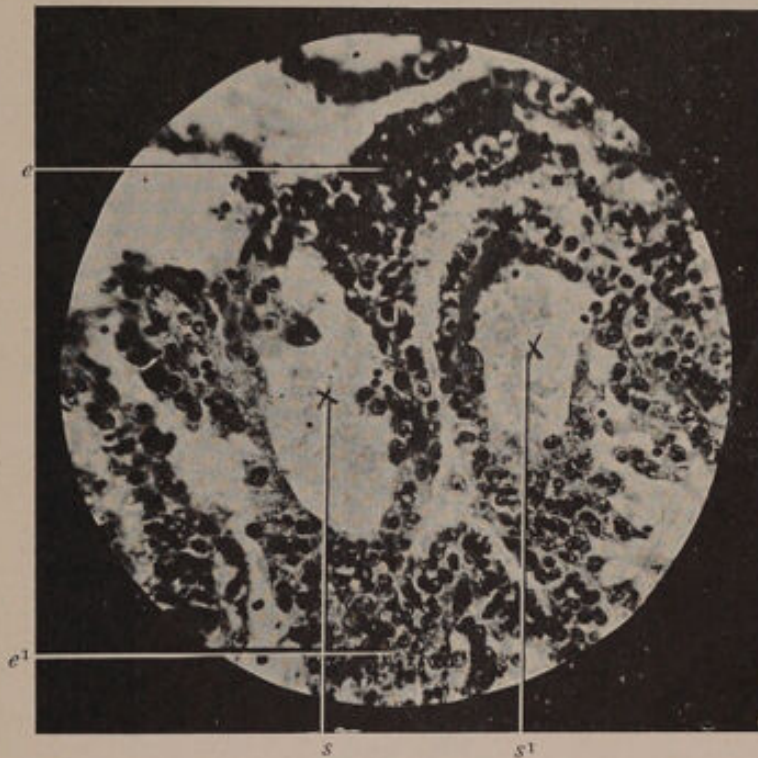


FIG. LII.

(10 days' Gestation.)

Two capillary spaces in the ectoplacenta. These two spaces were originally maternal capillaries. They have become completely walled round by the foetal cells and have lost their endothelial lining.

e, e', foetal ectoderm (ectoplacenta); *s, s'*, two spaces, originally maternal capillaries, filled with maternal blood but walled by foetal cells.

placenta. The two regions into which at the 9th day the placental mucosa came to be divided are now at the 10th day, in the maternal placenta much more evident. These two regions have considerably increased in size, especially the deeper region—the region of the uterine sinuses.

The intermediary region—reactionary zone—is conspicuous not so much by its growth, as by a marked histological change in its elements.

The beginning of this change at the 9th day I illustrated in a microphotograph (See Fig. 45), which represented the first appearance of the multinucleate decidual cells and which showed the derivation of these cells from the uninucleate cell of the perivascular sheaths. At this date—24 hours after the onset of the process—the intermediary region is composed solely of these multinucleate decidual cells, and the included blood-vessels. These cells are of great size, round or oval in shape,

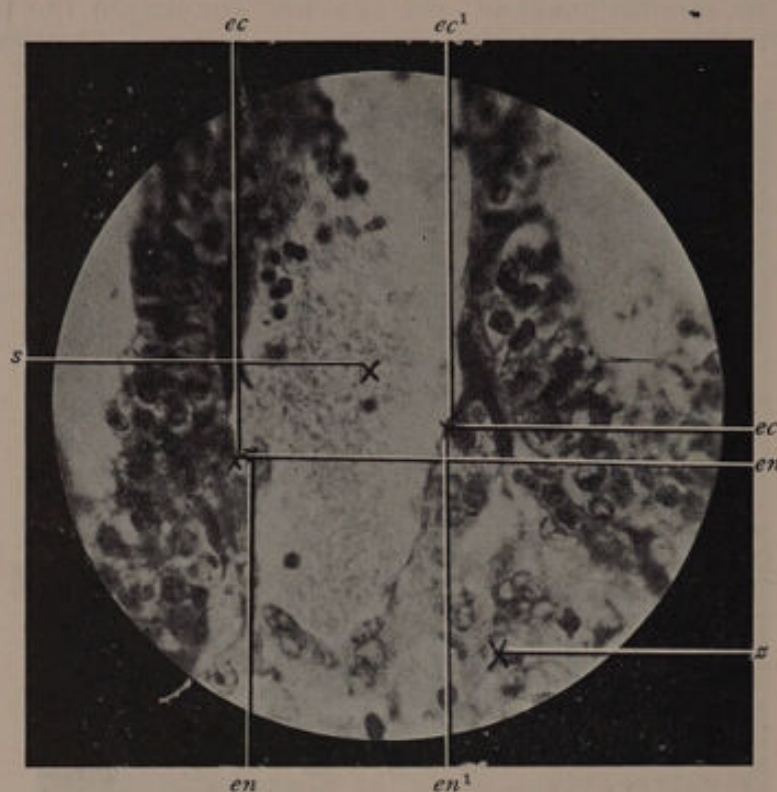


FIG. LIII.

(10 days' Gestation.)

Maternal sinus-capillary cut longitudinally. The distal portion (upper in microphotograph) is walled by foetal cells, while the proximal portion is still lined by its original endothelium. The junction of the two tissues, maternal and foetal, along the sides of the vessels is very evident and illustrates the way in which the foetal ectoderm surrounds the maternal blood space.

s, maternal sinus-capillary cut longitudinally and containing blood; *ec, ec¹*, limit of foetal ectoderm; *ec, en*, junction of ectoderm and of endothelium; *z*, intermediary zone; *en, en¹*, limit of endothelium.

and with a sharp cell outline. They possess 2, 3 or 4 large, round, evenly-stained nuclei which are always grouped together. The cells contain little cell protoplasm—a mere peri-nuclear zone, their main contents being fluid-like and translucent; in other words they are *vesicular*. (Fig. 59.)

These cells have been noted by most workers upon the rabbit's placenta; they are correctly described by Godet, Masquelin and Swæn, Masius, Minot and Duval, and incorrectly defined by such an observer as Ulesko-Stroganowa. Duval gives an excellent diagrammatic representation of these cells in his plates, but his account of their origin from the small connective tissue cells of the corium I think unsupported.

The origin of these cells, as we have seen at the 9th day, is from the uninucleate cell of the perivascular sheaths, and the actual process of

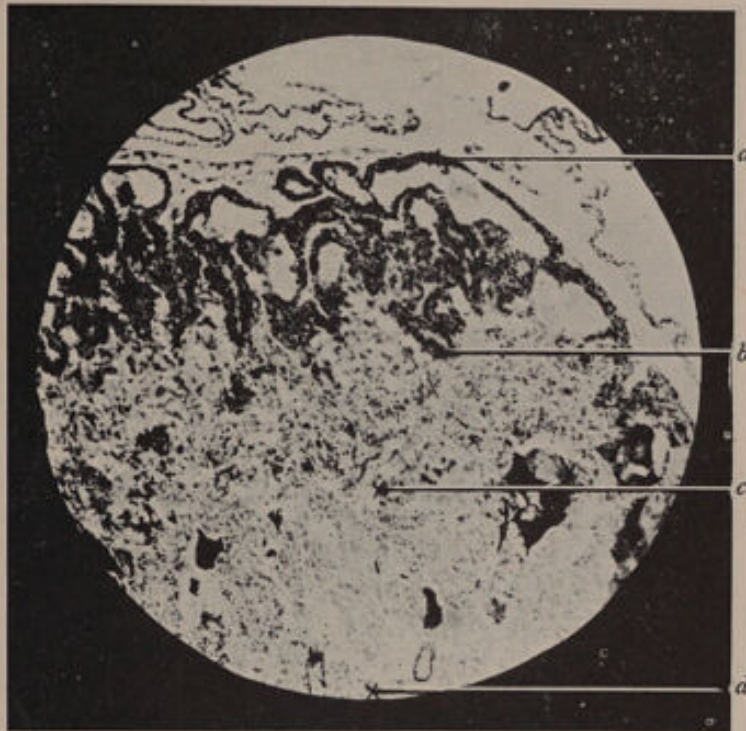


FIG. LIV.

(10 days' Gestation.)

Foetal placenta. A more central portion than that shown in Fig. 51. The intermediary region and a part of the region of the uterine sinuses—maternal placenta—are also shewn. The ectoplacenta now encloses many maternal blood spaces and is rapidly advancing upon the intermediary region, its deeper processes following always the maternal sinuses-capillary.

a, b, foetal placenta; *b, c*, intermediary region (maternal placenta); *c, d*, region of uterine sinuses; *b*, junction between foetal and maternal portion of placenta.

their derivation is now even more clearly intimated. The microphotograph (Fig. 60) illustrating this process shows a capillary cut longitudinally. At its deeper or proximal end, its endothelium is re-inforced by a thick sheath of perivascular *uninucleate* decidual cells. Towards its distal end, the end nearer the foetal ectoderm, these uninucleate cells

become large, multinucleate and vesicular; they detach themselves more and more completely from the vessel, until a perivascular sheath no longer exists, and the capillary is left with but its true endothelial wall. This change spreads proximally towards the mesometrium, along the vessel sheaths, as we shall hereafter observe in the further growth of the intermediary region.

Thus the intermediary region becomes uniformly cellular, there is no stroma, and the vessels have merely endothelial walls, and even this

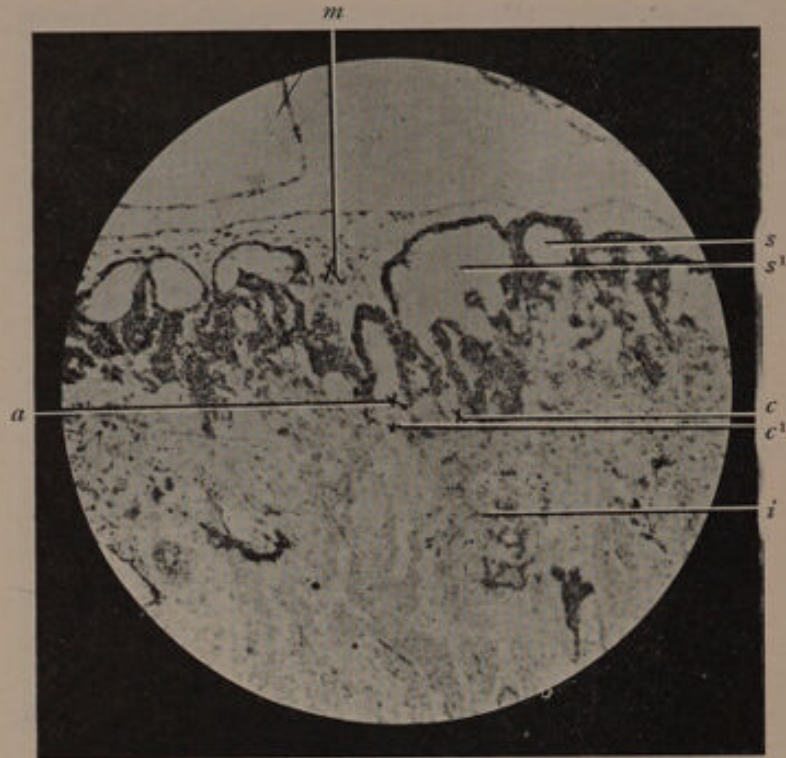


FIG. LV.

(10 days' Gestation.)

Fœtal placenta showing specially the deeper advance of the ectoderm along the maternal sinus-capillaries. The intermediary region of multinucleate decidual cells is shown.

a, area shown in Fig. 56; *m*, vascular mesoderm; *s, s¹*, maternal blood spaces in ectoplacenta; *c, c¹*, maternal sinus-capillaries along the walls of which the ectoderm is advancing; *i*, intermediary region.

endothelium is swollen and vitreous looking. A tissue more feeble to withstand even a slight addition of blood-pressure it would be difficult to imagine, and it is upon such tissue as this that the fœtal "villi" advance.

These "villi" as we have seen, follow in upon the vessels, replacing the endothelium by their own cells which are becoming more and more plasmodial. In places, now, the weakened endothelium of these vessels gives away, usually just before it is overtaken by the "villus," and their

maternal blood escapes *quickly* among the surrounding multinucleate cells. I give a microphotograph (Fig. 61) of such an instance. These cells are easily pushed aside, and in consequence there come to be formed extra-vascular blood-cavities. These blood-cavities are specially large and numerous at the junction of the foetal and maternal tissues, for here the vessel wall is weakest and the tissue most lax. In such cases the wall of these blood-cavities is formed in part of foetal, and in part of maternal tissue. Smaller hæmorrhages, moreover, occur here and there throughout the intermediary region, and from the smaller sized capil-

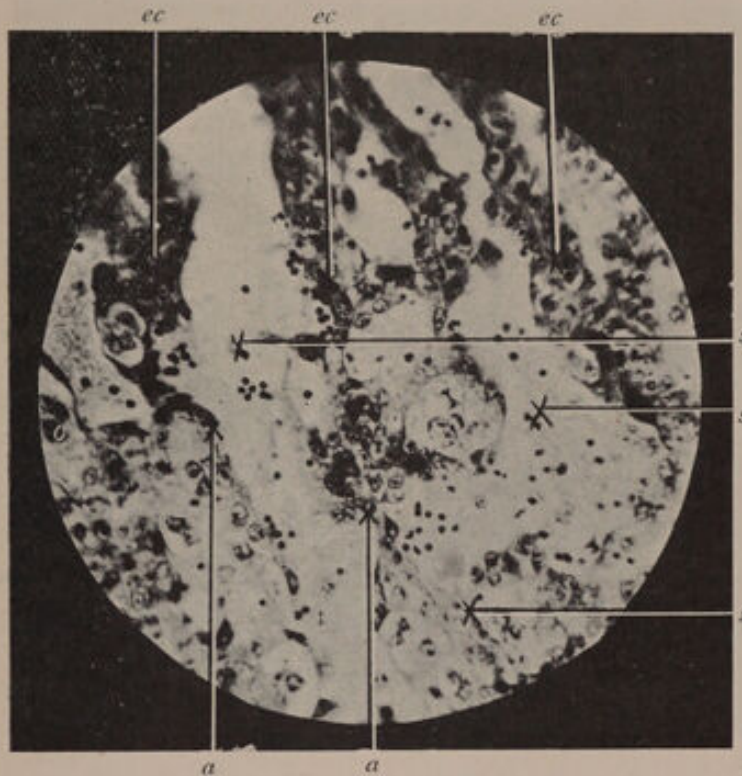


FIG. LVI.

(10 days' Gestation.)

High-power view of the advance of the ectoderm along the side walls of the sinus-capillary. Multinucleate decidual cells are seen.

a,a, limit of advance of foetal cells along the sinus-capillary walls; *ec,ec,ec*, foetal ectoderm; *s,s*, sinus-capillaries walled, in their distal (upper) part, by foetal cells and in their proximal (lower) part by maternal cells; *z*, intermediary zone.

laries. Here the confines of these hæmorrhages are composed solely of the compressed vesicular cells, and are ragged and uneven (Fig. 62). In addition to these *sudden* hæmorrhages throughout the intermediary region there occurs in its deeper areas another phase of the same process. Here, while as before the perivascular sheaths are reduced by the formation and separation of the multinucleate cells, and while the swollen and

unsupported endothelium gives way, the succeeding hæmorrhages occur *slowly* by reason of the greater density of the surrounding tissue. That is, the hæmorrhage takes the form of a gradual leakage, which follows the course of least resistance. The result is the formation of a *fibrinous tissue*, in the interstices of which lie entangled groups of red corpuscles with scattered leucocytes (Fig. 63). This fibrinous tissue is destined to increase greatly in amount and to play an important role in the further transformation of the maternal placenta. It invades the deeper region

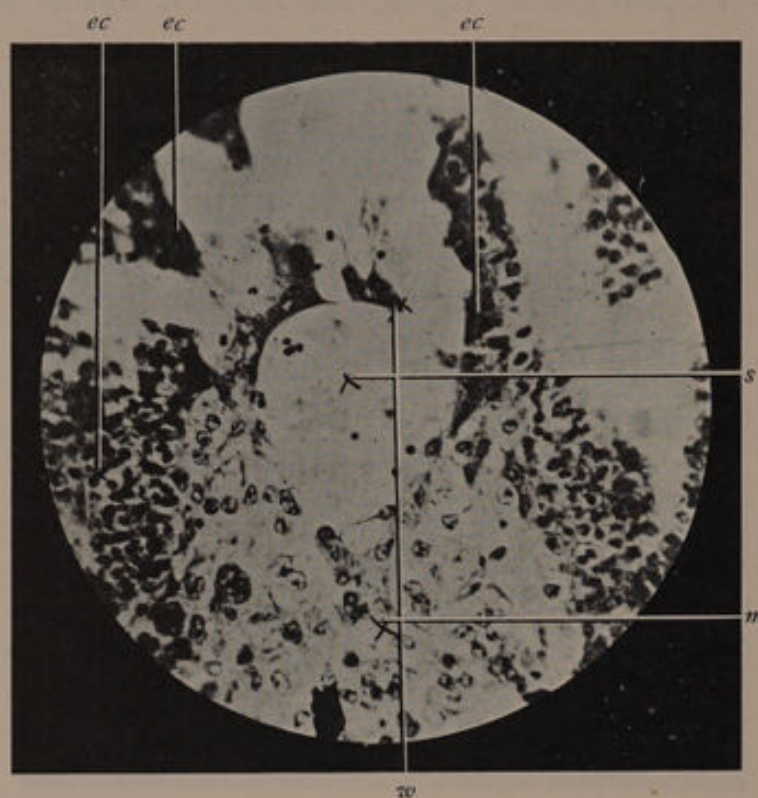


FIG. LVII.

(10 days' Gestation.)

Maternal sinus-capillary whose wall has ruptured before it has been completely surrounded by the foetal ectoderm. In this way the blood space finally included within the ectoderm is much larger than the original capillary space.

ec, ec, ec, foetal ectoderm; *s*, sinus-capillary partly surrounded by foetal ectoderm and whose wall has ruptured; *m*, multinucleate cells; *w*, ruptured wall of sinus-capillary.

of the uterine sinuses, following in upon the narrow tracks of undifferentiated corium, until many of the more superficial perivascular sheaths of this region come to appear as *islands* in the midst of it. Its contact with the uninucleate decidual cells of these sheaths is co-temporary with the change of these cells into the multinucleate and larger variety. In this way the intermediary region increases in thickness, and at the expense

of the deeper region, the region of the uterine sinuses. I call special attention to the formation of this fibrinous tissue because, in my knowledge, it has not been previously described in the placenta of the rabbit.

The islands of degenerated glandular epithelium, the *boundary-posts* of the 9th day, are now very extensively vacuolated. In many instances a sudden hæmorrhage has occurred into them from the surrounding weakened capillaries—weakened as I have above described—and they

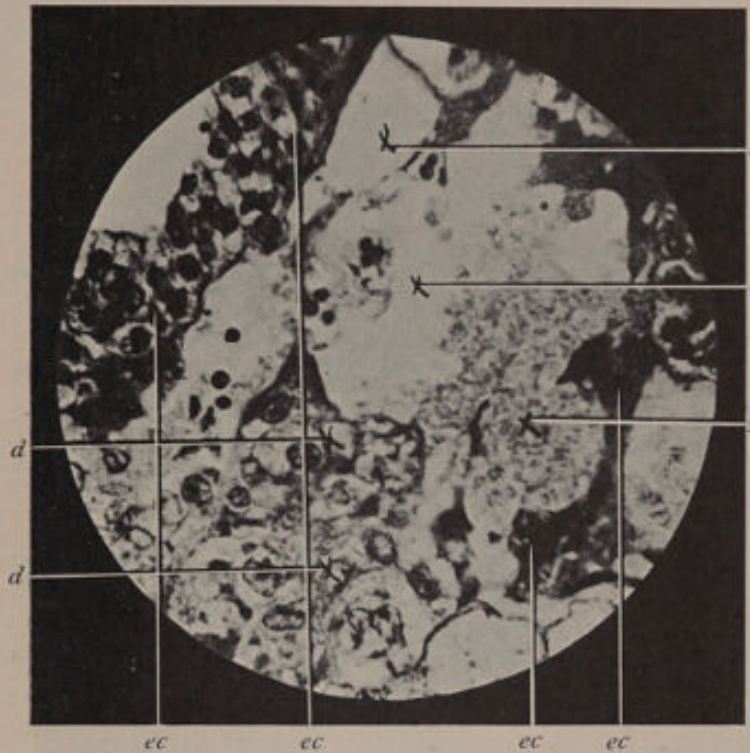


FIG. LVIII.

(10 days' Gestation.)

Three maternal sinus-capillaries, which have become through rupture of their walls an irregular blood-space and this space is being surrounded by ectoderm.

ec, ec, ec, ec, foetal ectoderm; *s, s, s*, three sinus-capillaries which have become one blood space. The space is being surrounded by foetal ectoderm; *d, d*, multinucleate decidual cells.

appear as large sharply-defined cavities filled with maternal blood. The microphotograph (Fig. 64) shows four such cavities.

The region of the uterine sinuses is possessed of still thicker perivascular sheaths. Between neighbouring sheaths there exist now but mere tracks of the original corium. The uninucleate decidual cells of these sheaths which at the 9th day became vesicular, still retain their clear content, and their outline is smooth and sharply-defined. The endothelium lining these sinus-like spaces is slightly thickened, but cell-outlines and nuclei are distinct (Fig. 65).

I have inserted here a photograph of a uterine cornu, the seat of a 10 days' pregnancy. There are four gestation sacs, two only of which I have opened and along their ventral aspect. My object in procuring these specimens was to show the naked-eye appearances at this stage of development, and if possible, to demonstrate the foetal "villi."

Photograph (Fig. 49) shows how nearly equidistant the several gestation sacs are arranged along the cornu; the walls of the closed sacs exhibit a marked vascularity in the number and size of their circularly-disposed vessels. In the two open sacs the foetus is seen to lie with its long axis directed obliquely across the intercotyledonary

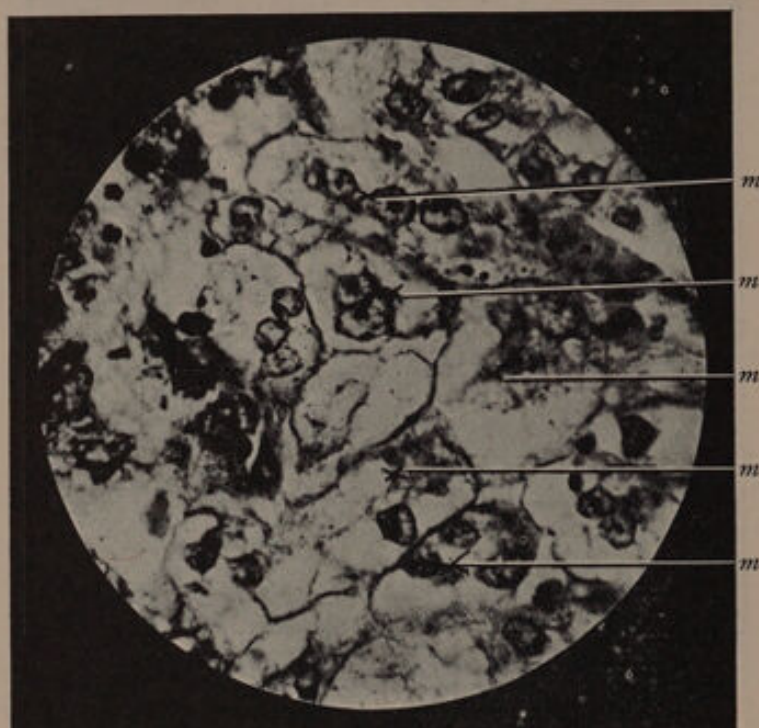


FIG. LIX.

(10 days' Gestation.)

Multinucleate decidual cells. The intermediary region is now constituted solely of these cells.

m,m,m,m, multinucleate decidual cells, vesicular.

groove. Partially surrounding the foetus is a darker horse-shoe shaped area—the area of placental attachment, the "*fer à cheval placentaire*" of van Beneden. The darker shading is due solely to the thickening of the foetal ectoderm over this region.

The most careful dissection failed to reveal macroscopically the foetal "villi." In the light of our present study this failure was to be anticipated, for my microphotographs show that foetal "villi" as generally conceived do not exist in the placenta of the rabbit. I record

this failure merely as additional evidence to the correctness of my microscopical observations.

The mucosa of the cornu between the gestation sacs is preserved, though its folds by the reciprocal approach of the adjacent sacs, have now lost their regular longitudinal direction. These folds between the two opened sacs are so compressed that they appear to run transversely.

GESTATION SAC OF 12 DAYS (FIG. 66).

(1) Fœtus and foetal placenta.

The fœtus is here cut longitudinally. Its growth during the previous 24 hours has been phenomenal. This increased rate of growth,

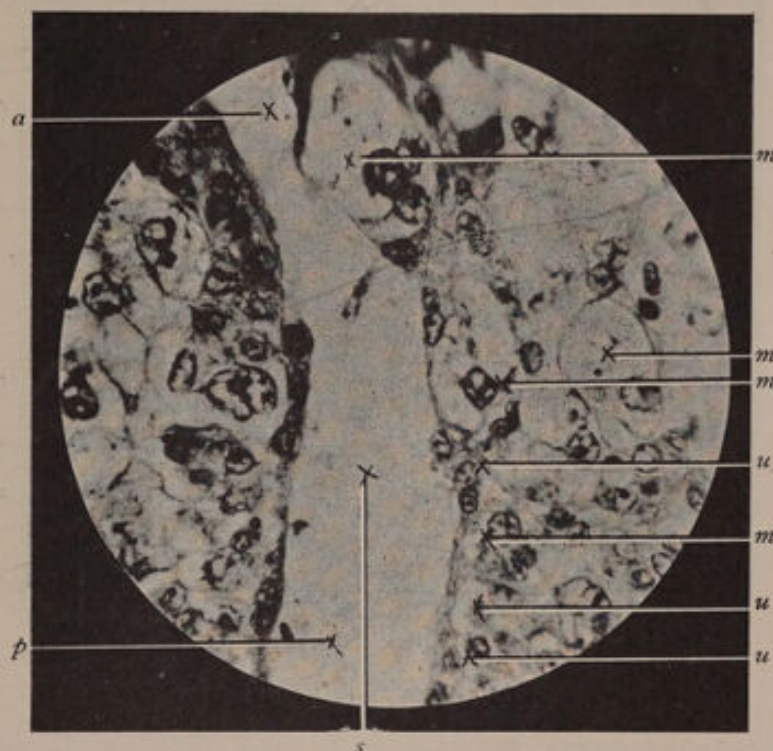


FIG. LX.

(10 days' Gestation.)

Shows again the origin of the multinucleate decidual cells. The proximal end (lower) of the sinus-capillary is surrounded by uninucleate cells, while the distal end is bordered by multinucleate decidual cells derived from the former.

s, sinus-capillary; p, proximal end of capillary; a, distal end of capillary; m,m,m,m, multinucleate decidual cells; u,u,u, uninucleate decidual cells.

it will be observed, follows upon the establishment of the allantoic circulation. The liver is now of considerable size and is everywhere saturated with nucleated foetal blood. The longitudinal section which I have photographed is nearly a mesial one and has cut many of the

viscera; it shows also the centralisation of the vascular membranes which go to be included in the short umbilical cord (Fig. 67).

The general disposition of the placenta—its two cotyledons, and the foetal and maternal portions of these—can be gathered from the large photograph. I have added a microphotograph (Fig. 68), small magnification, of one of these cotyledons to bring out more clearly the general arrangement of its parts. In this one the foetal portion can be more

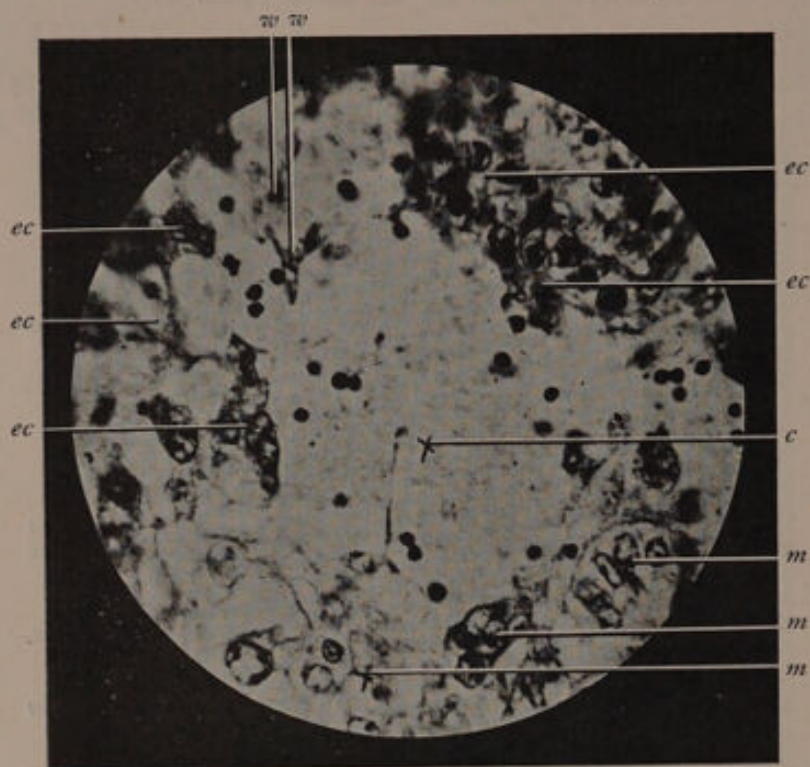


FIG. LXI.

(10 days' Gestation.)

Hæmorrhagic cavity between foetal and maternal tissues. The sinus-capillary has ruptured and its maternal blood been poured out between the foetal ectoderm on the one hand and multinucleate decidual cells of the intermediary region, on the other. This cavity is being surrounded by the ectoderm.

c, cavity filled with maternal blood; *m, m, m*, multinucleate decidual cells; *ec, ec, ec, ec, ec*, foetal ectoderm; *w, w*, fragment of capillary endothelium.

plainly distinguished from the maternal, and also the two regions of the latter—the intermediary region next the foetal placenta and the deeper region of the uterine sinuses. As compared with the 10th day the site of placental attachment is now seen to protrude markedly beyond the general line of the cotyledonary mucosa. This is due not only to the increased thickness of the foetal placenta, but also to rapid growth in the

intermediary region. Moreover the intercotyledonary fissure has opened out so that the surface of the placental lobes now face each other. The comparative regularity of the line of junction of the foetal and maternal tissues—the absence of lengthy “villi” is at once manifest.

The ectodermal laminæ of the foetal placenta have increased greatly in thickness, and the distinction between the two layers, plasmodial and cellular, is more sharply defined. At the 10th day these laminæ were divided into areas by ingrowths of mesoderm from the foetal surface.

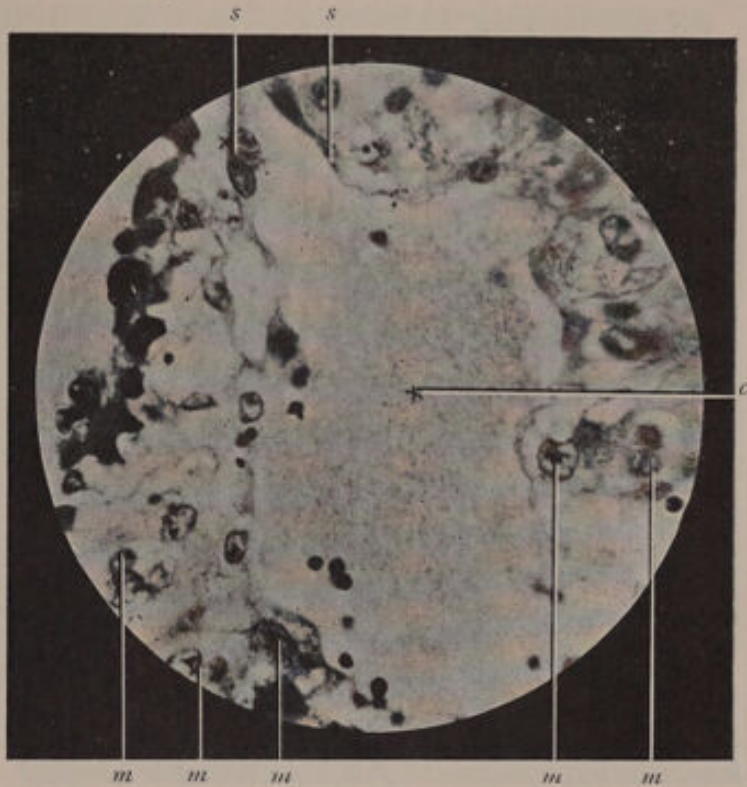


FIG. LXII.

(10 days' Gestation.)

Hæmorrhagic cavity in the midst of the intermediary zone. The wall is formed of multinucleate decidual cells crowded together by the extravasated blood.

s,s, sinus-capillary which has ruptured; *c*, cavity filled with maternal blood and walled by multinucleate cells; *m,m,m,m,m*, multinucleate cells.

These areas are now seen to have become much narrower; while at the same time they have markedly increased in length, for these mesodermic ingrowths plunging deeper and deeper, are now not so far behind the advancing margin of the ectoderm. These ingrowths have also greatly increased in thickness, and carry foetal vessels of considerable size. In this way the *areas* of the 10th day become at the 12th *columnar*. Duval calls them “*colonnes*.” *These columns in shape resemble test-tubes set with their open ends upon maternal tissue; the foetal end is closed* (Fig.

69). The wall of these columns is composed of foetal ectoderm, plasmoidal or cellular, and their axial cavity filled with maternal blood, is directly continuous through the open end of the column with the vascular system of the maternal placenta. These walls are of fairly regular outline and of uniform thickness. The closed foetal extremity of the column is somewhat dilated. Outside the walls is the mesoderm richly vascular, its vessels filled with nucleated blood. The two blood-systems, maternal and foetal, are in this way approximated. Between them intervene one



FIG. LXIII.

(10 days' Gestation.)

Area of fibrin-tissue with included red blood corpuscles. These areas occur in the deeper zone of the intermediary region and are due to slow extravasation—leakage through the impaired sinus-capillary wall.

f,f,f,f, fibrin-tissue; *m,m*, multinucleate decidua cells; *r,r*, red blood corpuscles.

or two layers of foetal ectoderm, plasmodial and cellular, some delicate fibrous tissue and the endothelial wall of the foetal capillary (Fig. 70). It will be seen that these long mesodermic ingrowths which on either side limit the ectodermal columns have the shape of villi. In a sense they can be regarded as allantoic villi, composed solely of vascular mesoderm, which have plunged into and are imbedded in the thick laminae of ectoderm. But the point to be kept in mind is this, that their

distal extremities do not represent points of advance into the maternal tissue, that they always stop some distance short of the more or less regular advancing line of the ectoderm. (See Fig. 68). The most that can be said of them is, that as the general mass of the foetal ectoderm advances deeper into the maternal tissue, these ingrowths of mesoderm follow. But these never *lead* the advance; they never reach maternal tissue at all. As we have seen at the 10th day the advance of the foetal



FIG. LXIV.

(10 days' Gestation.)

Shows glandular cul-de-sacs filled with maternal blood. The solid epithelial plugs in these cul-de-sacs become vacuolated, larger cavities arise and into these a hæmorrhage takes place from a near capillary.

f, f¹, foetal placenta; *g, g¹, g*, glandular cul-de-sacs filled with maternal blood; *p, p*, plugs of glandular epithelium becoming vacuolated; *I, I¹*, intermediary zone.

tissue is led by slight processes of ectoderm which reach inward along the maternal blood spaces of the intermediary region.

Thus at this date the structure of the foetal portion of the placenta is already determined; it will undergo further elaboration later, but its general principle is now apparent. *And this principle is an interdigitation of tissues certainly, but only of foetal tissues* (Fig. 70A).

Microphotograph (Fig. 71) gives a general view of the line of foetal ectoderm advancing upon the intermediary region; leading the van are

plasmodial masses—the plasmodial layer of the ectoderm, following upon and surrounding maternal blood spaces. Microphotograph (Fig. 72) gives a high power view of the foetal tissue which has been following along a capillary, suddenly widening its area of advance so as to include a large hæmorrhagic cavity, while microphotograph (Fig. 73) shows the foetal plasmodium advancing along the walls of a capillary.

2. Maternal placenta.

The intermediary region has increased in thickness at the expense of the deeper region. It consists as before solely of large multinucleate

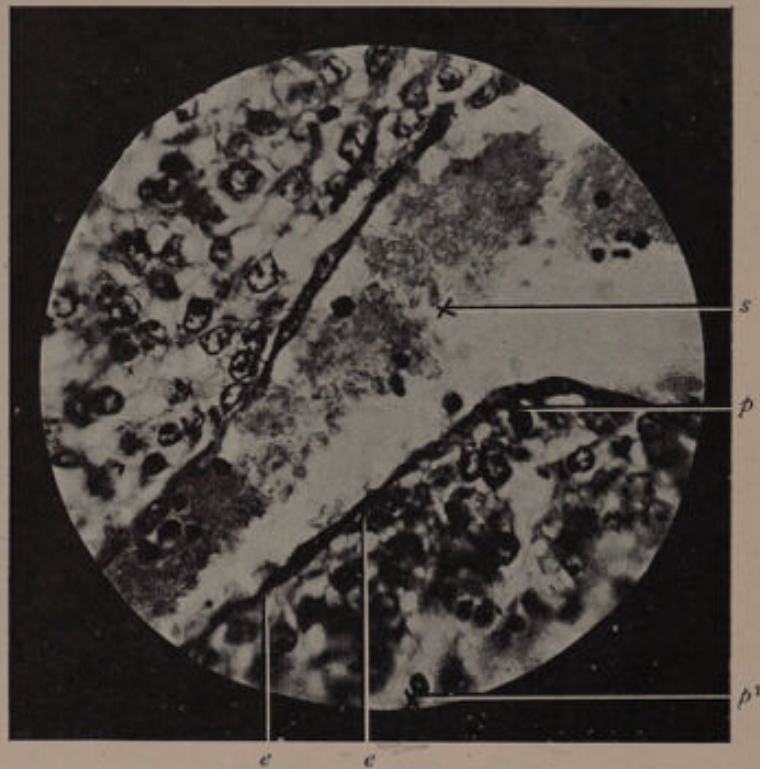


FIG. LXV.

(10 days' Gestation.)

High-power view of a uterine sinus. The endothelium, thickened, is intact and the uninucleate decidual cells of the perivascular sheath are distinct.

s, uterine sinus containing clotted blood; *p, p'*, perivascular sheath of uninucleate decidual cells; *e, e*, endothelium.

decidual cells, richly vascularised by large capillaries whose endothelium is thickened. Hæmorrhagic extravasations into the midst of these decidual cells are common; the swollen endothelium has given way at these places. The change in the capillary endothelium is not the result of the multiplication of the endothelial cells; instead, the single row of cells has thickened, each cell simply becoming swollen and more homogeneous, and with the nucleus and cell-outline indistinct. (See

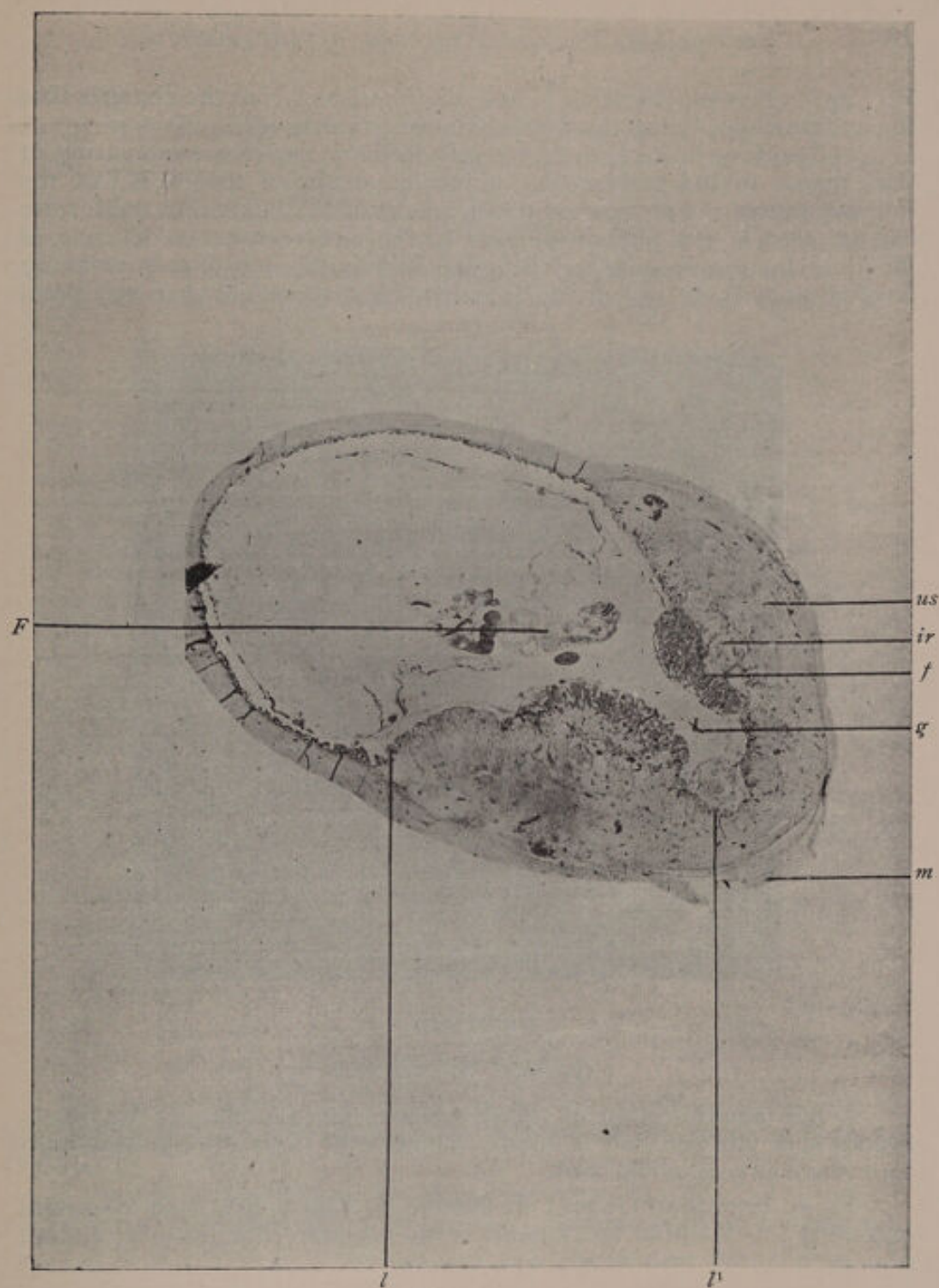


FIG. LXVI.

(12 days' Gestation.)

Transverse section of gestation sac of 12 days. The fœtus is cut longitudinally and the base of the yolk-sac is visible. The two lobes of the placenta, their maternal and foetal portions, with the intercotyledonary groove are shewn.

l, l', placental lobe; *m*, mesometrium; *g*, intercotyledonary groove; *f*, foetal portion of placenta; *ir*, intermediary region (maternal placenta); *us*, region of uterine sinuses; *F*, fœtus cut longitudinally. (Photo.)

Fig. 73). This modification is to be distinguished from the changes that the endothelium, lining the uterine sinuses, undergoes.

The multinucleate cells of the intermediary region are increasing at the expense of the perivascular uninucleate cells of the region of the uterine sinuses. The gradual development of the latter into the former can be seen at the line of junction of the two regions. This line of junction has now become very irregular, the multinucleate cells reaching into the underlying region much farther at some places than at others.



FIG. LXVII.

(12 days' Gestation.)

Longitudinal section of foetus. Shows various viscera and membranes both vitelline and allantoic, which with their vessels gather to form the short umbilical cord.

a, a, a, branchial arches; *h*, heart; *c*, spinal cord near posterior extremity; *v*, vitelline membranes with vessels; *l, l'*, liver; *b*, brain; *al, al, al*, allantoic membranes with vessels.

In this way the thinned and partly modified perivascular sheaths of a few of the most superficial of the uterine sinuses come to be surrounded by the multinucleate cells. (See Fig. 68).

The region of the uterine sinuses is thinner than before. It is further modified by the occurrence of large tracts of fibrin-tissue. (See Fig. 63). The origin of this fibrin-tissue from the slow leakage of the ruptured vessels of the intermediary region we have observed at the

tenth day. It has now greatly increased in amount and in extent. It has followed the lines of undifferentiated corium in between neighbouring perivascular sheaths, compressing these, until these sheaths with their included sinus spaces appear as mere *atolls* in its midst. It is along such fibrin-tissue tracks that the multinucleate cells take origin from the uninucleate cells of the perivascular sheaths; and so it is that the intermediary region appears to invade the region of the uterine sinuses. The uninucleate decidual cells are still vesicular, though their contour has

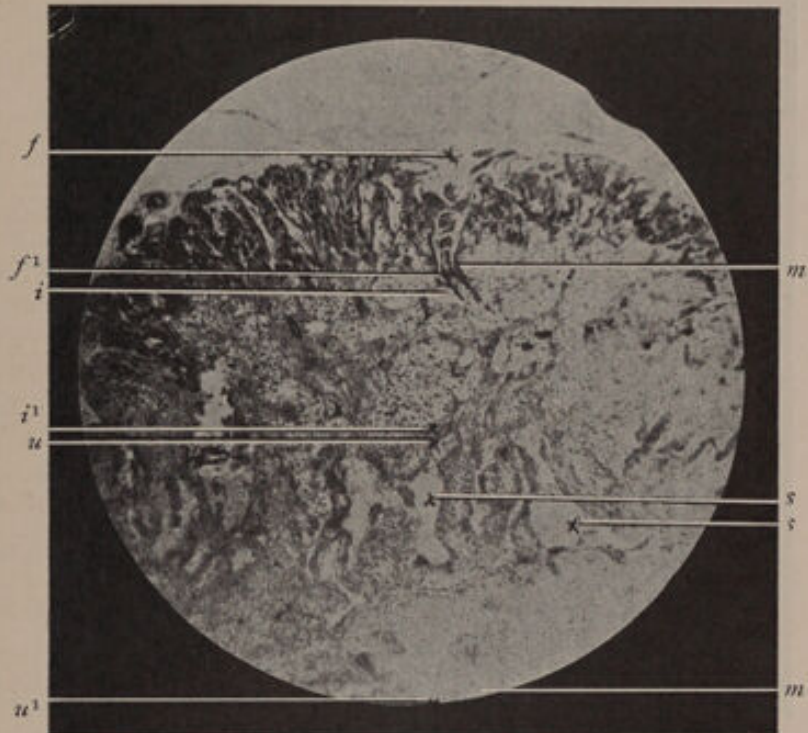


FIG. LXVIII.

(12 days' Gestation.)

The general disposition of one lobe of the placenta. The line of junction between foetal and maternal portions of the placenta is fairly regular.

f, f¹, foetal placenta; *m, m¹*, maternal placenta; *i, i¹*, intermediary region (multinucleate cells); *u, u¹*, region or uterine sinuses; *s, s¹*, sinuses.

become less rotund. The endothelium, lining the sinus-like spaces, is in much the same condition as at the tenth day. Though it is thickened, the cells remain distinct, and the cell contents well differentiated.

GESTATION SAC OF 14 DAYS. (FIG. 74).

(1) Foetus and foetal placenta.

The foetus is divided transversely through the liver and is notable only for its growth. The foetal placenta has increased in thickness, and

its ectoderm is still distinctly divisible into its layers—plasmodial and cellular. The columns or test-tubes have grown to much greater length, but they still retain as axis a well-defined maternal blood-space. (Fig. 75). But the ectodermal walls of these columns have become much more irregular, for here and there they are laterally invaded by the mesoderm, which pushes the ectoderm before it, and so comes to create convolutions in the column. Opposite these points of ingress and

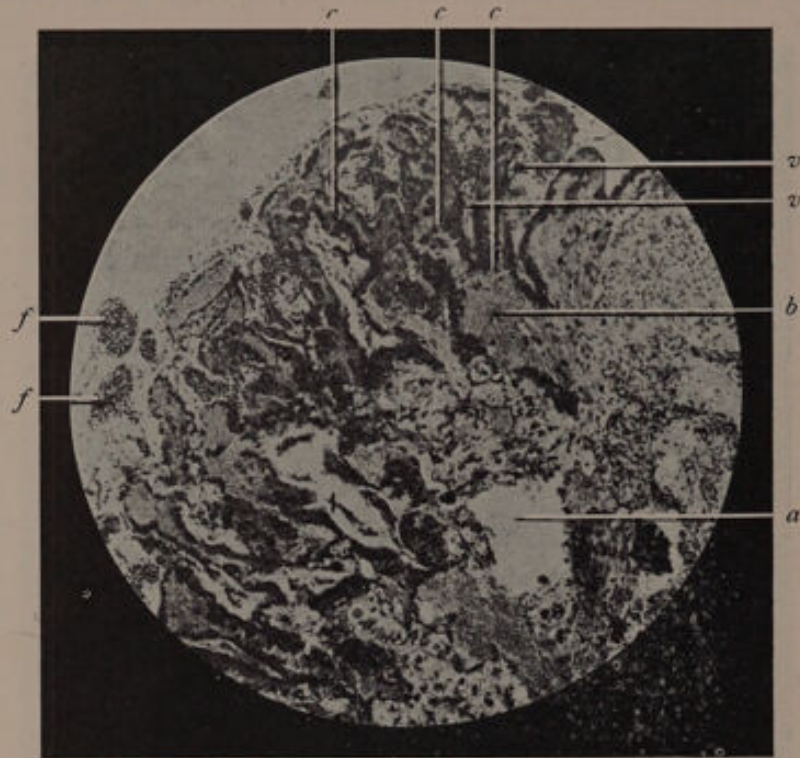


FIG. LXIX.

(12 days' Gestation.)

The foetal placenta—its general plan. The ectoplacenta is now divided into columns by recurrent ingrowths of vascular mesoderm. The walls of the columns are of ectoderm and their axes are cavities filled with maternal blood.

b, maternal blood cavity partly surrounded by ectoderm and continuous with the axial cavity of two columns; *v,v*, mesodermic "villi"; *f,f*, foetal vessels filled with nucleated blood; *c,c,c*, three ectoplacental columns, their walls are of ectoderm and their axes are maternal blood spaces; *a*, a rent artificially produced in intermediary region.

within the column the ectoderm grows inward into the maternal blood-space, fusing with other such ingrowths, but for the most part establishing a line of growth parallel to the parent side walls. The mesoderm carrying its vessels pursues these ingrowths, and so comes to continue its invasion in the long axis of the column. In this way the column is

transformed into a number of *tubes* disposed in a plane parallel to the long axis of the column.

Microphotograph (Fig. 76) shows the beginning of the process. The bud-like ingrowths into the main lumen of the column are seen to proceed from the plasmodial layer of the ectoderm, which sends in, in all directions, its homogeneous-looking processes. These unite with similar ingrowths from apposing walls and divide again, their main direction being always parallel to the parent wall. These plasmodial processes have a cellular core, for their growth depends upon the cell-multiplication

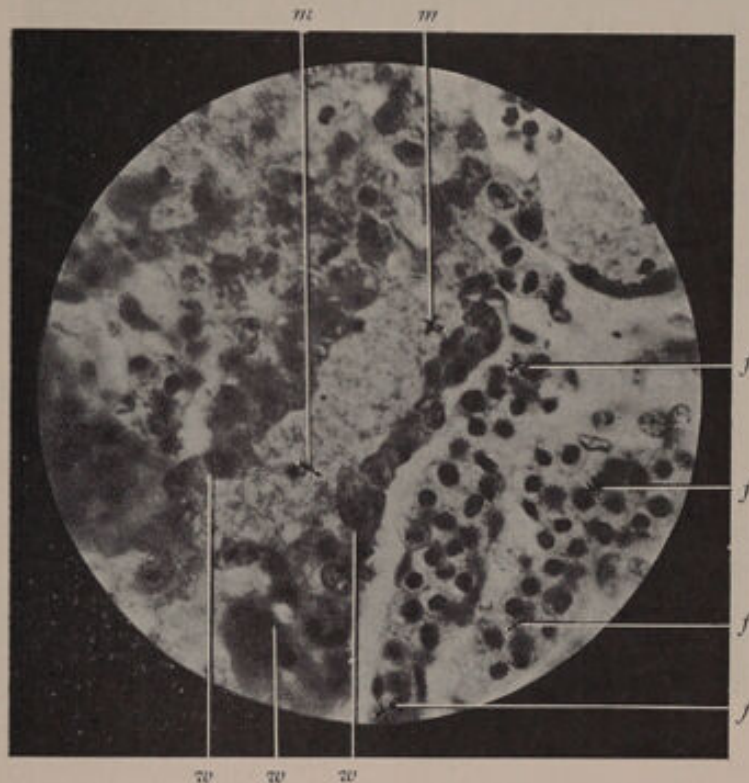


FIG. LXX.

(12 days' Gestation.)

The two blood systems, maternal and foetal. The foetal blood is nucleated. Between the two systems intervene ectoderm, mesodermic tissue, and the endothelial wall of the foetal capillary.

f,f,f,f, nucleated foetal blood contained in foetal capillaries; *w,w,w*, ectodermal walls of column containing maternal blood; *m,m*, maternal blood. The tissue separating the two blood systems is plainly seen.

of the cellular layer of the ectoderm, and the vascular mesoderm pushes in along these cellular axis. In this way the parent column comes to be divided into a set of parallel tubes—2, 3 or 4—for the maternal blood-space of the column has been partitioned into long tubular compartments, by this behaviour of its ectodermal walls. Such a set of tubes is called by Duval a "complexus tubule" or "lobe." A tube is thus simply a small

column, its axis is a smaller maternal blood-space, its walls are of thinner ectoderm, and around these the lighter dissepiments of vascular mesoderm. Microphotograph (Fig. 77) shows one such tube filled with maternal blood. Its ectodermal wall is largely plasmodial and represents in thickness at most a two-celled layer. The surrounding mesoderm is richly vascular, its vessels containing nucleated foetal blood. So at this date the two blood-systems are somewhat closer together, for there is

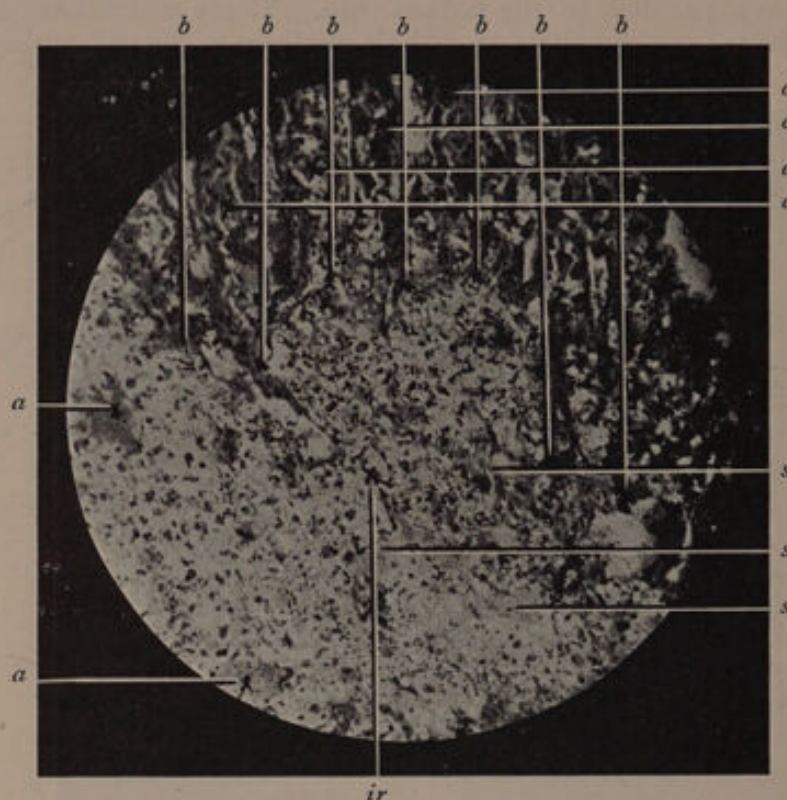


FIG. LXXI.

(12 days' Gestation.)

General view of junction of foetal and maternal tissues. The line of junction is fairly regular. The ectoplacental columns of the foetal placenta, the intermediary region of the maternal placenta, with its multinucleate decidual cells, its thin walled sinus-capillaries and fibrin-tissue areas are shown.

b, b, b, b, b, b, line of junction of foetal and maternal placenta; *c, c, c, c*, ectoplacental column; *s, s, s*, thin walled dilated capillaries; *i, r*, intermediary region of multinucleate decidual cells; *a, a*, areas of fibrin-tissue.

now a thinner ectodermic wall and a smaller amount of intervening mesodermic tissue. Compare 12th day.

The line of junction of foetal and maternal tissues has become slightly more irregular. (Fig. 78). The foetal ectoderm is still advancing along the maternal blood-channels, but its plasmodial edge is now less insinuating, it is blunter and more sharply defined. (Fig. 79). There are no extra-vascular blood-cavities to be surrounded, for the vessels in this

deeper region have stronger walls. But while the ectoderm is still advancing along the vessels, it is not now so uniformly advancing upon the whole intermediary region, in some areas its growth has already ceased. Thus advancing in some places along the vessels and stationary in others, the non-vascular portions, there results an interlocking of the maternal and foetal tissues. This interlocking is quite irregular in its arrangement, but in this way longer or shorter peninsula-like areas of

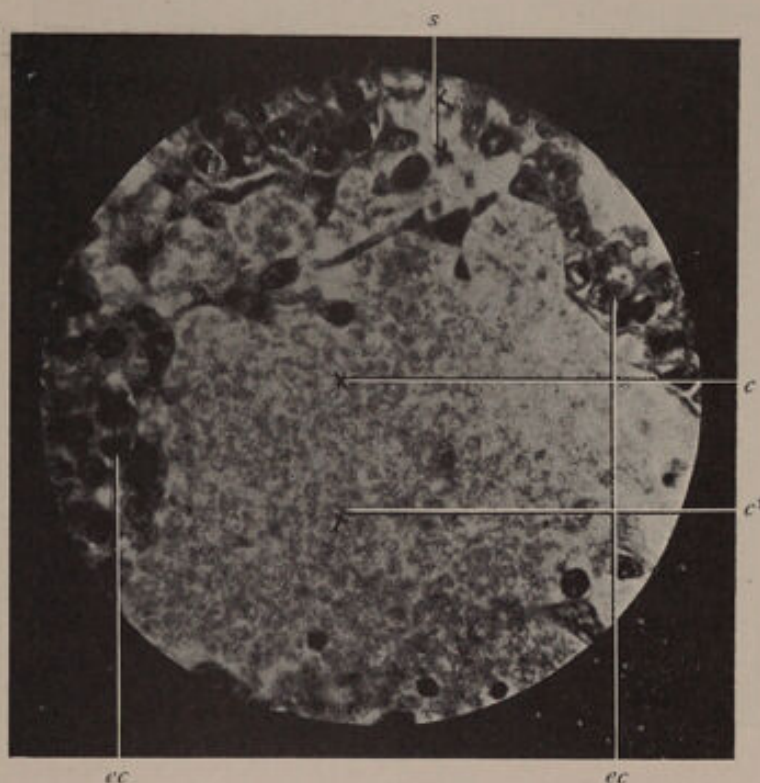


FIG. LXXII.

(12 days' Gestation.)

Behaviour of advancing processes of ectoderm. These processes following along the side wall of the sinus-capillary (see upper side of figure) when confronted with a hæmorrhagic cavity follow the walls of the cavity and so come to include it.

s, sinus-capillary whose wall has ruptured, which rupture has led to the formation of a hæmorrhagic cavity at the junction of foetal and maternal tissues; *c, c¹*, hæmorrhagic cavity; *ec, ec*, advancing processes of ectoderm following wall of cavity.

maternal multinucleate cells come to be found in the midst of the foetal placenta. But the point to be carefully observed is *that the plasmodial edge of the ectoderm is never broken through by these multinucleate cells. To them the foetal placenta presents everywhere an uninterrupted face.* (See Fig. 78.)

(2) Maternal placenta.

The intermediary region as such is greatly diminished in thickness. At the 12th day its multinucleate cells had begun to invade the deeper region, owing to their further transformation from the uninucleate perivascular cells along the tracks of fibrin-tissue. This fibrin-tissue has almost entirely disappeared, its place being now occupied by the multi-

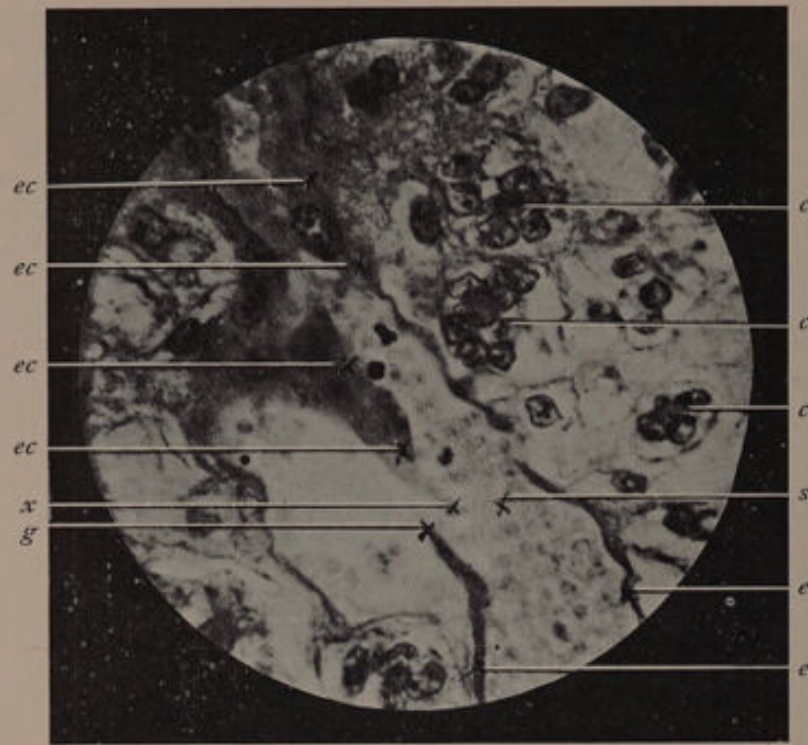


FIG. LXXIII.

(12 days' Gestation.)

Shows the ectoderm advancing along the walls of a sinus-capillary; a rupture of the vessel wall has occurred and is visible between *x*, (foetal ectoderm) and *g*, (maternal endothelium.) Maternal blood has been extravasated into the midst of the multinucleate cells and an adventitious blood cavity formed which in turn will be surrounded by the ectoderm.

ec, ec, ec, ec, ectoderm advancing along the walls of a sinus-capillary; *c, c, c*, multinucleate cells; *s*, sinus-capillary; *e, e*, endothelium thickened; *x*, marks the limit of ectoderm; *g*, the extremity of the ruptured endothelial wall.

nucleate cells, of the advent of which it was the harbinger. These multinucleate cells have multiplied at the expense of the perivascular sheaths, these sheaths becoming by the process thinner and thinner, until now the more superficial uterine sinuses encircled by their thin perivascular sheaths lie atoll-like in the midst, not of fibrin-tissue as at the 12th

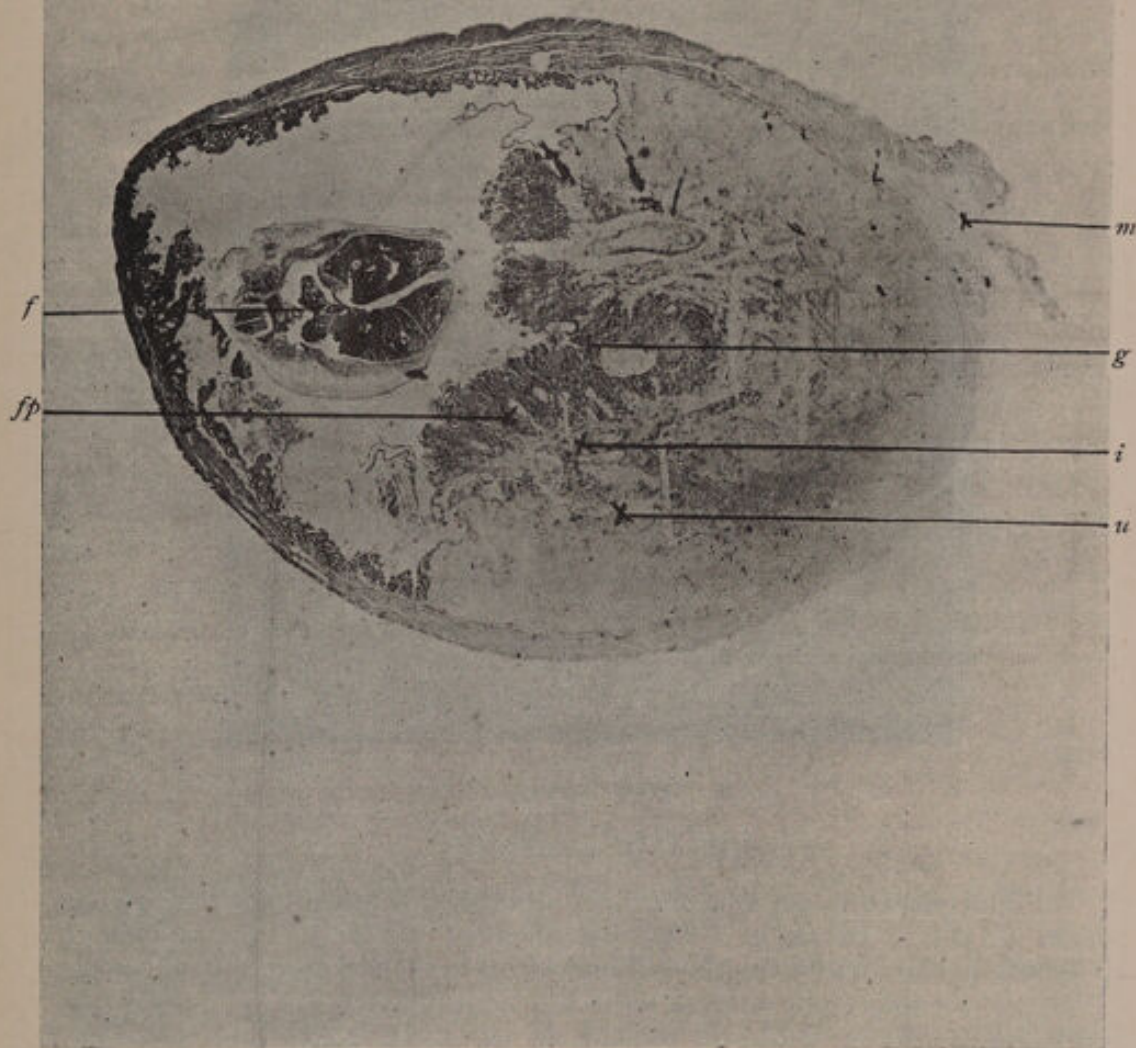


FIG. LXXIV.

(14 days' Gestation.)

Transverse section of gestation sac of 14 days. The foetus is cut transversely through the liver; its growth since the 12th day has been enormous. The foetal and maternal placenta and the different regions of the latter are shown.

m, mesometrium; *g*, intercotyledonary groove; *i*, intermediary region; *u*, region of uterine sinuses; *f*, foetal cut transversely through liver; *f, p*, foetal placenta (darker area). (Photo.)

day, but of multinucleate decidual cells. (Fig. 80). There thus results an intermingling of the tissues of the two regions of the maternal placenta—areas of the *multinucleate* decidual cell, surrounding the thinned perivascular sheaths of the *uninucleate* decidual cell. The multinucleate cells are now less rotund, while their cell-content is still clear it is less abundant, and in consequence the cell-outline is shrunk and wrinkled; the nuclei are also of smaller size.

The region of the uterine sinuses, as we have just seen, has been considerably reduced in its thickness by the invasion, from the interme-

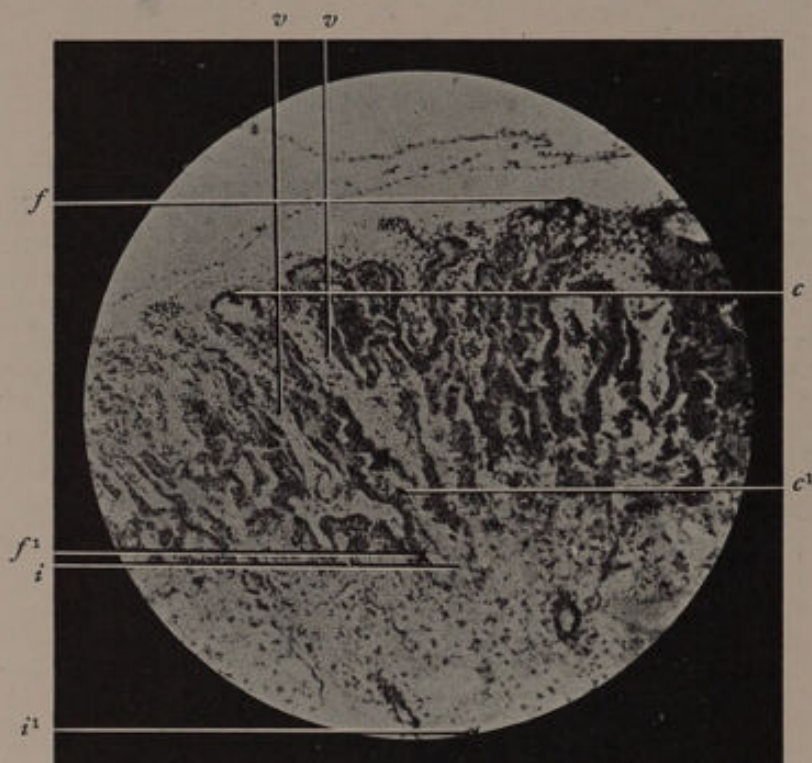


FIG. LXXV.

(14 days' Gestation.)

Foetal placenta, ectoplacental columns with septa of vascular mesoderm ("villi") between. The intermediary region of the maternal placenta is shown and the line of junction of foetal and maternal placenta.

c, c¹, ectoplacental column with axis containing maternal blood and with ingrowths of vascular mesoderm on either side; *v, v*, vascular mesodermic septa "villi"; *f, f¹*, foetal placenta; *i, i¹*, intermediary region.

diary region, of the multinucleate cells. (See Fig. 80). The uninucleate cells of this region have lost very largely their arrangement into perivascular sheaths. There persist only here and there tracks of the original corium, and the large sinus-like spaces so come to lie in the midst of a tissue almost entirely undifferentiated—a tissue of uninucleate cells. These cells are somewhat shrunk.

The uterine sinuses, especially the more superficial ones, have greatly increased in size, for the surrounding tissue has become less dense, less resistant, due to the formation of the multinucleate decidual cells.

The endothelial lining of these sinuses has undergone a marked change; its cells have become swollen and granular, with large, round or oval nuclei. Their granular protoplasm is frequently vacuolated. Fig. 81 shows these cells, and how their swollen and enlarged bodies protrude into the sinus and so give to its walls a scalloped appearance.

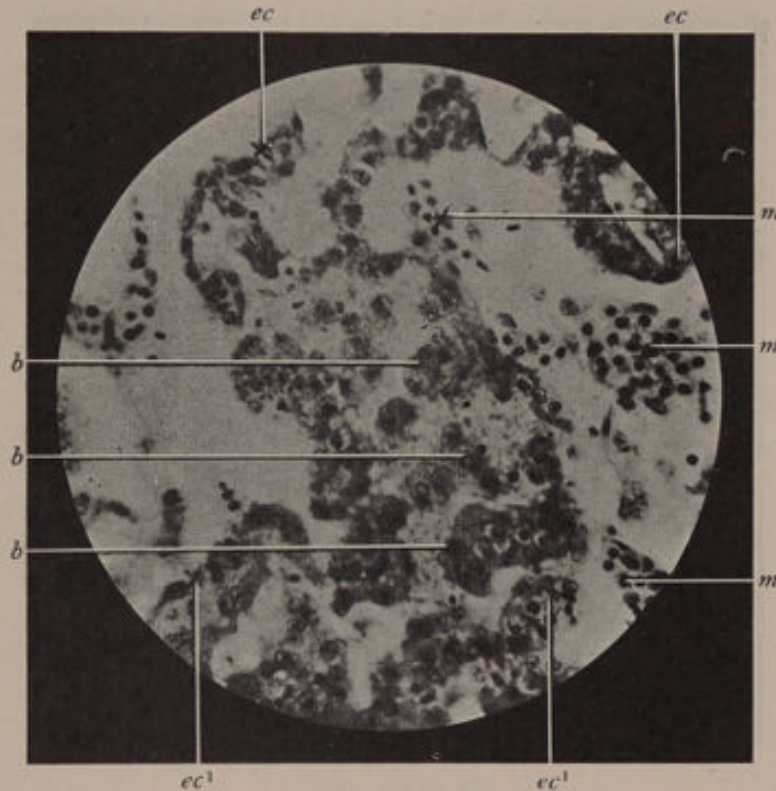


FIG. LXXVI.

(14 days' Gestation.)

Ectoplacental column beginning to divide into smaller columns or "tubes." The ingrowths, in part plasmodial, are shown.

ec, ec, ectoplacental column beginning to divide into "tubes"; *ec¹, ec¹*, the same column showing a more advanced stage of division; *b, b, b*, ectodermal ingrowths, in part plasmodial, which initiate the division of the column; *m, m, m*, vascular mesoderm which in course comes to occupy the axes of the ectodermal ingrowths.

In the more superficial sinuses these large cells have multiplied by direct cell-division, until here the endothelium comes to be represented by several layers of these large cells. (Fig. 82). These cells show marked degenerate changes, vacuolated protoplasm and fragmented nuclei, and are becoming separated and detached from the sinus wall. Fig. 83 shows a group of such cells escaping into the lumen of the sinus. This

separation and detachment leads rapidly to the destruction of the endothelial wall. But during the same time, between and underneath these separating layers of degenerative endothelium, are deposited laminae of dense fibrin with entangled leucocytes. These laminae are arranged concentrically round the sinus-space, and the deeper of them are beyond the endothelium altogether for they lie directly upon the uninucleate decidual cells of the perivascular sheaths. (Fig. 84). *In this way as the endothelial wall disappears, a wall of fibrin comes to take its place.* The



FIG. LXXVII.

(14 days' Gestation.)

Three "tubes" the result of a division of a column and showing the two blood systems, maternal and foetal, with the intervening tissue.

c,c, column almost completely divided into three "tubes"—a "lobe"; *l,l,l*, three "tubes" containing maternal blood and separated by *s,s*, intertubal septa; *s,s*, mesodermic septa with vessels containing nucleated foetal blood; *l,l,l*, interlobar septum, large foetal vessel shown.

great importance of this process, in the further modification of the maternal placenta, will in subsequent stages be more apparent.

GESTATION SAC OF 16 DAYS.

(1) Foetal placenta.

At the 12th day I indicated that the surface of the foetal placenta protruded considerably beyond the general line of the cotyledonary mucosa. This protrusion has increased as the "columns" have length-

ened, and in addition there is now a change in shape. Each half of the foetal placenta has become curved, with its convexity directed towards the interior of the gestation sac, and its concavity towards the musculature. Upon this concave aspect the two extremities of the foetal disc are approximated, and the concavity itself is occupied by the intermediary region of the maternal placenta. In this way a reniform shape is produced on either side of the intercotyledonary groove; this shape as represented in central sections, persists to the end of gestation, and the

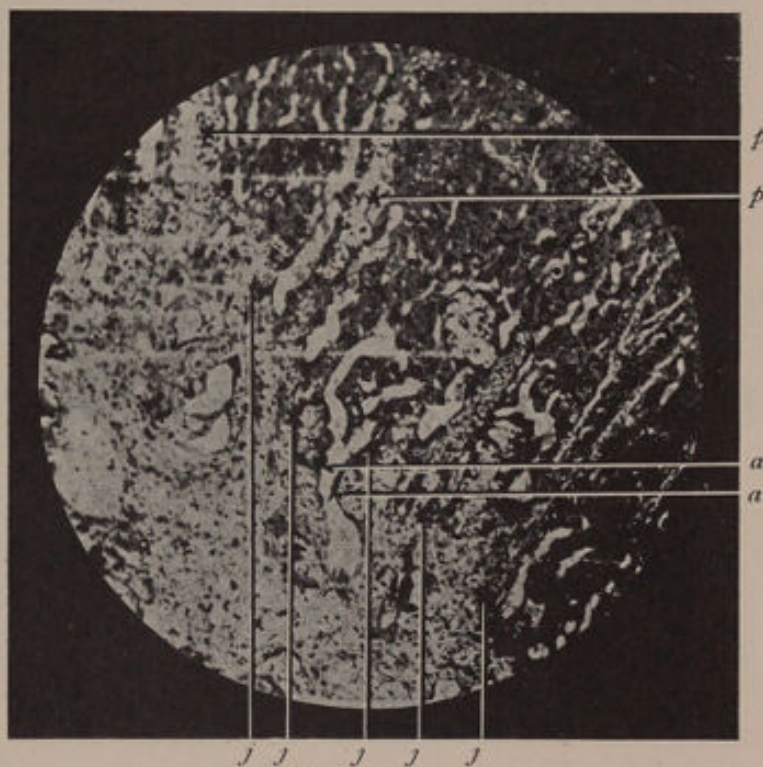


FIG. LXXVIII.

(14 days' Gestation.)

The line of junction of foetal and maternal tissues. The maternal extremities of the ectodermal lobes are shown.

a,a, area shown in Fig. 79; *j,j,j,j,j*, line of junction of foetal and maternal placenta; *p,p*, areas of multinucleate decidual cells (maternal) lying peninsula-like in the foetal placenta.

mature placenta of the rabbit is bi-lobate and kidney-shape. The explanation of this above change of shape is to be found in the different rate of development of different portions of the foetal placenta, the central portions are always more advanced than the lateral portions. Consequently the central "columns" become entirely plasmodial or reach their mature length earlier; the lateral portions continue to fulfil their growth, and the central portions remaining more or less a fixed point, the concavity of the foetal disc becomes established, and the extremities of this concavity by a continuation of the same process are approximated. (Fig. 85.)

At the 14th day each column of the placenta had come to be divided into a number of small columns or tubes. These tubes we saw were in structure simply columns in miniature, and the several tubes derived from one column were loosely grouped together into a company or lobe. This arrangement still persists, but now the tubes are more narrowly pressed together, their general course is straighter, and the mesoderm between them is more compressed. (Fig. 86.) The cells of these tubes are very largely plasmodial, the cellular ectoderm—well-defined cells with



FIG. LXXIX.

(14 days' Gestation.)

Junction of foetal ectoderm and maternal endothelium along the walls of a sinus-capillary. Shows that the deepest penetration of the foetal cells is along the vessels.

ec, ec, ec, foetal ectoderm; *e, e*, maternal endothelium; *j, j*, junction of foetal ectoderm and maternal endothelium; *s*, sinus-capillary walled in part by foetal cells and in part by maternal cells; *m, m*, multinucleate decidual cells of intermediary region.

active nuclei—being represented only at intervals. These cellular foci, one, two, or three cells, are scattered throughout the length of the plasmodial walls of the tubes. This plasmodial wall represents in many places but a one-celled layer, meaning by this that its plasmodium is, in these areas equal in thickness to but a single row of ectodermal cells. (Fig. 87.) The mesodermic villi closely surround these walls, and so there is thus established a closer approximation of the two blood-systems.

Compare 12 and 14 days. The line of junction of the foetal and maternal tissue is more irregular than at the 14th day, and the peninsula-like areas of multinucleate cells which project into the foetal tissue, are more numerous. Sections of such projections whose long axes occupy different planes appear as islands of multinucleate decidual cells in the very midst of the foetal tissue. But I repeat that the foetal tissue presents to the maternal tissue an ectodermal, plasmodial face, broken

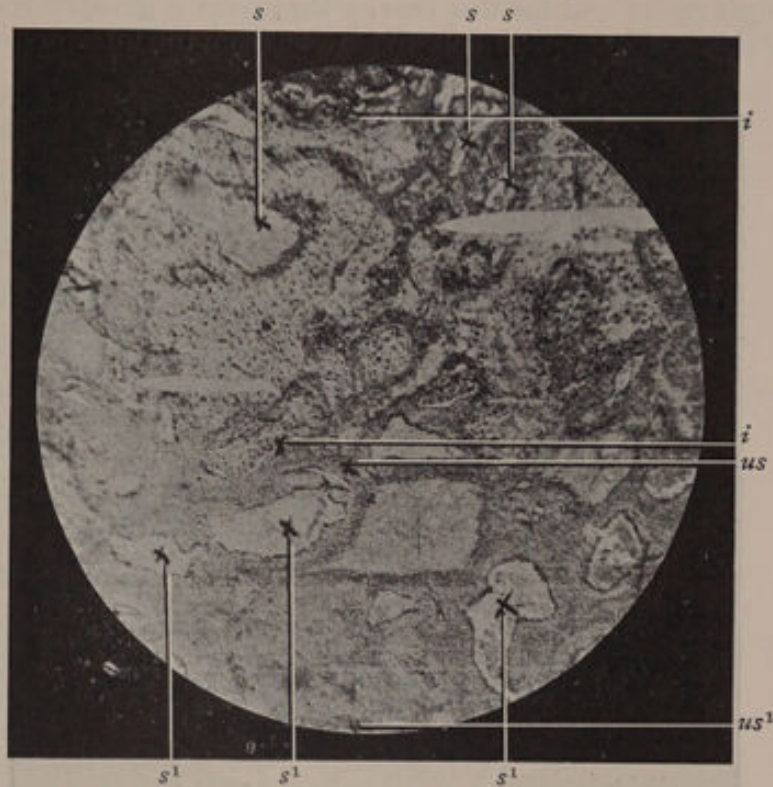


FIG. LXXX.

(14 days' Gestation.)

Intermediary region of maternal placenta. The perivascular sheaths of uninucleate decidual cells which surround the uterine sinuses are themselves surrounded by areas of multinucleate decidual cells.

i, i, intermediary region greatly thickened; *us, us¹*, region of uterine sinuses, greatly thinned; *s, s, s*, sinuses surrounded by a thin perivascular sheath lying in the midst of multinucleate cells; *s¹, s¹, s¹*, sinuses still lying in the region of uterine sinuses.

only by the passage of the vessels. The plasmodial edge of the foetal ectoderm, even upon the maternal vessels, is well-defined and unmistakable.

(2) Maternal placenta.

The intermediary region as a definite region has largely disappeared. It forms now only the "hilum" to the kidney-shaped disc of the foetal placenta. But while there no longer exists a large well-defined zone of

multinucleate cells, certain areas of these cells are found, on the one side, in the deeper region of the uterine sinuses, and on the other side in the foetal placenta. The areas which seem to project into the foetal placenta are due, as we have shown, merely to the fact that the foetal ectoderm in its general invasion had ceased to advance at these places. These points where the ectodermic cells had thus early stayed their advance represent the least vascular areas of the intermediary region; no vessels run through them, and for this reason they offer a greater resistance to the foetal cells. These peninsula-like areas from the intermediary region,

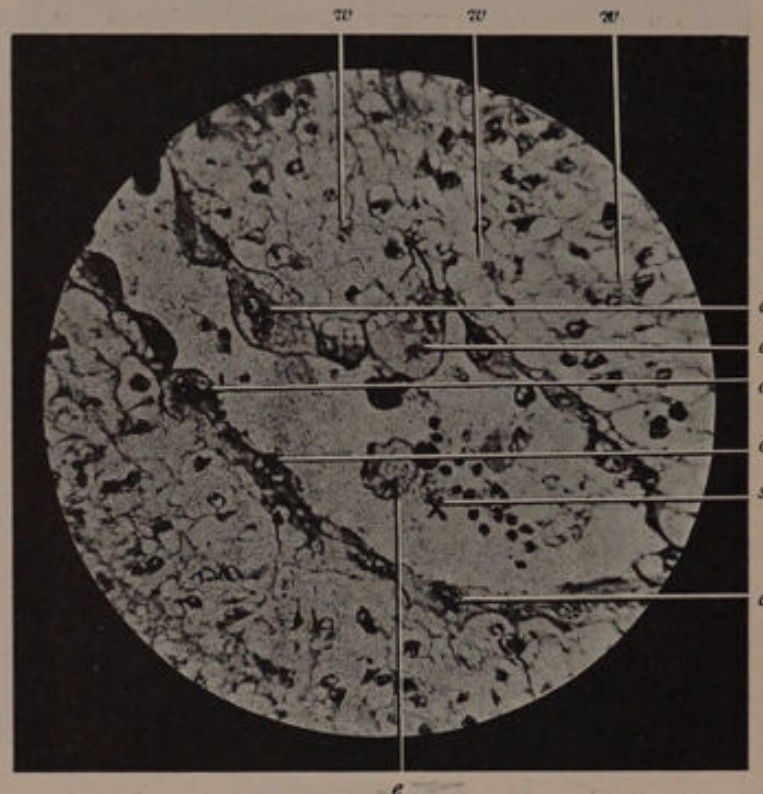


FIG. LXXXI.

(14 days' Gestation.)

Behaviour of the endothelium lining a sinus. The endothelial cells are large and swollen and are beginning to multiply.

s, uterine sinus; *c,c,c,c,c*, endothelial cells swollen and beginning to multiply; *u,u,u*, uninucleate decidual cells forming a perivascular sheath; *e*, detached endothelial cell.

while they have increased in number and in length, are still quite irregular in their arrangement.

Microphotograph (Fig. 88) gives a low power view of such peninsula-like areas. The foetal tissue has penetrated past them into the maternal tissue, following upon the maternal vessels. The line of foetal tissue is unbroken save at the passage of the vessels.

The wide advance of foetal tissue between these peninsula-like areas can in no way be interpreted as "foetal villi."

The region of the uterine sinues is now for the most part a composite tissue. The perivascular sheaths of uninucleate decidual cells are thin; between these are wide reaches of multinucleate decidual cells. There is still, however, a considerable zone next the musculature where only the uninucleate decidual cell is found. In this zone the sinues are comparatively small, their epithelial lining while swollen, is still intact. The more superficial uterine sinues have increased in size during the past 48 hours. Their epithelial lining is still further degenerated and detached, and the surrounding fibrin-laminæ are thicker and more numerous.

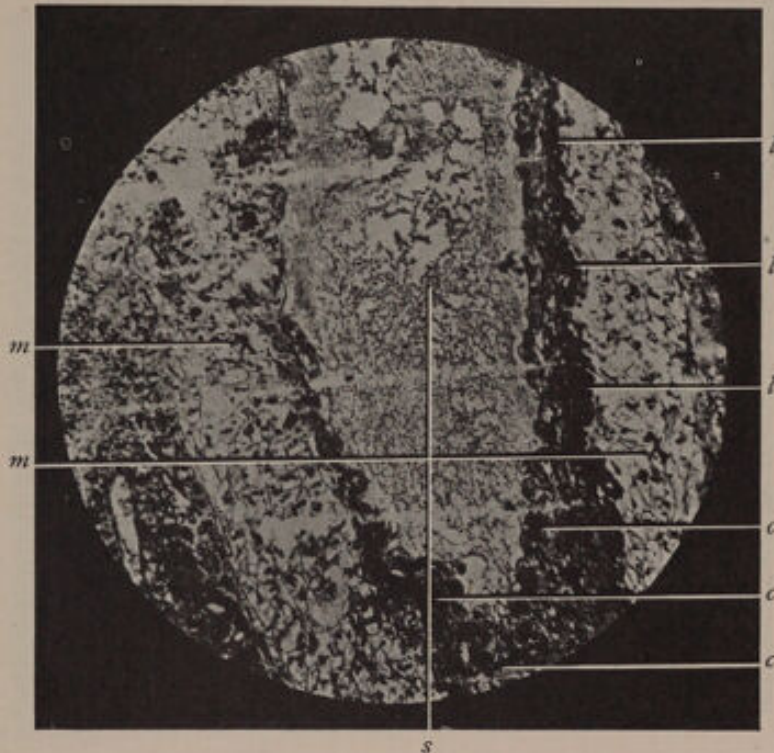


FIG. LXXXII.

(14 days' Gestation.)

Shows endothelium of a more superficial sinus. The endothelial cells have multiplied and in places (see lower end of sinus) are several layers in thickness. Laminæ of fibrin are being deposited outside the partly detached cells.

s, superficial uterine sinus filled with clot; *l,l,l*, laminæ of fibrin; *c,c,c*, endothelial cells several layers in thickness; *m,m*, multinucleate decidual cells.

Microphotograph (Fig. 89), illustrates the more advanced phases of this process. In this microphotograph the wall of the sinus, in places completely denuded of its endothelium, is largely formed by the laminæ of fibrin. Entangled between the firm fibrin-layers are red-blood corpuscles and many leucocytes.

This process of fibrin formation has not been, so far as I know, hitherto described in the rabbit's placenta.

GESTATION SAC OF 18 DAYS.—(FIG. 90.)

(1) Foetal placenta.

The reniform-shape of each placental cotyledon is still more evident, for the extremities of the concave surface of the foetal placenta are further approximated by reason of the continued growth in length of the lateral "lobes." At the 16th day the walls of the tube were regular and of comparatively uniform thickness, chiefly plasmodial, the cellular layer being represented only by detached rows or groups of active cells placed always

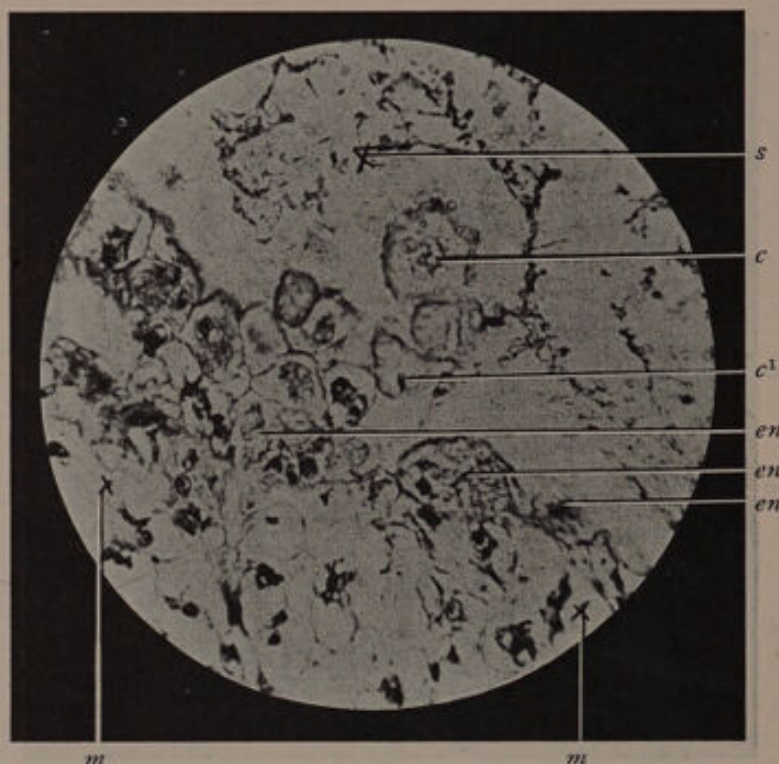


FIG. LXXXIII.

(14 days' Gestation.)

Shows a group of endothelial cells becoming detached and escaping into the lumen of the sinus

s, uterine sinus with blood-clot; *c, c¹*, group of endothelial cells becoming detached; *en, en, en*, lining endothelium, the cells large and swollen; *m, m*, multinucleate decidual cells.

next the mesoderm. These rows or groups of active cells have already at this date given origin to a further change in the structure of the simple tube. (Fig. 91.) For now opposite these cellular foci, the plasmodial wall grows inward, in pointed processes, into the maternal blood lumen of the tube. These processes fuse with similar ingrowths from the same and opposite walls, but maintain on the whole a direction more or less parallel to the parent walls. In addition and at the same time the vascular mesoderm surrounding the tube grows inward at these same foci, indents the plasmodial wall, and so comes to convolute the tube. Fine

mesodermic elements with small capillaries pursue as before this new plasmodial branching, and divide it thus, into two plasmodial halves by coming to occupy the axes of these different processes. (Fig. 92.) These changes transpire between the 16th and the 18th days, though as we shall see, the finer tubes—"tubules"—do not reach their final shape and arrangement until the 22nd day. The "tubule" is identical in structure with the tube; it is simply a tube in miniature, for only is the maternal blood cavity of its lumen smaller and its plasmodial walls thinner, the mesodermic septa that divide it from its neighbours finer, and

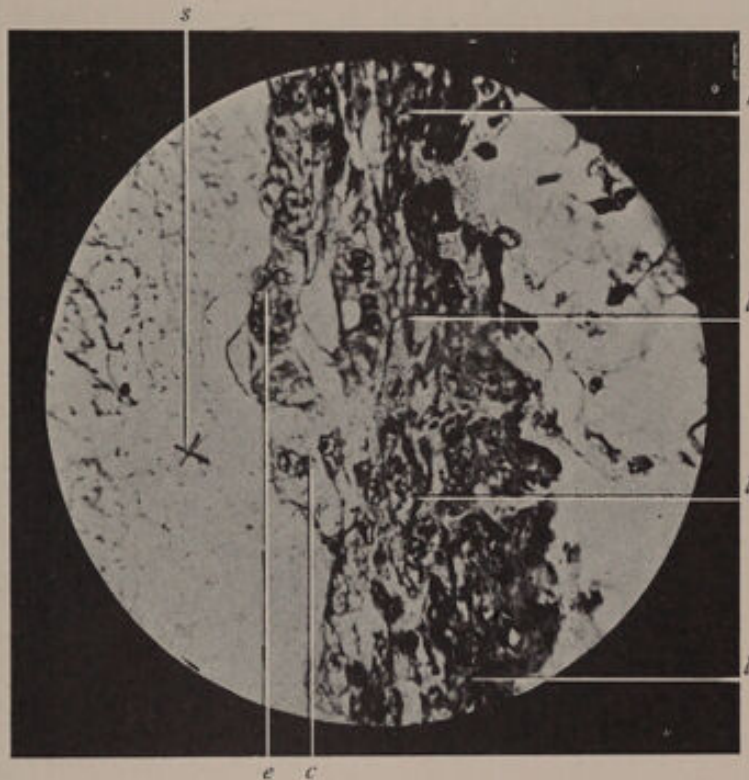


FIG. LXXXIV.

(14 days' Gestation.)

Laminae of fibrin with leucocytes deposited between and underneath the separating layers of degenerated endothelial cells. These laminae in places constitute the wall of the sinus.

s, sinus with blood-clot; c, c, endothelial cells partly detached; l, l, l, l, laminae of fibrin formed beneath the detaching endothelium.

the foetal capillaries included therein more microscopic. The blood systems, foetal and maternal, are hereby still more closely approximated. (See Fig. 92.)

Thus the "tubule" is formed from the tube at the 18th day exactly as at the 14th the *tube* is formed from the *column*. The process is in every way identical, for in all essentials the "tubule" is simply a very small *column*.

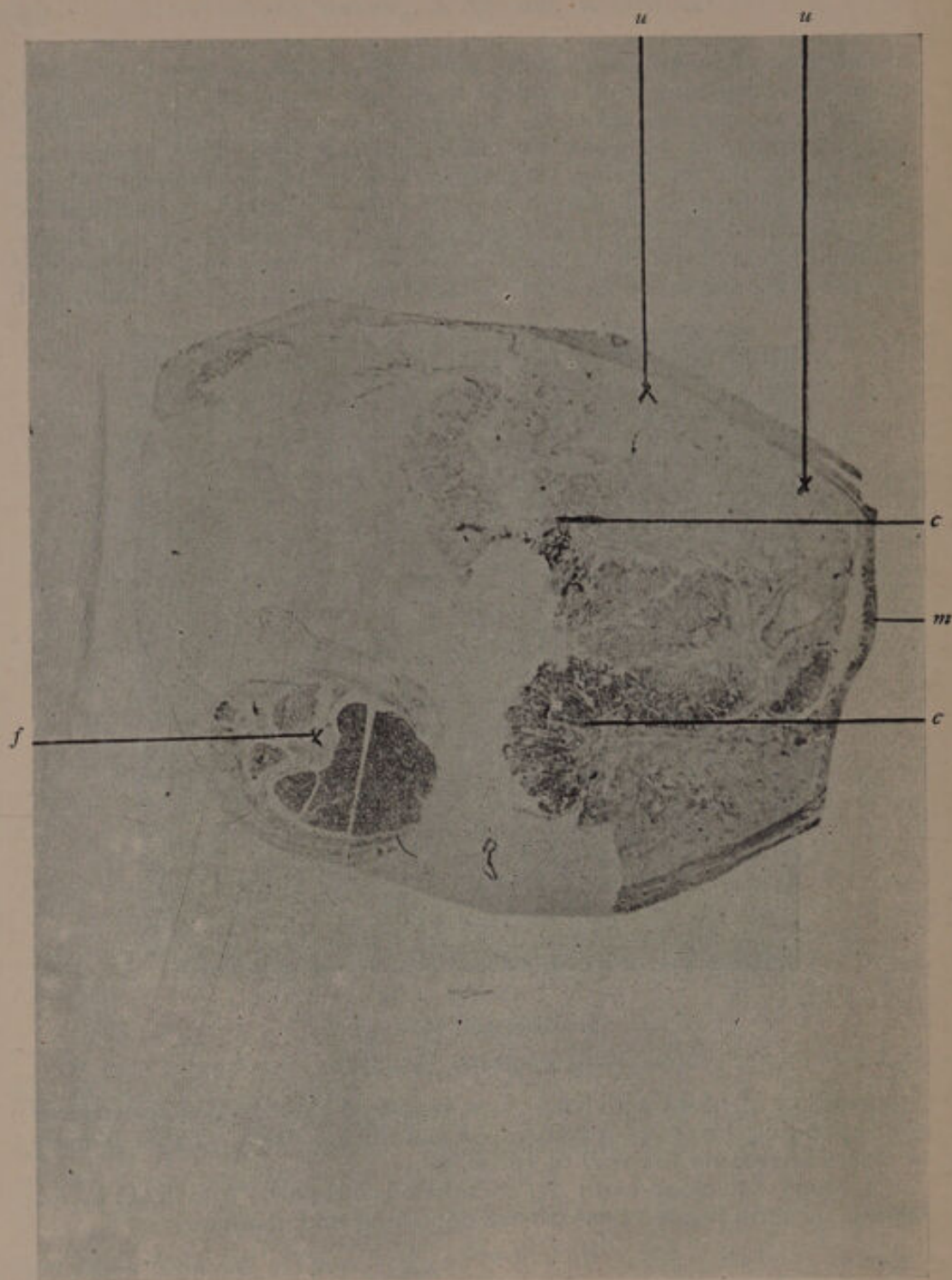


FIG. LXXXV.

(16 days' Gestation.)

Transverse section of gestation sac of 16 days. One wall of the sac is wanting. The foetus is cut transversely.

c,c, the two placental cotyledons; *m*, mesometric pole of sac; *u,u*, deep region of uterine sinuses; *f*, foetus cut transversely. (Photo.)

(2) Maternal placenta.

The intermediary region no longer occupies even the "hilum" of the foetal placenta, for herein there are now seen the more superficial of the uterine sinuses. (See Fig. 90.) As at the 16th day areas of multinucleate cells still appear to run into the foetal placenta, while other areas lie between and surround the still thinner perivascular sheaths of the larger uterine sinuses. These multinucleate cells are now smaller and their nuclei have atrophied. The changes in these cells are seen

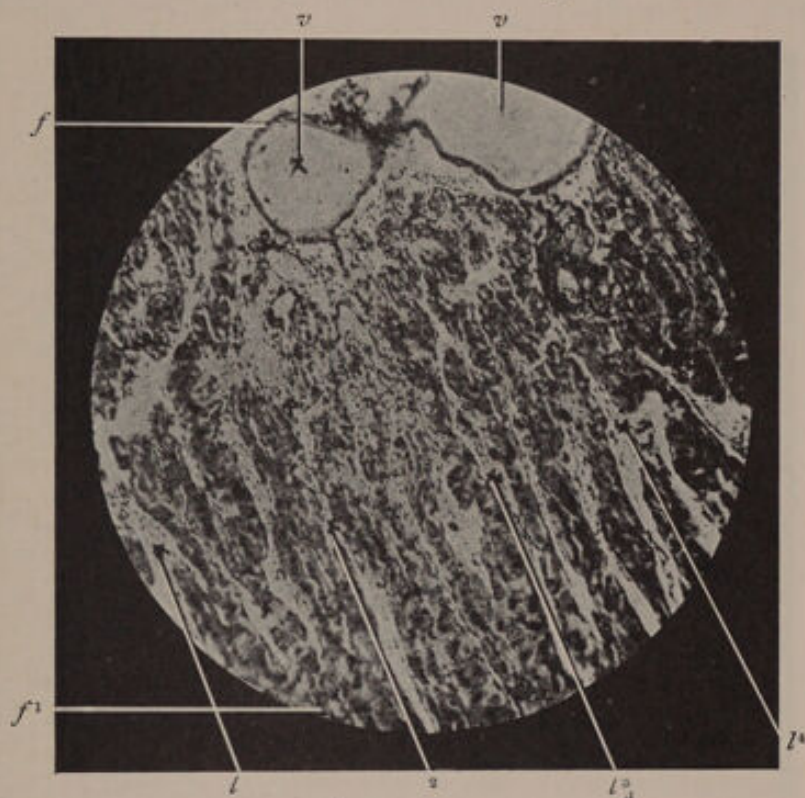


FIG. LXXXVI.

(16 days' Gestation.)

Foetal half of three "lobes" of the foetal placenta. Each "lobe" comprises several "tubes" and represents the "column" of the 14th day.

f, f' , foetal placenta, its foetal or proximal half, i.e. the half next the foetus; l^1, l^2, l^3, l^4 , three placental "lobes" (the indicating lines are drawn in the interlobar septa so that one lobe is included between any two neighbouring lines); v, v' , distal blood spaces filled with maternal blood on the foetal surface of foetal placenta.

especially in the region of the uterine sinuses, while not so evident in the cells of the areas which project into the foetal placenta. So the intermediary region as a zone has definitely disappeared. In all subsequent stages the maternal placenta is represented solely by the zone of the uterine sinuses, a complex tissue, composed of decidual cells, multi- and uninucleate, and of the lately formed fibrin-laminae.

By the gradual disappearance of the intermediary zone the uterine sinuses have come more and more closely to approach the foetal placenta: until now the more superficial of these have come to occupy its "hilum," and are but narrowly separated from its deep face. (See Fig. 90.) These superficial sinuses, now having come under the force of lateral compression, exerted upon the "hilum" by the continued growth of the lateral portions of the foetal placenta, have become modified into a shape more or less uniform. So compressed, they acquire a long axis which extends

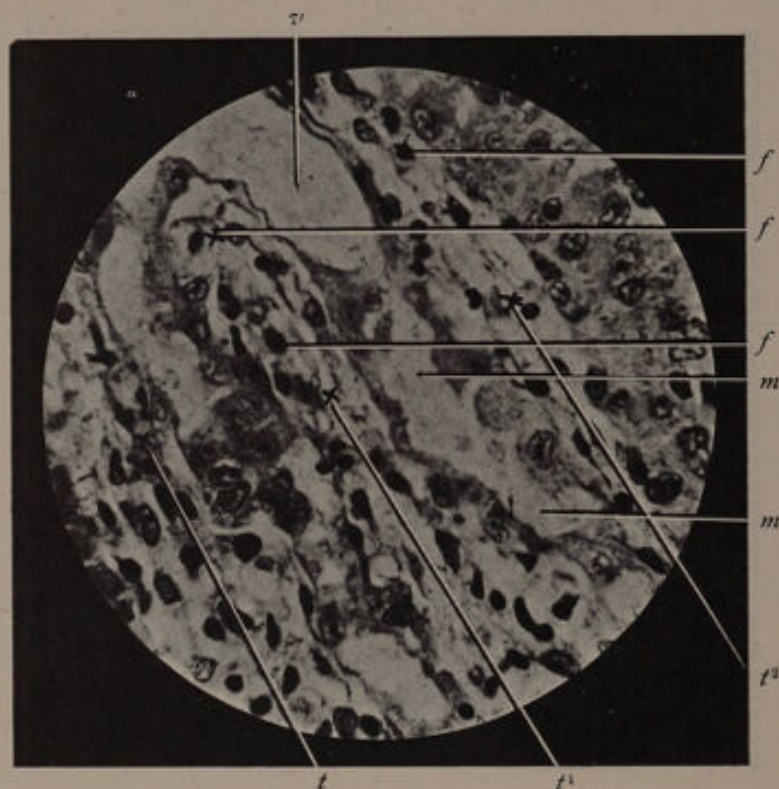


FIG. LXXXVII.

(16 days' Gestation.)

The "tubes" with vascular mesodermic septa (foetal placenta). The ectodermal walls of the "tubes" are thin, largely plasmodial, their axes are filled with maternal blood, while on either side in the mesodermic septa run the foetal capillaries.

t, t^1, t^2 , Two ectodermal "tubes" of foetal placenta (the tube the more distinctly seen lies between t^1 and t^2); f, f, f , foetal capillaries with foetal blood; m, m , axial maternal blood space of "tube"; v , terminal blood space with maternal blood.

always more or less in the plane of the section. Consequently these sinuses appear as long vessel-like spaces.

The deeper sinuses have still increased in size and retain their irregular shape.

The walls of these sinuses, both superficial and deep, are now composed for the most part of fibrin-laminæ, for the endothelial cells are

still further degenerated and detached. (Figs. 93 and 94.) These fibrin-walls have become much thicker. Round about these newly-formed walls lie areas of cellular tissue, made up of the thin remains of the perivascular sheaths—uninucleate cells and interlying tracks of multinucleate cells. These decidual cells, both uni- and multinucleate, are greatly atrophied, and are already in some places almost unrecognizable. The deepest region of the uterine sinuses, that next to the musculature, while it has become thinner is more sharply delineated. It constitutes now a definite zone (see Fig. 90), wherein the cells are solely uninucleate,

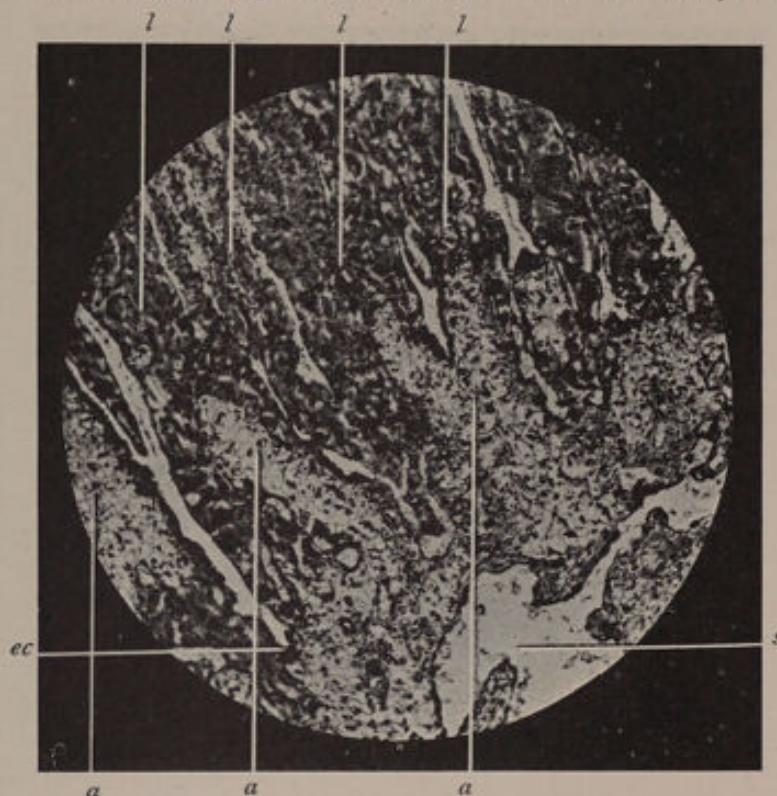


FIG. LXXXVIII.

(16 days' Gestation.)

Maternal half of foetal placenta (darker area), with intermediary region (lighter area) of maternal placenta, and the junction between these, which is the junction between foetal and maternal tissues.

l,l,l,l, four "lobes" of foetal placenta—their distal ends; *a,a,a*, three areas of multinucleate decidual cells lying peninsula-like in the foetal placenta; *ec,ec*, deep penetration of foetal ectoderm along a sinus-capillary (note how the ectoderm follows along the sinus walls); *s*, uterine sinus.

the sinuses remain small and retain intact their swollen endothelial lining. This zone, though it becomes greatly reduced, persists until the end of gestation, for it is through this area, at parturition, that separation of the placenta takes place. Duval has noted this zone, and calls it "couche protectrice," designating thereby its function. He has, I believe, erroneously interpreted its origin.

GESTATION SAC OF 20 DAYS.—(FIG. 95.)

(1) Foetal placenta.

The foetal placenta is now almost entirely plasmodial; cells with distinct outline and nuclei are scattered and few. Consequently it has reached its limit of growth and modification. The "tubules" have come to lie loosely side by side with the vascular mesoderm in thin dissepiments between them. Their plasmodial wall is thin, barely half the thickness of an ordinary cylindrical cell, and in places it is represented by a mere

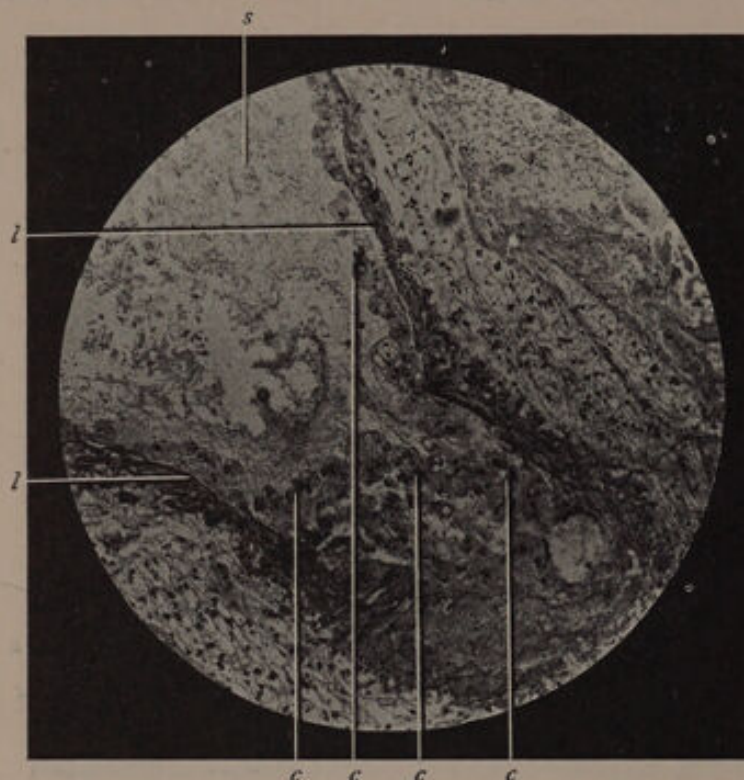


FIG. LXXXIX.

(16 days' Gestation.)

Uterine sinus with detached endothelium and thick walls of fibrin-lamellæ.

c, c, c, c, endothelial cells of sinus, multiplied, swollen and detached; *s*, uterine sinus; *l, l*, lamellæ of fibrin which here form the wall of the sinus.

hyaline line. The mesoderm is also unevenly distributed: accompanying the smaller capillaries there are simply a few cellular threads. (Fig. 96.)

At the 20th day the foetal blood ceases to be nucleated, and in consequence from this date until the end of gestation, the two blood systems, maternal and foetal, cannot of themselves be differentiated. But the containing blood-channels always afford a sufficient distinction; the maternal channels are plasmodial while the foetal channels are of the

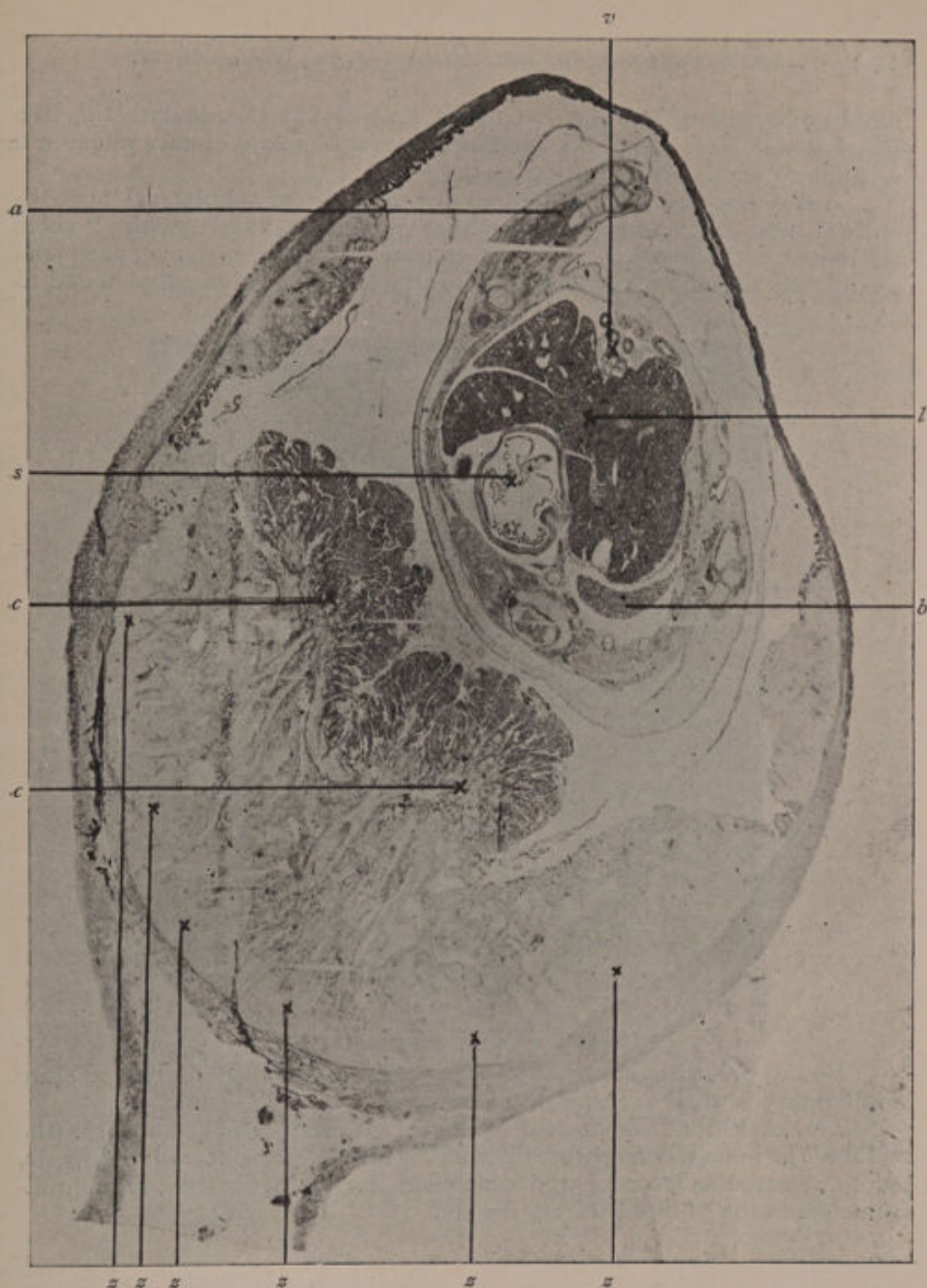


FIG. xc.
(18 days' Gestation.)

Transverse section of gestation sac of 18 days. The foetus is cut transversely and the liver, stomach and umbilical vessels are shown. The placental cotyledons show the adult reniform shape and there is seen the first faint delimitation of the zone of separation.

c, c, the two placental cotyledons with groove between; *s, s, s, s, s, s*, zone of separation; *a*, a limb of foetus; *v*, umbilical vessels; *l*, liver; *s*, stomach; *b*, lung.

(Photo.)

nature of capillaries. The structures that divide at this date the two blood-systems are a thin plasmodium, a thread or two of mesoblast and a capillary wall. (See Fig. 96.)

Duval describes and figures an arrangement of tubules or "canalicules" into a "complexus canaliculaire," or lobule with "voies efférentes, et afférentes du sang maternel." Though my specimens exhibit all the appearances figured or described, I have quite failed to

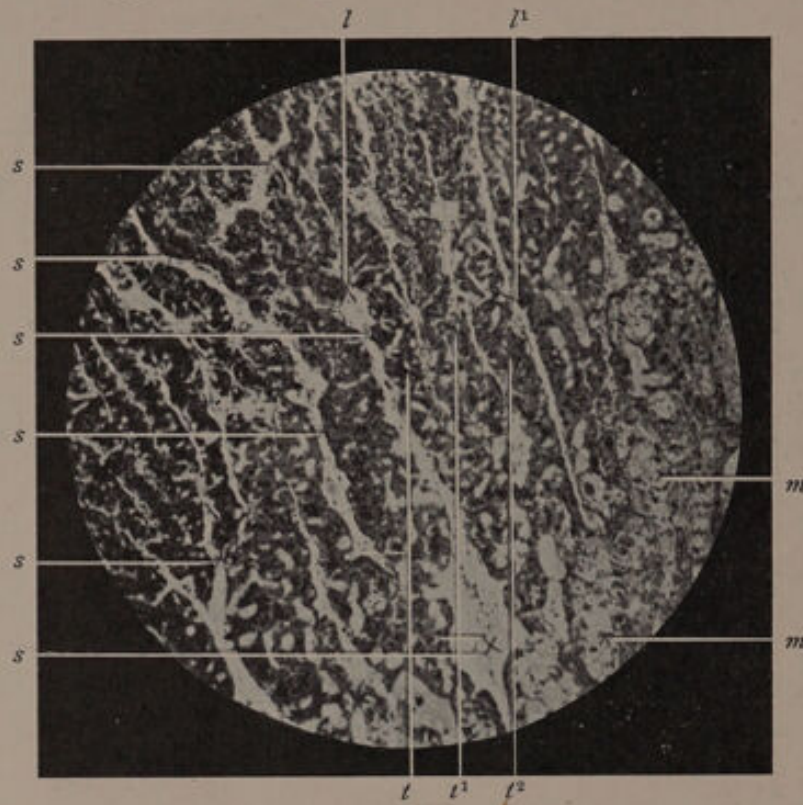


FIG. XCI.
(18 days' Gestation.)

Fœtal placenta showing "tubes" becoming convoluted, a state preliminary to their division into "tubules."

l, l^1 , a "lobe" composed of three "tubes" marked t, t^1, t^2 , (the "lobe" is bounded laterally by wider septa of mesoderm); s, s, s, s, s, s , septa of vascular mesoderm in which run the fœtal vessels; m, m , multinucleate cells of intermediary region.

follow such a classification. By the very particularity of his description Duval has become elaborate and fanciful.

(2) Maternal placenta.

While areas of multinucleate cells are to be found both in the maternal and fœtal placenta, the whole of the maternal portion of the placenta is now to be included in the region of the uterine sinuses save the narrow zone of separation next the musculature. At the 18th day the superficial of these uterine sinuses lie in the so-called "hilum" of

the foetal placenta, are vessel-like in shape, and reach close to the deep face of the foetal plasmodium. The deeper sinuses are of very irregular shape and have increased considerably in size, the tissue intervening between them becoming bridge-like in its narrowness. The endothelial lining of these sinuses has now completely disappeared, and their wall is composed solely of fibrin-laminæ. (Figs. 97 and 98.) These fibrin-walls have already come to bulk largely in the aggregate of the tissues of the maternal placenta, the cellular areas between them—multi- and

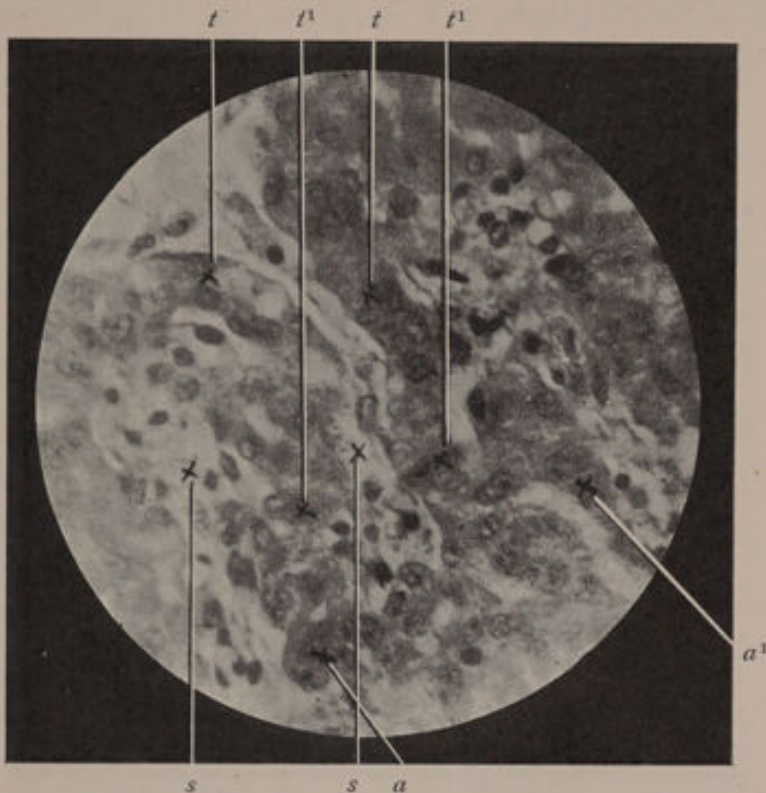


FIG. XCII.

(18 days' Gestation.)

Foetal placenta—a high-power view of a "tube" becoming divided into "tubules." The ectodermal walls are now almost entirely plasmodial.

a, a', placental "tube," the portion which appears uppermost in the Figure is already divided into two "tubules," viz: *tt'* and *tt'*; *s, s*, septa of mesoderm with foetal vessels. The axis of "tube" or "tubule" is always a maternal blood space.

uninucleate decidual cells—having become narrower and more compressed.

In the *zone of separation* the uninucleate decidual cells have lost their vesicular appearance. They have diminished in size and are of irregular shape, with small or fragmented nuclei peripherally placed. These changes give to this tissue a finely retiform appearance.

GESTATION SAC OF 22 DAYS—(FIG. 99.)

(1) Foetal placenta.

In the foetal placenta the tissues, both ectoderm and mesoderm, are more closely compacted. The "tubules" are become smaller in proportion to the surrounding vascular mesoderm. This is due to an increase in the size and number of the allantoic vessels, rather than to an additional growth in the mesodermic tissue itself. (Fig. 100.) Compare at 18 days. In fact at this date there are no longer to be discovered



FIG. XCIII.
(18 days' Gestation.)

Uterine sinus in maternal placenta with detaching endothelium and wall of fibrin-laminae.

ss, uterine sinus; c,c,c,c, endothelial cells swollen and becoming detached; l,l,l, fibrin-laminae which are coming to form the wall of the sinus; u,u, uninucleate decidual cells.

between the closely set "tubules" even cellular threads of mesoderm. The whole interval between successive "tubules" is occupied by the enlarged and engorged foetal vessel, the endothelial wall of the vessel lying directly in contact with the plasmodial wall of the "tubule." This plasmodial wall, while in its whole extent it has become thinner, is in many places quite invisible. In these places the endothelium of the foetal vessel, walls in, on the one hand, its own foetal blood, while on the other hand, it forms also the boundary wall of the "tubule." In other words the sole structure intervening between the two blood-systems—

maternal and foetal—is the endothelial wall of the foetal capillary. Microphotograph (Fig. 101) shows such areas where the plasmodial wall of the tubule is completely denuded, and where the maternal blood bathes directly the outer surface of the foetal vessel.

Such areas represent the ultimate phase in the modification of the foetal placenta, for in all subsequent stages the one change observable beyond the increase in the size and number of the foetal vessels, is the gradual thinning of the plasmodial walls of the "tubules," and the extension of these areas of complete denudation. (See successive microphotographs) (Figs. 87, 92 and 101.) The whole plasmodial wall of the



FIG. xciv.

(18 days' Gestation.)

High-power view of uterine sinus with detaching endothelium and fibrin-laminae.

s, uterine sinus with blood clot; l,l,l, fibrin laminae; c,c,c,c, detached endothelial cells.

"tubule" does not thus disappear, nor does it disappear from lengthy areas. As we have shown these plasmodial walls were always of very uneven thickness, indeed they presented to their contained maternal blood a scalloped edge, a succession of little bays lying between pointed processes. It is only the thinner wall of these "bays" that wears through and it is only at these intervals that the maternal blood is submitted to direct contact with the foetal endothelium. These intervals are alternated by areas of greater or less length where the plasmodial wall of the

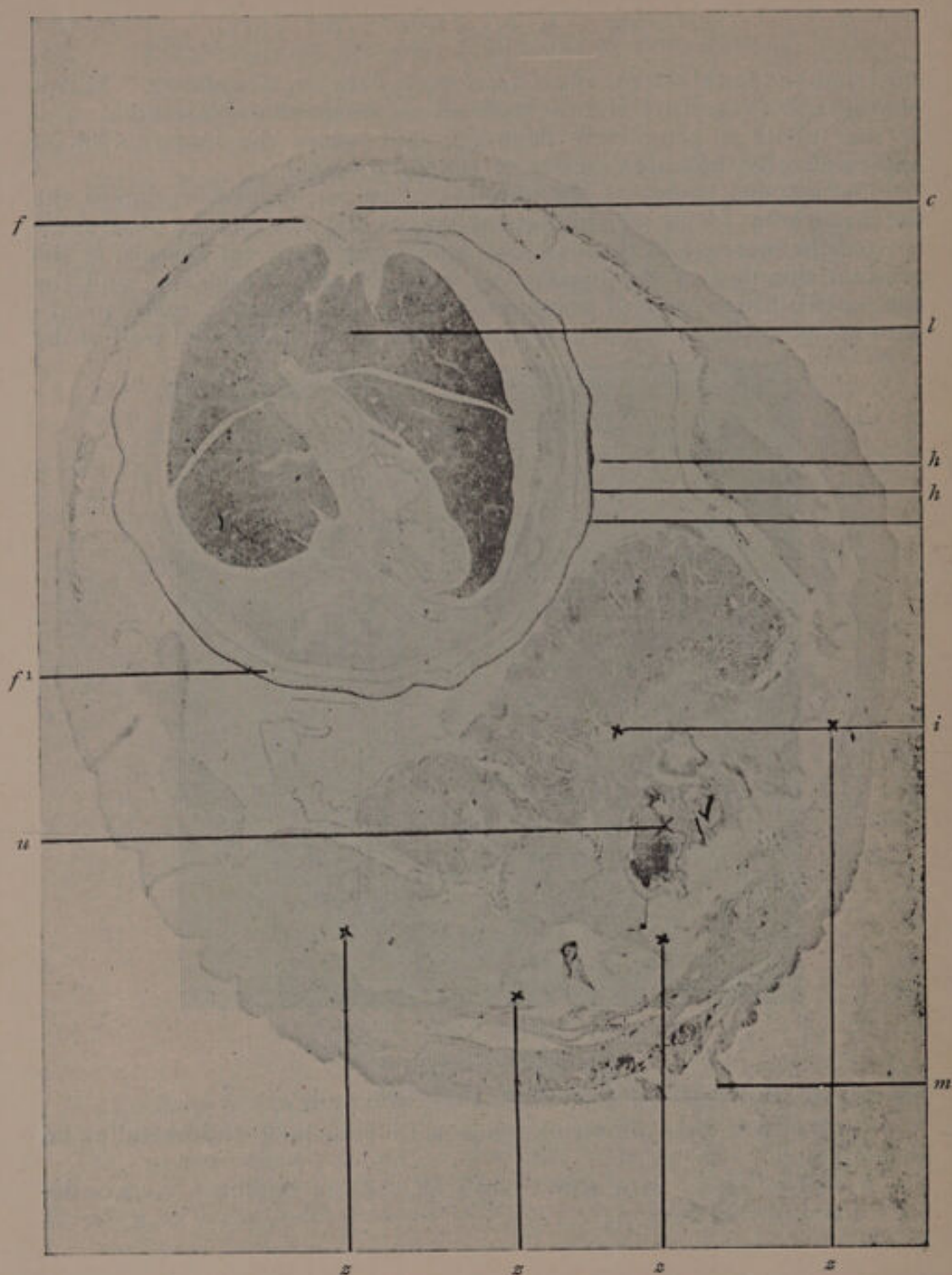


FIG. xcv.
(20 days' Gestation.)

Transverse section of gestation sac of 20 days, cut at the liver level. A short section of the umbilical cord, numerous hair follicles in the foetal cutis vera and the five lobes of the liver are shown. The separation zone of the placenta is now distinct.

f, f¹, foetus; *c*, umbilical cord; *l*, liver; *h, h, h*, cutis vera with hair follicles; *i*, intermediary region; *m*, mesometrium; *u*, region of uterine sinuses; *s, s, s, s*, zone of separation. (Photo.)

"tubule" persists. In this way, in the rabbit's placenta the foetal capillary hangs naked in maternal blood, but naked only in patches.

In this and all subsequent stages, while the foetal blood system is engorged, the maternal blood system is shown, for the most part, empty. I have found that short of artificial injections, this is the only way to picture the separation of the two blood systems.

(2) Maternal placenta.

Areas of multinucleate cells, peninsula shaped or completely detached, which from the 14th day have appeared to invade the foetal

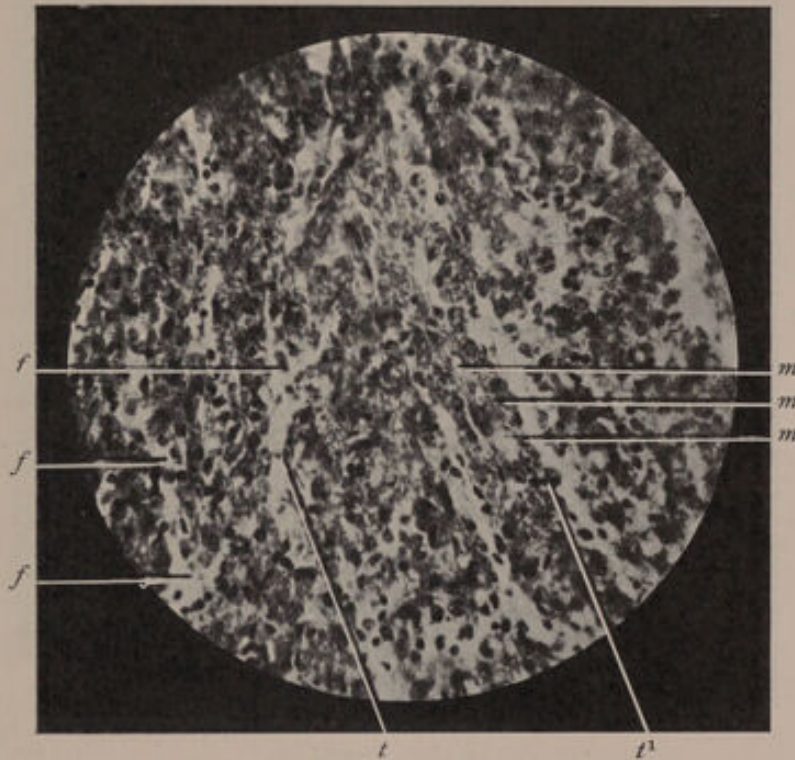


FIG. XCVI.
(20 days' Gestation.)

Section of an area of the foetal placenta. A "tube" is shown almost completely divided into "tubules." The ectoderm is almost entirely plasmodial and a proportional increase of vascular mesoderm is observable.

t, t¹, "tube" showing its subdivisions "tubules"; *m,m,m*, maternal blood spaces (empty), seen in the right-hand "tubule"; *f,f,f*, mesodermic septa vascularised with foetal blood (the near approach of the two blood streams, maternal and foetal, is seen).

placenta are still conspicuous. These areas persist, though they lose their definite cellular character, until the end of gestation. For this reason the line of junction of foetal and maternal placenta remains irregular. But the point I wish again to illustrate and insist upon is that there is across this line of junction no intergrowth of foetal and maternal

processes. The line of demarcation between the two tissues is everywhere sharp and distinct. The foetal ectoderm is, as it were, laid upon the maternal placenta, laid unevenly it is true, but laid unbrokenly, for its deep face is simply interrupted at the passage of the maternal vessels. Microphotograph (Fig. 102) gives the junction along a vessel of foetal plasmodium and maternal endothelium. The distinction between the two tissues even here is plain.⁴

This unequivocal differentiation of the two tissues persists throughout the age-history of the placenta.

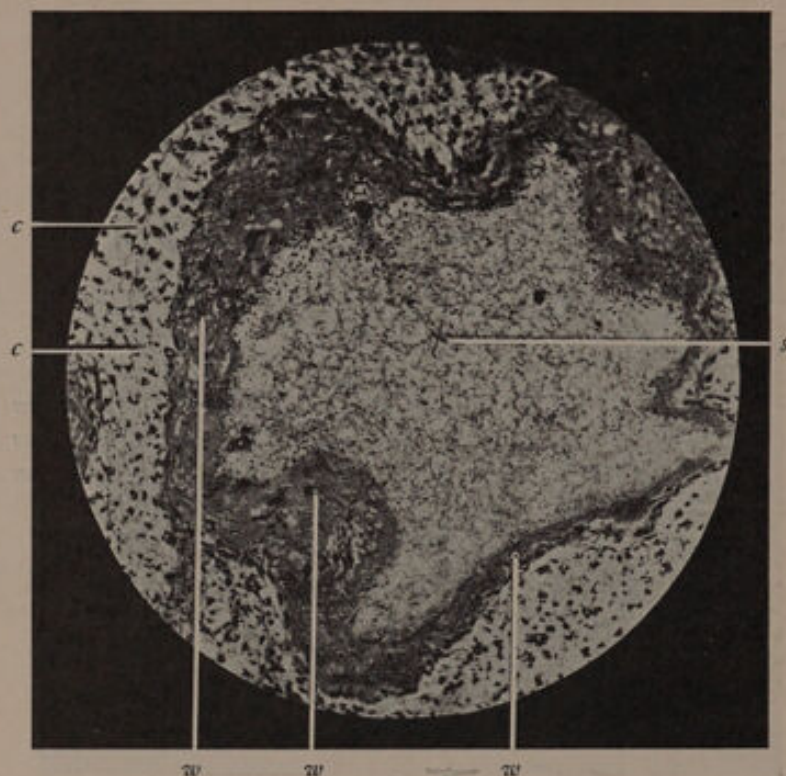


FIG. xcvii.

(20 days Gestation.)

Uterine sinus in maternal placenta. The endothelium has entirely disappeared and its wall is solely composed of fibrin-laminae.

s, uterine sinus with blood-clot; *w,w,w*, wall of fibrin-laminae; *c,c*, uninucleate perivascular cells. Note their shrunken nuclei.

The multinucleate vesicular decidual cells in those areas which appear to have invaded the foetal placenta, show now definite signs of change. They lose their bright translucent appearance and their more or less regularly rotund shape. They become crowded more closely together, while between them and also within them, appears a dull granular substance with here and there fibrin-threads, and a few red blood corpuscles. This substance is coagulated blood plasma, and is due unmistakeably to a slow escape of blood from the vascular spaces which surround these areas, for the process begins always at the periphery and gradually works towards the centres of these areas. (Fig. 103.)

This change is advanced further in some of the areas than in others, and its later effects we shall see in the subsequent stages.

The uterine sinuses have become larger and more irregular, and the composite tissue surrounding them is more compact. The fibrin-walls have increased in extent, and have crowded more closely upon the interposed decidual cells. In addition to the fibrin-lamellæ concentrically disposed about a sinus, longer or shorter fibrin-processes are shot out tangentially from these. These fibrin-processes penetrate and divide

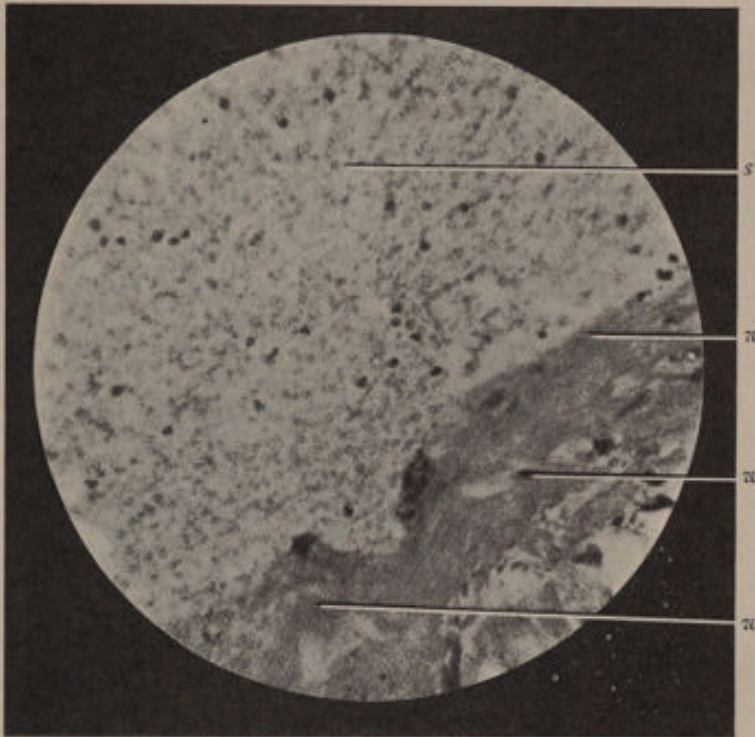


FIG. XCVIII.
(20 days' Gestation.)

Uterine sinus—a high-power view of its wall of fibrin-laminae.

s, uterine sinus filled with blood; w,w,w, wall of fibrin-laminae. The dark spots are the nuclei of decidual cells which have been entangled in the midst of the fibrin.

the compressed decidual cells, and meet similar fibrin-processes from the wall of neighbouring sinuses.

The zone of separation has suffered no further diminution in its depth. Its structure in appearance is more finely retiform, its vesicular cells becoming more angular; the swollen endothelium of its few and small blood-sinuses is intact.

GESTATION SAC OF 24 DAYS.—(FIG. 104.)

(1) Fœtal placenta.

The plasmodial walls of the tubules are somewhat thinner and the areas of *complete denudation* are extended. Their maternal blood lumen is empty while the adjacent fœtal vessels are filled. (Fig. 105.)

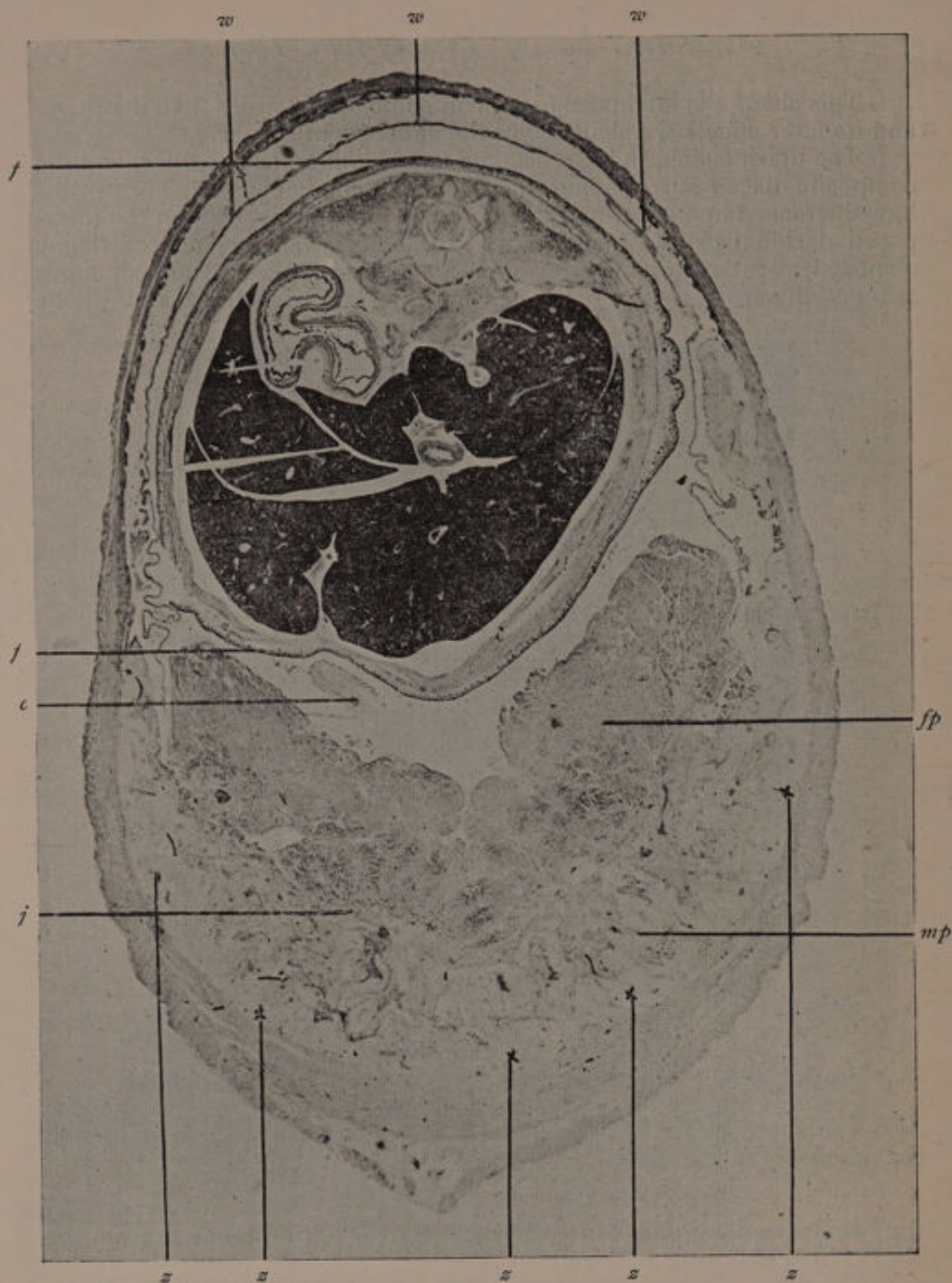


FIG. XCIX.
(22 days' Gestation)

Transverse section of gestation sac of 22 days. The foetus is cut through the liver, the hair follicles in its skin are more numerous and distinct; the superior wall of the yolk-sac is intact; the foetal and maternal portions of the placenta are unmistakeable and the zone of separation more distinct.

f, f, foetus; *c*, umbilical cord; *w, w, w*, superior wall of yolk-sac, invaginated and now inferior; *fp*, foetal placenta; *mp*, maternal placenta; *j*, junction between the two; *s, s, s, s, s*, zone of separation.

(2) Maternal placenta.

I show in microphotograph (Fig. 106), the appearance under a very low power of the region of the uterine sinuses. This tissue now is spongiform in character, for the sinuses have increased enormously in size. The nature of the tissue itself we already know; its subsequent modifications I shall give with the later stages.

The general appearance of the zone of separation is also brought out in this microphotograph.

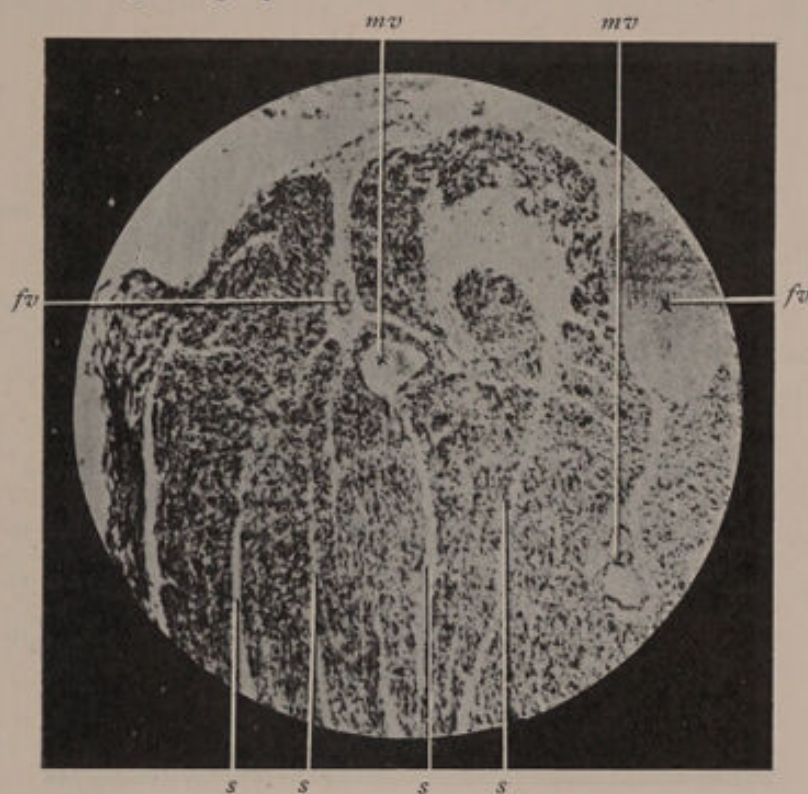


FIG. c.
(22 days' Gestation)

Foetal placenta—groups of "tubules," their foetal extremities. The plasmodial walls of the tubules are thin.

mv, mv, maternal vessels (empty); *fv, fv*, foetal vessels filled with foetal blood; *s, s, s, s*, wider mesodermic septa (vascular) which separate the groups of "tubules." (See Fig. 101.)

GESTATION SAC OF 26 DAYS.—(FIG. 107.)

(1) Foetal placenta.

The tubules show little or no change, the denudation areas are possibly of greater extent. (Fig. 108) simply corroborates the character of the division remaining between maternal and foetal blood, and continues the regular sequence of the series.

(2) Maternal placenta.

The areas of multinucleate cells which appear to lie in the foetal placenta have now, in many instances, completely undergone the change,

the beginning of which we observed at the 22nd day. These areas are now dense and granular, with interlacing strands of fibrin traversing them throughout. Their large vesicular cells have entirely disappeared, only are seen within the interstices of the fibrin network, irregular groups of the darkly-stained fragments of their nuclei and cell-walls. The appearance of these areas is thus amorphous, with interlacing fibres of fibrin, and with the dark remains of the multinucleate cells scattered irregularly throughout their extent. The regions of the uterine sinuses

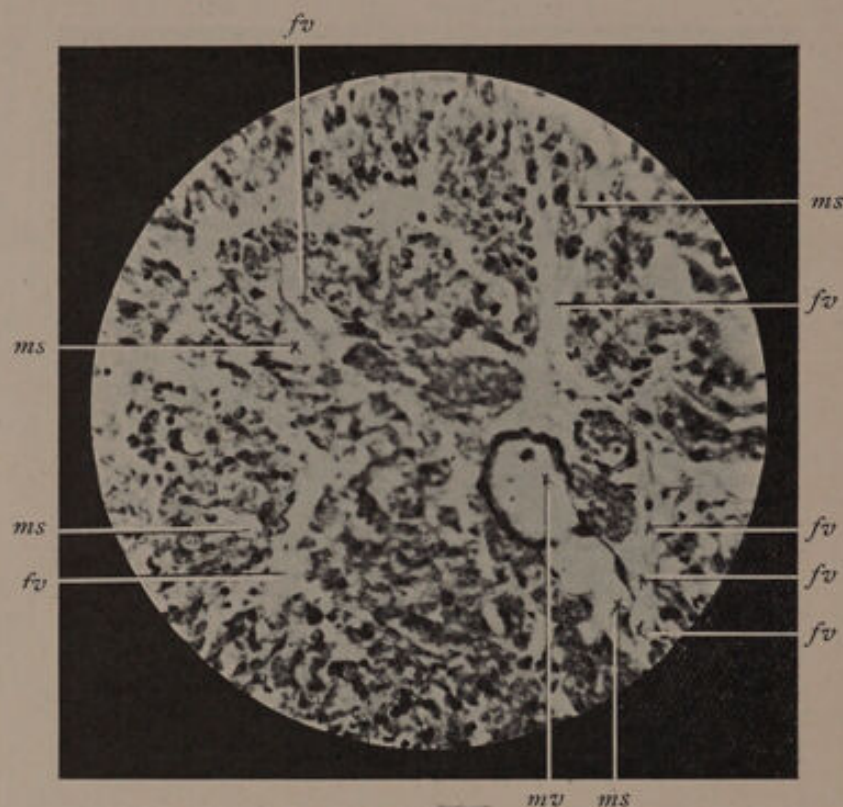


FIG. CI.

(22 days' Gestation.)

High-power view of "tubules" (foetal placenta). The plasmodial wall of the "tubules" has in places completely disappeared (see *ms,ms,ms* and *ms*, where the only tissue intervening between the two blood systems, maternal and foetal, is the wall of the foetal vessel).

mv, maternal vessel (empty) ; *ms,ms,ms,ms*, maternal blood spaces in the axes of "tubules" ; *fv,fv,fv,fv,fv,fv*, foetal vessels.

and zone of separation show little change ; they will be intimately studied at the 28th day.

GESTATION SAC OF 28 DAYS.—(FIG. 109.)

(1) Foetal placenta.

In general appearance the foetal placenta is less plasmodial and more richly vascular. This is due to a further thinning of the plasmodial walls, and to added growth of the foetal vessels, for the maternal blood-channels

are here empty. Microphotograph (Fig. 110) gives a high power view of several of these "tubules" with the interlying foetal capillaries. The plasmodial walls of the tubules are at intervals altogether wanting, and here the maternal and foetal blood streams have but an endothelial wall between them. These denuded intervals make up in the aggregate about half the length of the extent of the *tubules* shown in the microphotograph. As nearly as I can judge this represents the truth in respect of the entire length of the tubule.

The foetal placenta undergoes no further change. At the 30th day

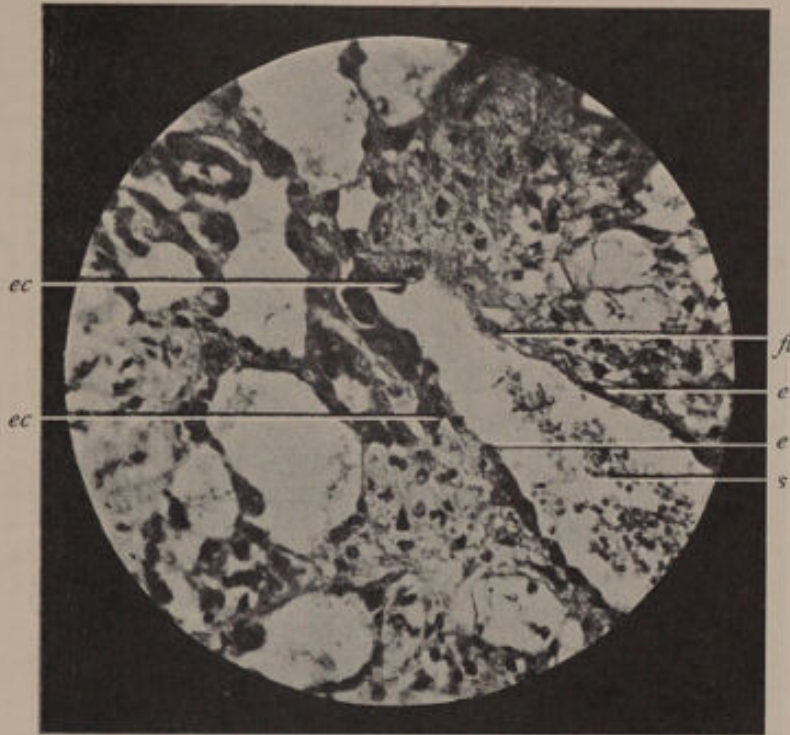


FIG. 110.
(22 days' Gestation.)

Maternal placenta—uterine sinuses. Shows the deepest ingrowths of foetal ectoderm along the walls of a sinus whose endothelium has in part disappeared. One part (the upper) of the sinus is walled by ectoderm, the lower part by its own endothelium, and between these the wall is composed of fibrin-laminae.

s, uterine sinus ; e,e, endothelium ; ec,ec, foetal ectoderm ; fl, fibrin-laminae.

it remains identical in appearance, and at this later date parturition occurs.

(2) Maternal placenta.

The areas of maternal tissue lying peninsula-like or detached in the foetal placenta show the characters described at the 26th day. After the 26th day there occurs no further change in these areas. The composite

tissue of the uterine sinuses presents a change from the 22nd day, in that it is more largely composed of fibrin tissue—concentric lamellæ and irregular strands of fibrin, while the cellular elements are more finely fragmented. These cellular elements are reduced now to the condition merely of *chromatic debris*, fragmented nuclei and broken cell-walls. This *débris* is scattered about throughout the ground mass of fibrin-tissue, and lies in irregular clusters between the fibrin-threads or lamellæ (Fig. 111.) The main collection of this *débris* lies more or less in the axes of the bridges of fibrin-tissue which now separate the large sinuses.

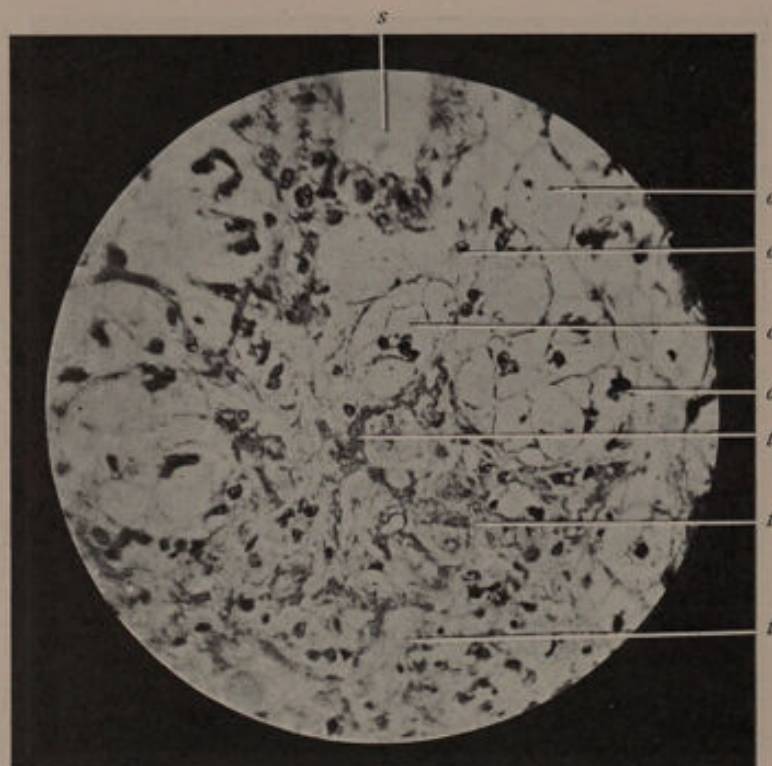


FIG. 111.
(22 days' Gestation.)

The fate of the multinucleate decidual cells. These become œdematous, lose their outline and give place to areas of fibrinous tissue in which their cell debris remains embedded.

s, uterine sinus; *c, c, c, c*, multinucleate decidual cells; *t, t, t*, fibrinous tissue with decidual cell debris in its midst.

This position is to be anticipated for the reason that from the beginning of the formation of the concentric fibrin-lamellæ at the 14th day, these decidual cells have been, by the gradual increase of these lamellæ, crowded further and further away on every side from the blood sinuses.

In this way the fate, to all the decidual cells—both multi- and uninucleate down to the zone of separation—is to be accounted.

The zone of separation has not appreciably diminished in depth since the 24th day. It is still solely composed of uninucleate decidual

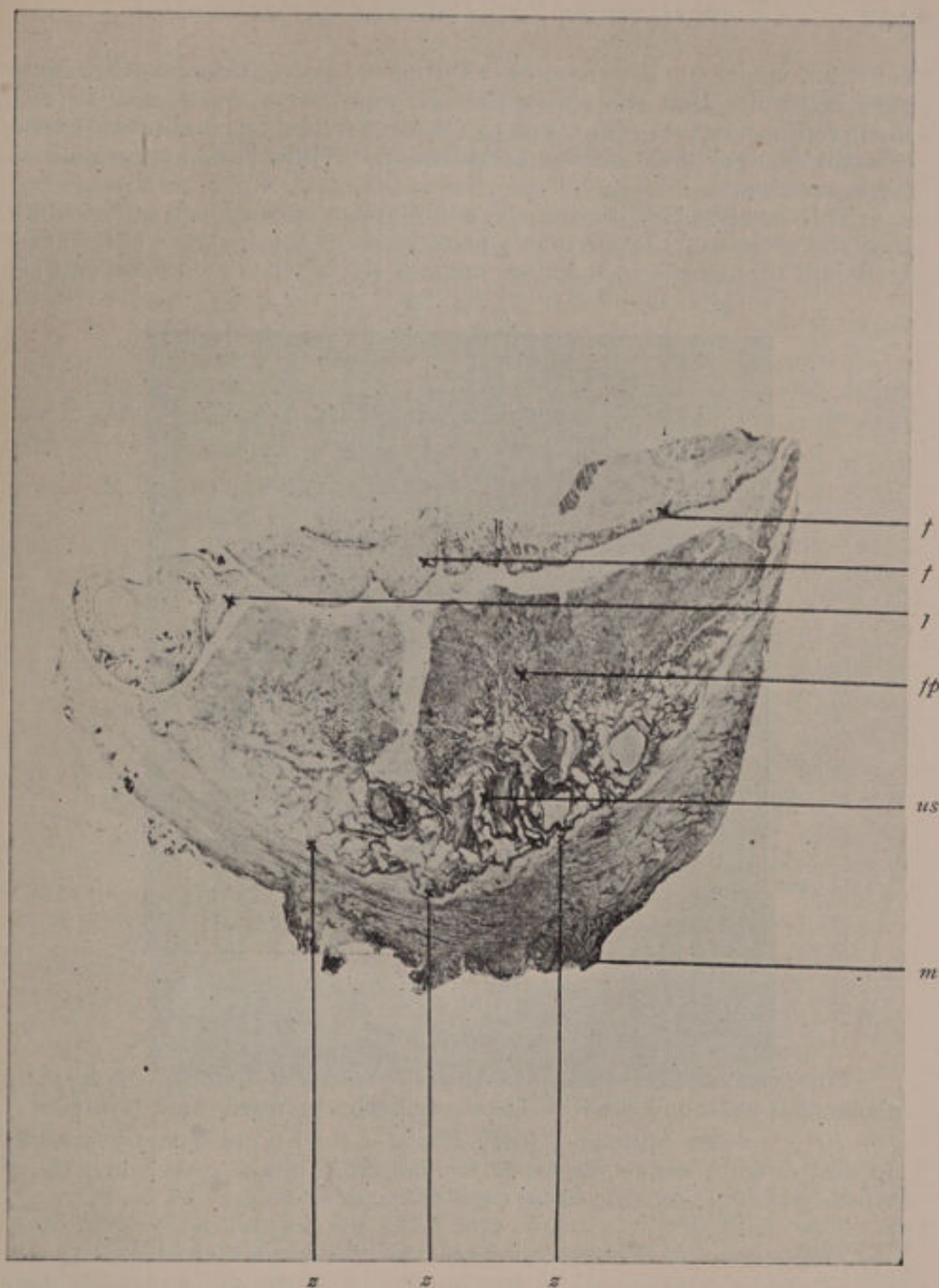


FIG. CIV.

(24 days' Gestation.)

Transverse section of a placenta of 24 days. Part of the foetus only is shown as the complete sac proved too large a block for the microtome. The uterine sinuses have increased in size.

f, f, f, foetus, hair follicles larger and more numerous; *fp*, foetal placenta; *us*, region of uterine sinuses (maternal placenta); *m*, mesometrium; *s, s, s*, zone of separation. (Photo.)

cells, but so greatly are these cells shrunk, and so thinned are become their cell-walls, that the appearance is now that of most delicate and finely retiform tissue. (Fig. 112.) The small blood-channels of this zone are still lined by their swollen endothelium. There is no appearance of fibrin lamellæ.

This swollen condition of the endothelium is continued at this date into the vessels of the circular muscle layer of the uterus. (Fig. 113.) Only is it the vessels in the inner area of the circular muscle-layer that

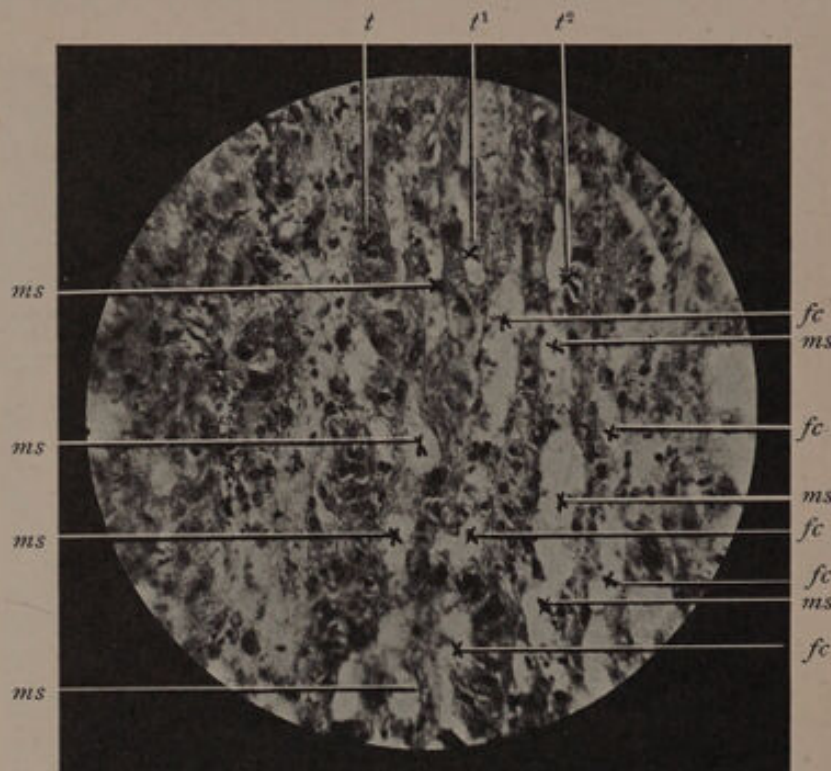


FIG. CV.

(24 days' Gestation.)

An area of foetal placenta showing three "tubules" with their plasmodial walls and the wide foetal capillaries between these "tubules."

*t, t*¹, *t*², three "tubules" (their course in the Figure is nearly straight up and down); *ms, ms, ms, ms, ms, ms*, maternal blood spaces in axis of "tubule"; *fc, fc, fc, fc, fc*, foetal capillaries.

are affected. The vessels in the outer half of the layer possess their normal endothelium.

GESTATION SAC OF 30 DAYS.—(FIG. 114.)

(1) Foetal placenta.

The appearances are those of the 28th day. The foetal vessels are large and are filled with blood, while the maternal spaces are empty.

(2) Maternal placenta.

The only evident change is in the zone of separation. The retiform character of this zone is still more delicate, and already near the musculature small rents are to be observed in it. (Fig. 115.) These rents are probably physiological as I was fortunate enough to secure these specimens after the onset of the signs of parturition. The line of separation can be easily followed, it passes through the midst of the zone. Consequently after separation the circular muscle-layer is not bared; there remains attached to it a definite margin of decidual cells.

PLACENTAL SITE AFTER PARTURITION.

This specimen was secured immediately after the delivery of the secundines. When exposed the uterine cornua had already returned

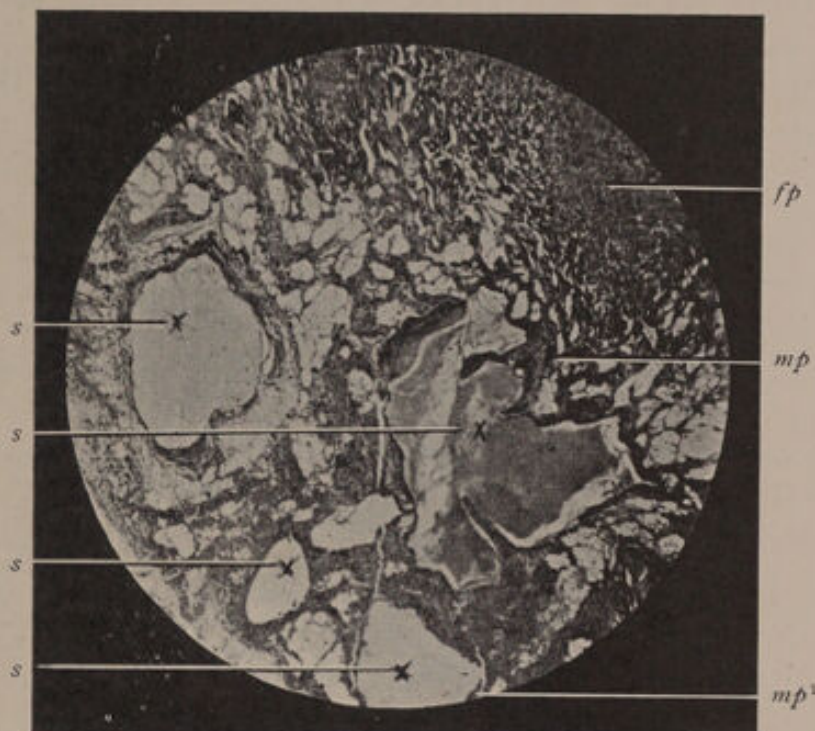


FIG. CVI.

(24 days' Gestation.)

Region of uterine sinuses (maternal placenta) as seen under a three inch lens. The sinuses are filled with blood clot and their walls are composed solely of fibrin-laminae. Areas of decidual cells are still found."

fp, foetal placenta; *m, mp¹*, maternal placenta; *s, s, s, s*, uterine sinuses filled with blood-clot and walled by laminae of fibrin-tissue.

almost to the ordinary non-gravid size. Photograph (Fig. 116) is of the same magnification as photograph (Fig. 114), at 30 days. By comparison of the two the resulting placental scar is only about a third of the extent of the former placental attachment. The muscle-walls of the uterine cornu have firmly contracted, witness their great increase in thickness,

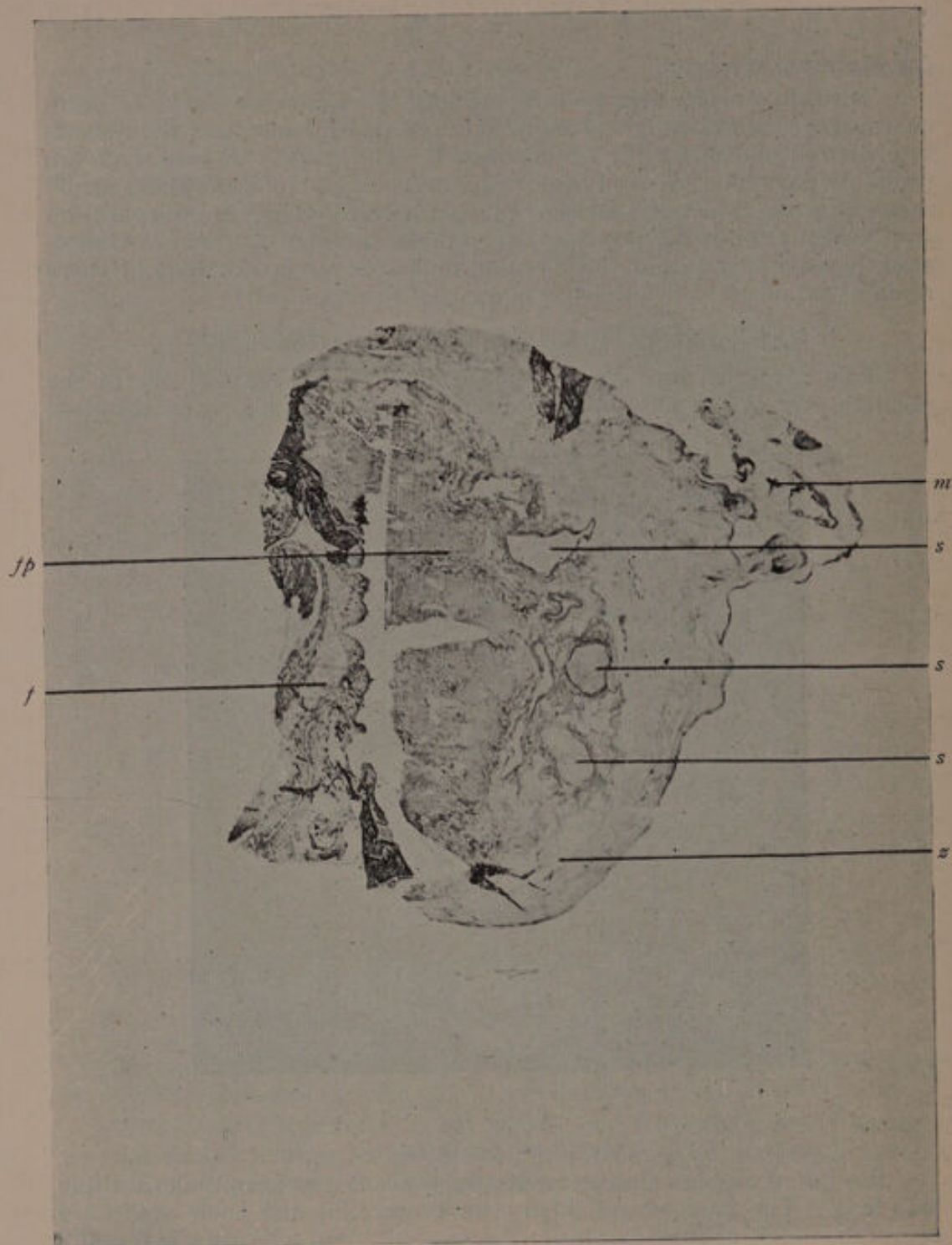


FIG. CVII.
(26 days' Gestation.)

Transverse section of gestation sac of 26 days. A part only of the foetus shown. The intermediary region of the maternal placenta is no longer distinguishable. In the region of the uterine sinuses, the sinuses are fewer in number but are increased in size.

fp, foetal placenta; *f*, foetus; *m*, mesometrium; *s*, zone of separation; *s,s,s*, uterine sinuses. (Photo.)

and the epithelial edges of the scar have been in this way approximated. Microphotograph (Fig. 117) shows this epithelial margin and the ragged edge of retiform tissue beyond it. There are some superficial hæmorrhages along this ragged edge, but the amount of the extravasation is very small, and the uterine cavity itself was quite free of blood. The small blood-channels of the separation zone with their lumina further diminished by the great swelling of their endothelium, and the rapid contraction of the muscle-layers behind, must account, in part at least, for this. In the rabbit, parturition is practically bloodless.

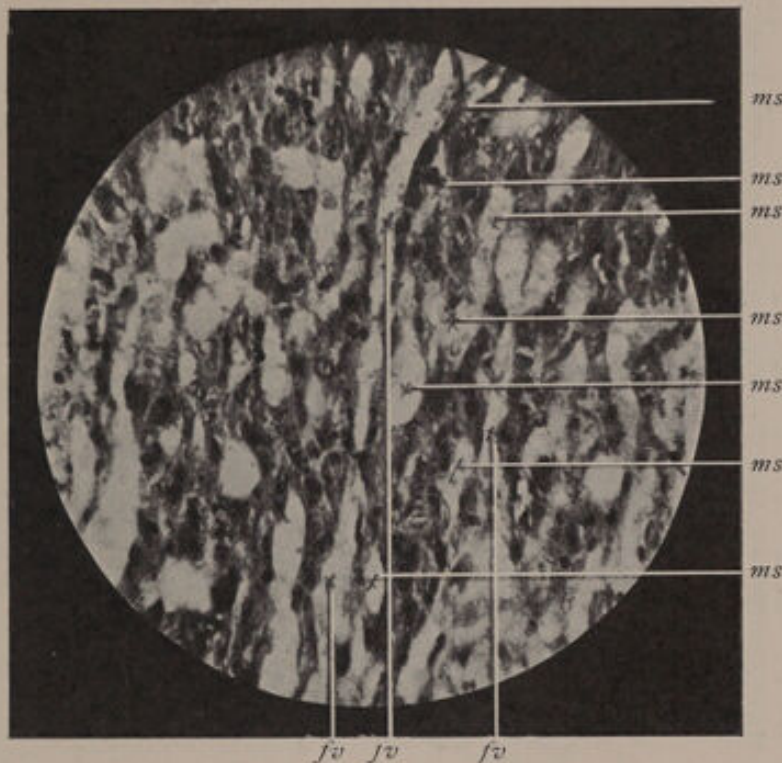


FIG. CVIII.

(26 days' Gestation.)

Area of foetal placenta showing plasmodial "tubules" and foetal vessels. The areas of denudation in the "tubules" are increasing in number and in size.

ms,ms,ms,ms,ms,ms,ms, maternal blood spaces in the axes of "tubules" with their plasmodial walls in part denuded; *fv,fv,fv*, two larger foetal vessels containing foetal blood. Their course is vertical in the Figure and between them lies a set of "tubules."

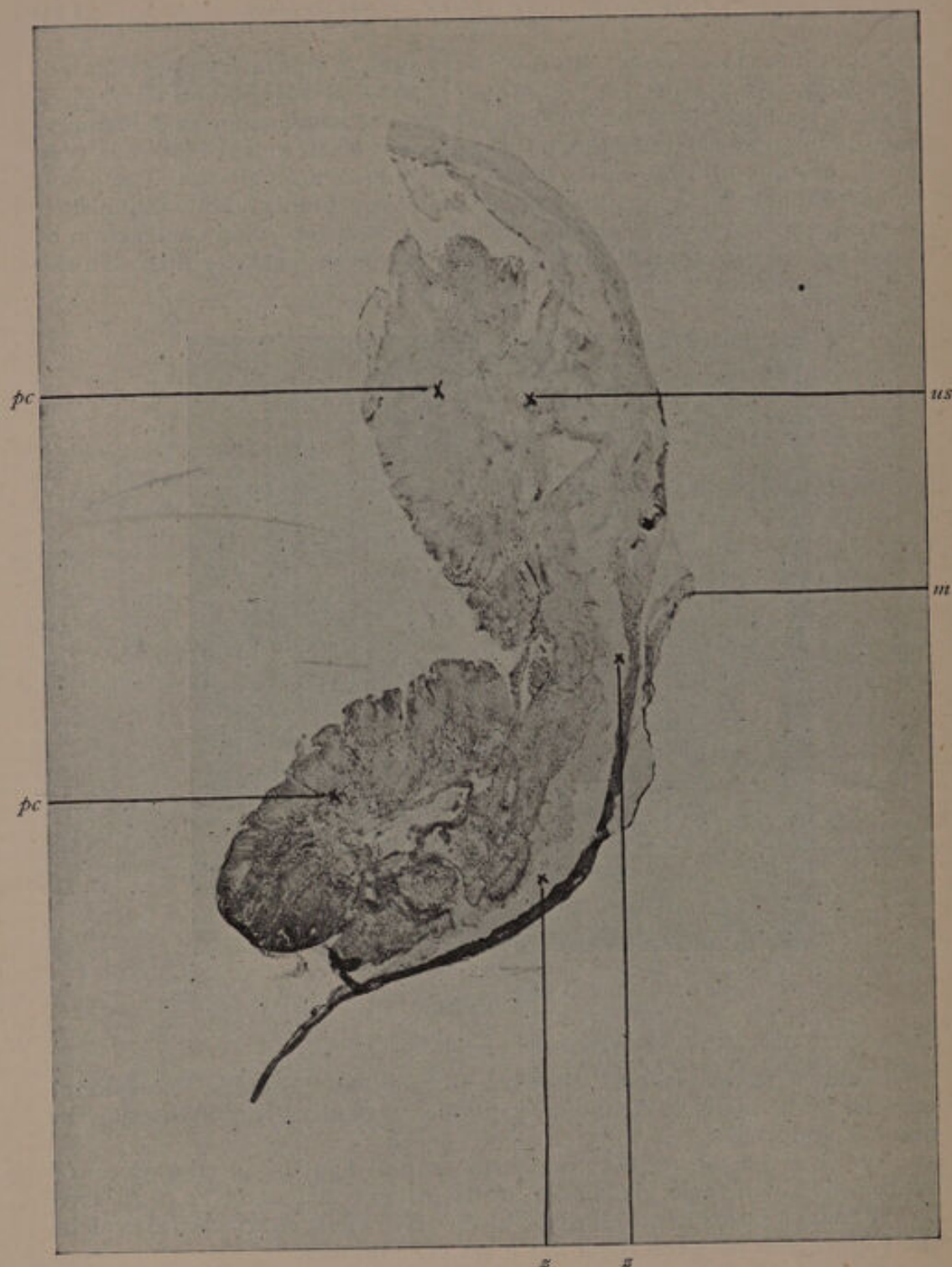


FIG. CIX.

(28 days' Gestation.)

Transverse section of placental half of gestation sac of 28 days. No portion of the foetus is shown. The two kidney-shaped placental cotyledons, the foetal portion and maternal portion of each cotyledon and the zone of separation is distinctly visible.

pc, pc, placental cotyledons; *us*, region of uterine sinuses; *s, s*, zone of separation; *m*, mesometrium. (Photo.)

SUMMARY OF THE HISTOLOGY AND HISTOGENY.

My observations begin with a short study of the inner genitalia of the rabbit—the uterine cornua and tubes, and a comparison is given between parous and nulliparous cornua.

The age-series of pregnancies, begun at the 4th day, shows during days 5, 6, and $6\frac{1}{2}$ the growth and development



FIG. CX.

(28 days' Gestation.)

Area of foetal placenta showing "tubules" and foetal vessels. The two blood systems are now separated in most instances only by the endothelial wall of the foetal vessel, since the plasmodial wall of the "tubule" has in many places entirely disappeared.

ms,ms,ms, empty maternal blood spaces—the axes of "tubules;"
fc,fc,fc, foetal vessels containing some foetal blood.

of the two *placental cotyledons*. These cotyledons are simply areas of the *mesometric folds* of the uterine mucosa, enormously hypertrophied. This hypertrophy is due to a hyperplasia of the connective-tissue elements of the sub-mucosa, with great increase in the size and number of the capillaries. The main mass or corium of the cotyledons is thus constituted

of star-shaped or fusiform cells, with long branching processes, lying in the midst of an extensive ground substance. The epithelial covering of the cotyledons grows *pari passu* and remains intact, its cylindrical cells becoming larger and more distinct, while their glands have become, by this general hypertrophy, elongated and tubular. The non-mesometric mucosa atrophies rapidly during these four days. Within it

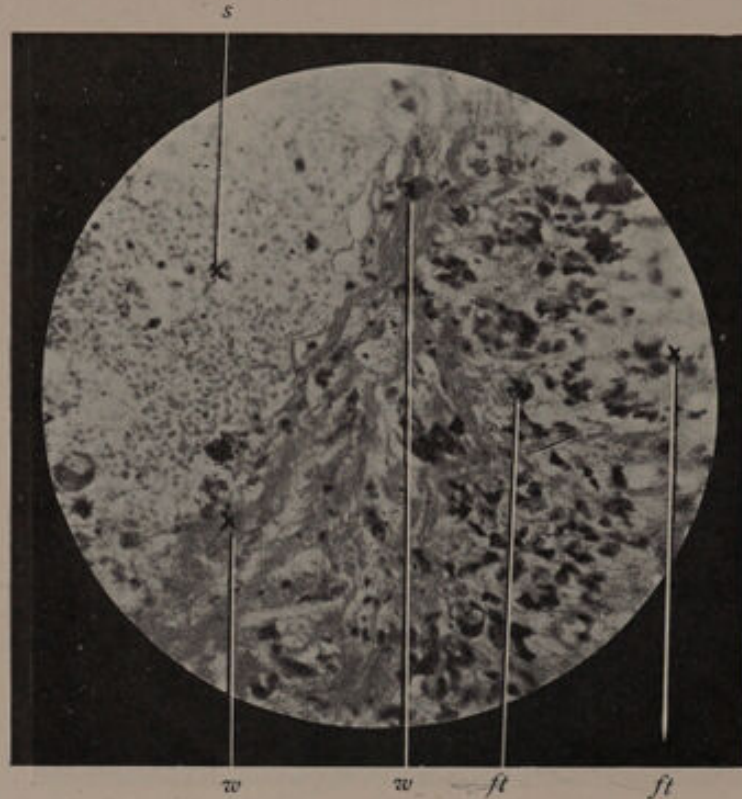


FIG. CXI.
(28 days' Gestation.)

Shows the fibrin-wall of uterine sinus in maternal placenta, and the extension of the fibrin-tissue into the surrounding areas of decidual cells. Chromatic fragments of these cells are seen entangled in the fibrin tissue.

s, uterine sinus filled with blood-clot; *w,w*, wall of sinus formed by fibrin-laminae; *ft,ft*, fibrin-tissue with the chromatic debris of decidual cells.

at the 6th day appear *giant-cells*. These cells are derived from the epithelium, either surface or glandular, and they persist until the 14th day.

At the 7th day first appears the *uninucleate* perivascular decidual cell; it arises from the connective-tissue cell of the corium. The ovum, or blastosphere, as it has now become,

remains altogether unattached within the newly-formed gestation sac. At the 7th day the embryonal area is outlined and is directed towards the two cotyledons.

At the 9th day the bi-lateral attachment of the embryo to the placental cotyledons is effected. The embryo itself is placed with its back toward, and more or less opposite to, the *intercotyledonary groove*. On either side of the embryo

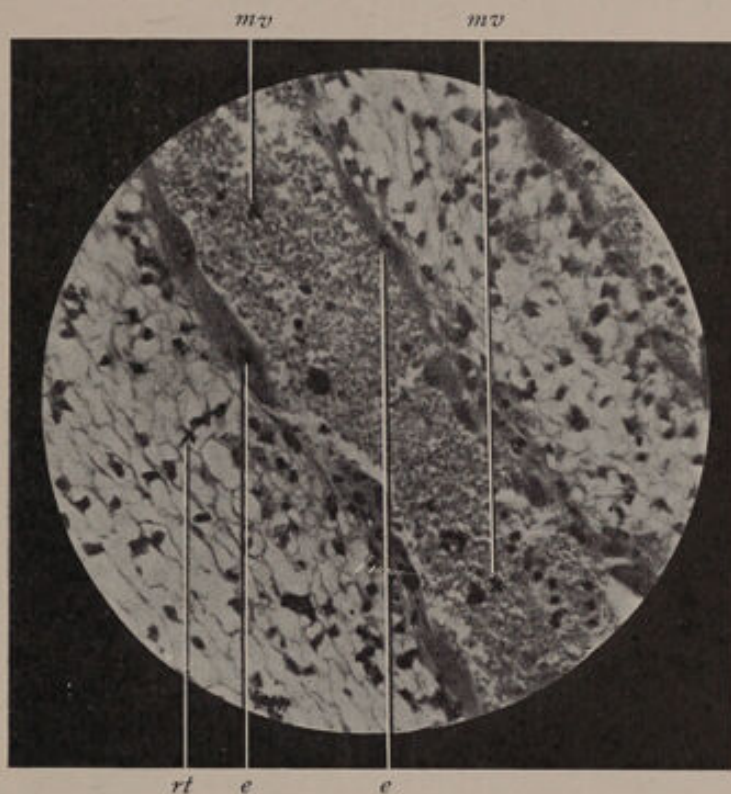


FIG. CXII.

(28 days' Gestation.)

Maternal vessel in the "zone of separation." The endothelium though thickened, is intact and in consequence no fibrin-laminæ have formed. The retiform character of the tissue of the separation zone is seen.

mv, mv, maternal vessels in the "zone of separation;" *e, e*, endothelial lining of vessel, its cells swollen; *rt*, retiform tissue of uninucleate-decidual cells.

the ectoderm presents a thickened area, several rows of ectodermic cells, the area of *placental attachment* which is apposed to the surface of the corresponding cotyledon. The attachment is one of "two plane surfaces," for by this time

the covering epithelium of the cotyledons has become greatly thickened by the increase of cell protoplasm and fragmentation of nuclei, so that the gland-mouths are blocked, and the cotyledons come to present an unbroken face to the *ectodermal laminae*. The area of placental attachment quickly extends, the ectodermal cells multiplying rapidly, while the underlying maternal epithelium is "corroded" and thinned. The ectoderm at this stage is altogether cellular.

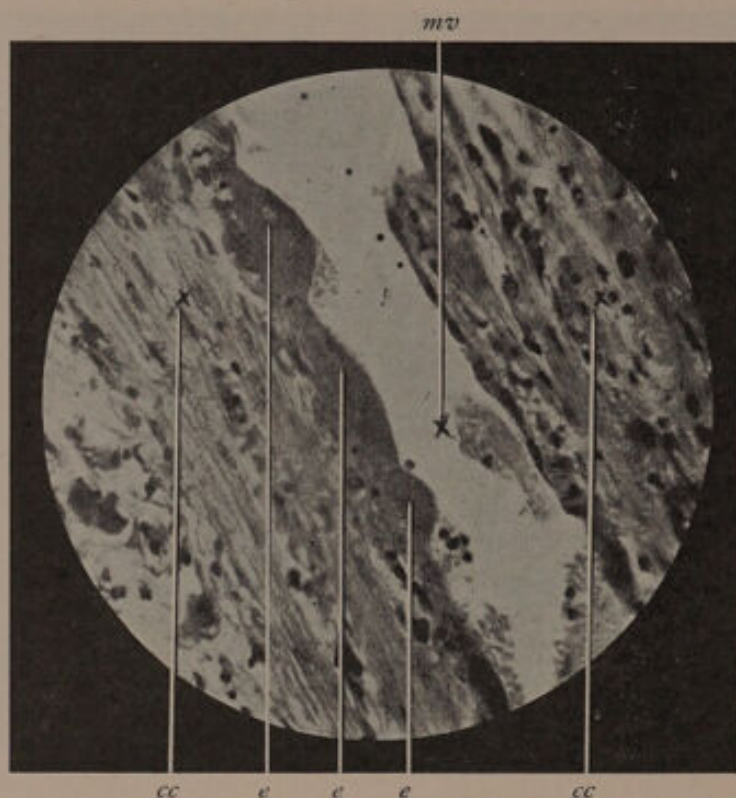


FIG. CXIII.
(28 days' Gestation.)

Maternal vessel in the circular muscular coat of the uterine cornu, underlying the site of placental attachment. Its lining endothelium is thickened, some of the cells being enormously swollen.

mv, maternal vessel; *cc,cc*, circular muscular coat; *e,e,e*, swollen endothelial cells.

At $8\frac{1}{2}$ days the ectodermal laminae have increased in thickness while their area of attachment is further extended. A *yolk-sac* placenta is determined, limited peripherally by the *sinus terminalis* which contains nucleated foetal blood. The posterior portion of the embryo is roofed in by the

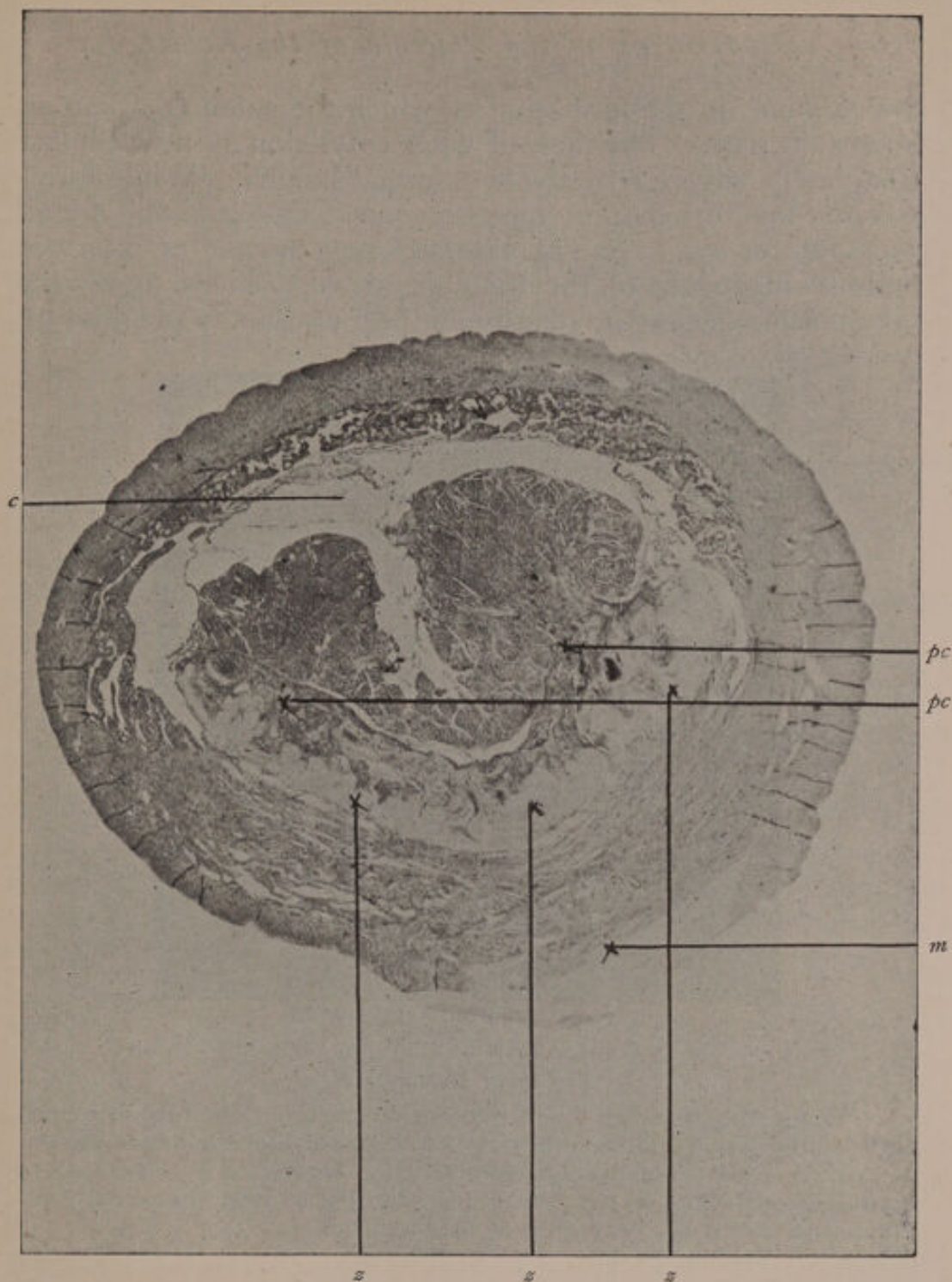


FIG. CXIV.
(30 days' Gestation.)

Transverse section of gestation sac of 30 days. The foetus has been expelled, in part naturally, for the rabbit was secured in the act of parturition. The partially contracted muscular walls and its placental mucosa are thick. The "zone of separation" is well shown, and separation of placenta has actually begun.

pc, pc, placental cotyledons; *m*, mesometrium; *s, s, s*, zone of separation; *c*, cavity of gestation sac; foetus expelled. (Photo.)

amniotic sac, in the formation of which the side-folds play an important part. The face of each cotyledon is now almost completely covered by the ectodermal lamina. While formerly the line of fusion of the two tissues, maternal and foetal, was more or less in one plane, there now appear at intervals bud-like ingrowths of the foetal ectoderm. These ingrowths take place opposite the gland-mouths, now solidly plugged by



FIG. CXV.

(30 days' Gestation.)

"Zone of separation" with separation begun. The retiform character of the tissue and the relatively small size of the vessels are shown.

s, s, s, zone of separation, commencing separation is witnessed to by the several rents in the retiform tissue; c, c, circular muscular coat of uterine cornu; us, us, region of uterine sinuses.

their own thickened epithelium, and soon come to plunge into these. The uninucleate decidual cell exists now in great numbers grouped always into *perivascular sheaths* about the maternal blood-channels. In the deeper areas of the cotyledons these sheaths are thick; the channels are no longer capillaries, they are of large size and irregular shape, but their endothelium is preserved. They are sinus-like and the

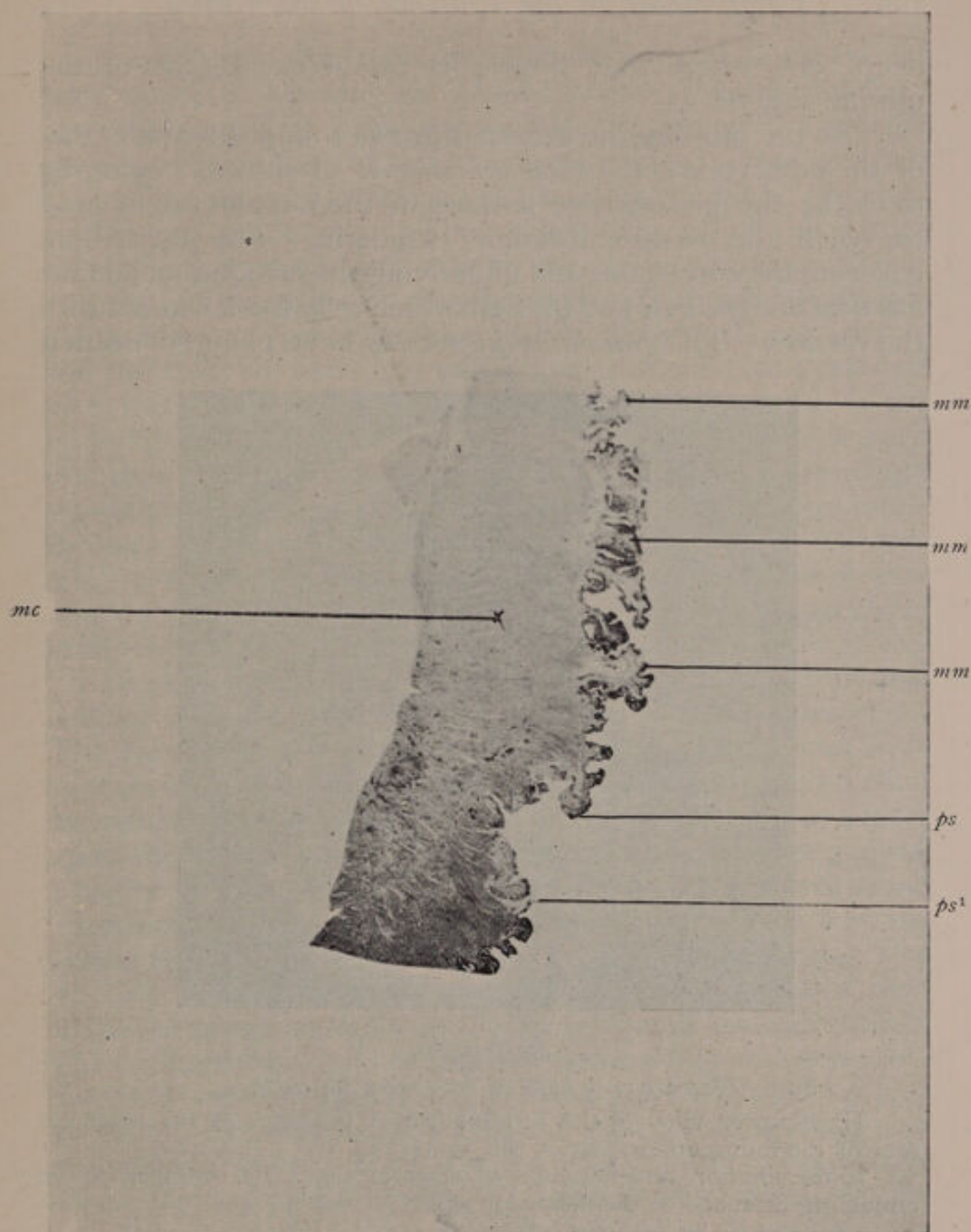


FIG. CXVI.

Placental scar half an hour after Parturition.

The "uterus" has been laid open, only that part of its wall near the placental site is shown.

mc, muscular wall of "uterus;" *mm,mm,mm*, uterine mucosa near placental site, immediately after delivery of secundines; *ps,ps¹*, site and area of placental attachment, note how its size is diminished. (See Fig. 117.)

deep zone where they appear is called the region of the uterine sinuses.

At the 9th day the *allantois* grows round the hinder end of the embryo into the *external cœlome*. I show it beginning to clothe the mesodermic surface of the amnion on its way to reach the extra-embryonic ectoderm. The epithelium covering the cotyledons and underlying the ectodermal laminæ *has now disappeared* and the embryonic cells are in contact with the *corium*. The *glandular ingrowths* have plunged deeper,

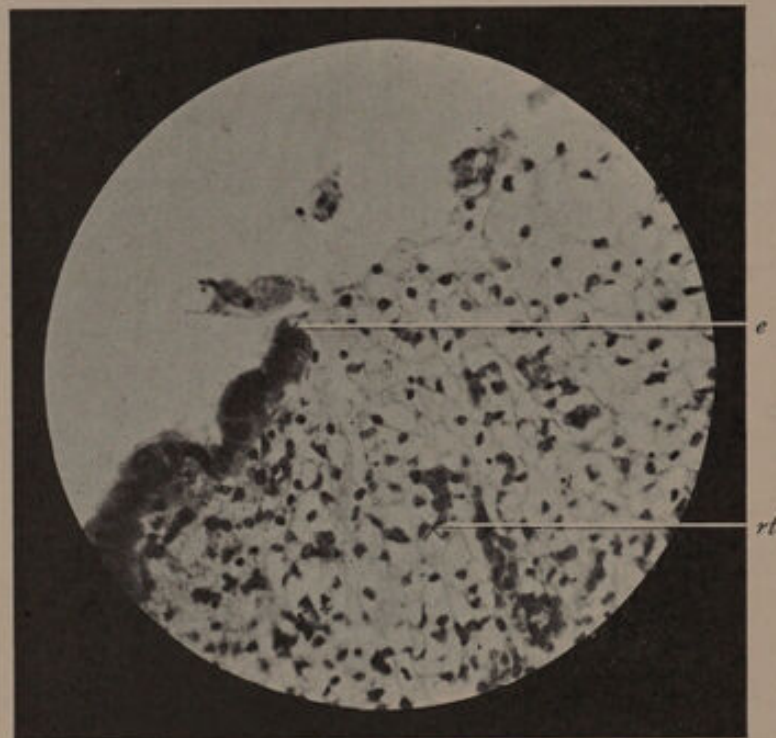


FIG. CXVII.

Placental scar half an hour after Parturition.

High-power view of the termination at the edge of the placental scar of the lining epithelium of the "uterus."

e, termination of epithelium at edge of scar; *r,t*, retiform tissue remaining attached to the muscular wall.

but now a second series of ectodermal processes enter directly into the maternal corium, in the neighbourhood always of a superficial capillary. The tissue of the corium disappears from before their advance even as the surface epithelium had previously done, and the ectodermal processes soon come to surround and include the capillary. Upon the contact of the

foetal ectoderm with the corium there is established in the latter *a zone of reaction, an intermediary region*, intermediary between the foetal ectoderm and the region of the uterine sinuses. The tissue of this reactionary zone is distinguished by having become œdematous, and throughout it are scattered many leucocytes. The vessels here are of the nature of capillaries; their perivascular sheaths are thin, consisting at most of two layers of decidual cells. The solid stalk-like gland-ducts disappear in the midst of this reactionary tissue, and the deepest glandular *cul-de-sacs*, also solid, so great has been the hypertrophy of their epithelium, are isolated in the midst of the tissue of the cotyledon. Their position is such that they appear like *boundary posts* between the intermediary region and the region of the uterine sinuses. In this intermediary region there now arises the *multinucleate decidual cell*. *This cell develops directly from the perivascular uninucleate decidual cell*, and is first found near the most superficial capillaries, that is, those nearer the ectoderm.

At the 10th day the *allantois* has reached the ectodermal laminae and the mesoderm of these has become vascular. The *allantoic circulation* is now established. The *foetal liver* appears as a solid outgrowth from the *mesenteron*. The ectodermal laminae have increased greatly in thickness, advancing upon the tissues of the intermediary region. This general advance is, as it were, led by deeper ingrowths which penetrate along the course of the maternal vessels. Where the vessel is cut longitudinally we can trace the process. The ectoderm surrounds the distal end of the vessel and then advances along its walls, gradually replacing its endothelium which disappears. The foetal tissue *swallows* as it were, the maternal capillary space. The ectodermal ingrowths which at the 8th day invaded the blocked gland-mouths have now no further glandular track, for the solid gland channels have disappeared. Their further direction is determined by the near blood-vessels. The more superficial of the ectodermal cells—those next the maternal tissue—begin to show a plasmodial change. The maternal capillaries which appear completely surrounded by the foetal ectoderm have entirely lost their endothelium and lie, as maternal blood-spaces, in the midst of this ectoderm. The advancing ectodermal lamina surrounds and includes—*swallows*—not only maternal vessels

but also irregular hæmorrhagic cavities in the intermediary region, for the endothelium of the maternal capillaries, swollen and degenerated in front of the ectoderm, ruptures here and there, and especially at the junction of the two tissues—foetal and maternal, and there result hæmorrhagic cavities with ragged cellular walls, and containing maternal blood; and these blood-cavities it is which are in their turn surrounded and included—*swallowed*—by the advancing ectoderm. The ectodermal laminæ now come to be divided into areas or “columns” by the vascular processes or septa of mesoderm which penetrate them from their foetal surface. The intermediary region is composed solely of vesicular multinucleate decidual cells. In their midst run the maternal vessels with simply a thickened endothelial wall, for here the multinucleate cells have been formed from the cells of the perivascular sheaths, and at the expense of these sheaths. Ragged maternal blood-cavities, with walls of compressed multinucleate cells occur in the superficial zone of this region. The areas of amorphous epithelium, the solid glandular *cul-de-sacs* already extensively vacuolated, become occupied by extravasated blood, and appear as distinct blood-cavities. In the deep zone blood extravasation occurs slowly, and there are formed areas of fibrin-tissue. The region of the uterine sinuses is composed very largely of perivascular sheaths, the original corium lying as mere tracks between them. The sinuses are increased in size, and their endothelium, though swollen, is intact.

At the 12th day the elaborated ectodermal laminæ may be designated the *foetal placenta*. Its areas are now definitely column-like. These columns are *test-tube* in shape with their open ends set upon the maternal tissue. Their walls are composed of ectodermal cells, and their axes are filled with maternal blood (swallowed maternal blood-spaces) which communicates directly, through their open ends with the vascular system of the maternal placenta. These columns or test-tubes are bounded laterally by vascular mesodermic septa, whose capillaries are filled with nucleated foetal blood. These mesodermic processes never reach maternal tissue, they are plunged only into the midst of the foetal ectoderm. *The above is the fundamental plan of the foetal placenta*; this plan is afterwards merely elaborated. The tissues now separating the two blood-systems—maternal and foetal—are a

layer of ectoderm, 2 or 3 cells in thickness, mesodermic tissue and an endothelial wall. The foetal placenta becomes reniform in shape, the hilum being occupied by the intermediary region. This region shows now few hæmorrhages, it is denser. Multinucleate cells, derived from the uninucleate cells of the perivascular sheaths of the superficial uterine sinuses, are continually being added to it. The fibrin-tissue has begun to penetrate the region of the uterine sinuses, following along the tracks of the original corium. In the midst of this tissue lie, *annular-like*, the sinuses with their perivascular sheaths. The contact of this fibrin-tissue with the uninucleate cells is contemporaneous with their transformation into multinucleate decidual cells. The region of the uterine sinuses is thus invaded and diminished.

At the 14th day the foetal placenta is increased in depth, and is in part plasmodial. The ectodermal walls of the columns are more irregular, the division of these columns into smaller columns or *tubes* has begun. These tubes are simply columns in miniature, their maternal blood-axes are smaller, their ectodermal walls thinner, and the separating mesodermic partitions are finer. The advance of the deep face of the foetal placenta upon the maternal tissue is now less uniform. As formerly, the advance is led by deeper reaching processes extending along the maternal vessels. The deeper advance of these processes is not great, and yet upon the non-vascular areas of the intermediary region, the ectoderm makes even less progress. The union of the foetal and maternal tissues becomes thus permanently irregular and the more resistant areas of multinucleate cells come to lie peninsula-like in the midst of the foetal placenta. But the two tissues, maternal and foetal, do not interdigitate, *the deep face of the ectoderm clothes completely the maternal placenta*, being interrupted only at the passage of the maternal vessels. The intermediary region, as such, has become more limited, though it appears to invade the region of the uterine sinuses, owing to the transformation (along the lines of the fibrin-tissue) of the uninucleate into the multinucleate decidual cell. This fibrin-tissue and attendant multinucleate cell-formation does not penetrate as deeply as the musculature. There is thus marked off, next the musculature, a zone—the zone of separation—where the uninucleate cell persists till the end of

gestation, and the sinuses remain small. The lining endothelium of the superficial sinuses swells, its individual cells hypertrophy and multiply to form 2 to 3 layers. In places these cells become detached, and outside them are deposited lamellæ of fibrin which here come to constitute the true wall of the sinus.

At the 16th day the *smaller columns* or *tubes* are definitely formed. The several tubes derived from each large column remain grouped together to form *lobes* of the placenta. These *lobes* vary in size and are separated from one another by wider partitions of vascular mesoderm. The individual tubes of each lobe are likewise separated by vascular mesoderm, but only by thin partitions. The ectodermal wall of each tube represents a layer of one or at most two cells in thickness. Thus the tissues separating the two blood systems, maternal and foetal, are *this ectodermal wall, a few mesodermic cell-elements and the endothelium of the foetal capillary*. The intermediary region of multinucleate cells has now resolved itself into irregular areas which reach into the area of the foetal placenta on the one hand, and on the other, extend into the tissue of the region of the uterine sinuses following the tracks of fibrin-tissue. This fibrin-tissue has largely disappeared, it is now replaced by multinucleate decidual cells. The uterine sinuses with their uninucleate perivascular sheaths lie *annular-like* in the midst of these multinucleate cells. These uterine sinuses approach more nearly to the deep face of the foetal placenta. They are increased in size, and their lining endothelium has still further multiplied and become detached. The walls of fibrin-lamellæ are thicker. The zone of separation is now distinctly delimited. It is distinguished by its small sinuses with their preserved endothelial lining, and by the uniform distribution between these of uninucleate decidual cells. The multinucleate cells are not found in this zone since the multinucleate cells arise in the region of the uterine sinuses only to the same depth as the fibrin-tissue has penetrated.

At the 18th day the foetal placenta is largely plasmodial. The tubes have now begun to show changes identical with those shown by the *columns* at the 14th day, in other words, they have begun to divide into smaller tubes—tubules—which have the same structure. Their small axis is a maternal blood-space, their thin walls are of ectoderm now largely

plasmodial, and they are divided from one another by foetal capillaries, accompanied by a few thread-like cells of mesoderm. So thin are these plasmodial walls in places that they appear as mere hyaline lines. The junction between foetal and maternal tissue is more irregular; the areas of multinucleate cells, lying peninsula-like in the foetal placenta, are of greater length. When these areas are cut obliquely to their long axes, the sections of them appear to lie detached in the midst of the foetal placenta. But the line of junction of foetal and maternal tissues is everywhere complete and distinct. Even along the maternal vessels the junction of their endothelium with the foetal plasmodium is sharp and unmistakeable. The uterine sinuses are larger, and for the most part their walls are composed of fibrin-lamellæ, here and there only are layers of endothelium cells partly detached. The perivascular sheaths are invaded by these lamellæ and the decidual cells, both uni- and multinucleate, are becoming compressed. The zone of separation has now a retiform appearance, for the uninucleate cells which alone compose it, are shrunken and angular with their nuclei peripherally placed.

At the 20th day the *tubules* are definitely formed, and the foetal placenta has now reached its mature stage. Between the tubules are now visible foetal capillaries only, the fine mesodermic elements no longer accompanying these. Hence the tissues that now intervene between the two blood-systems are a *thin plasmodial wall and an endothelial wall*. The foetal blood ceases to be nucleated. The uterine sinuses have now lost all trace of their endothelium; their walls are composed entirely of fibrin-lamellæ. These thickening fibrin-walls of neighbouring sinuses crowd between them the cellular elements, greatly atrophied and reduced, of the region. The small sinuses of the *zone of separation* retain their swollen endothelial wall; there are no fibrin-lamellæ here.

At the 22nd day the growth of the foetal placenta is completed. It is entirely plasmodial, and irregularly sown with scattered and indistinct nuclei. At intervals throughout its length the thin hyaline wall of the *tubule* has disappeared and at these places the maternal blood bathes directly the external surface of the foetal capillary. At such places the foetal capillary lies naked to the maternal blood, and the only tissue here intervening between the two blood-systems is its endo-

thelial wall. The uterine sinuses have now approached close to the deep face of the foetal placenta. There is leakage of their contained blood through the fibrin-walls, and in this way there slowly appears in the midst of the surrounding decidual cells, both uni- and multinucleate, areas of coagulated lymph, with fibrin-threads and scattered blood corpuscles. This change extends into the areas of multinucleate cells, lying peninsula-like in the foetal placenta. It begins at the periphery of these areas, close to the blood-channels, and reaches toward the centre. These areas acquire thus a solid, vitreous appearance; scattered throughout them is the chromatic débris of their pre-existing cells.

At the 24th and 26th days the plasmodial walls of the tubules become more largely and more frequently denuded.

These areas of denudation are never of great extent, and alternate with stretches of persistent plasmodial wall. The foetal capillary does lie naked to the maternal blood, but only in patches, in the placenta of the rabbit. The tissue of the region of the uterine sinuses is now largely composed of fibrin-lamellæ.

At the 28th day the foetal capillaries have increased in size, while the plasmodial walls of the tubules have still further diminished. The uterine sinuses reach close to the foetal placenta. The tissue between the enlarged sinuses is a composite one. The walls of the sinuses are composed of fibrin-lamellæ; outside these and between them and the lamellæ of a neighbouring sinus is a zone of coagulated lymph, in the midst of which lies the débris—fragmented nuclei and broken cell-walls—of the uni- and multinucleate decidual cells. This is the constitution of the maternal placenta at parturition. The zone of separation is more finely retiform. Its small sinuses retain their thickened endothelium; this change of endothelium—hypertrophy of its individual cells—extends proximally into the superficial capillaries of the circular muscle-layer.

At the 30th day parturition occurs. Separation takes place through the midst of the zone of separation, for a margin of its attenuated decidual cells is left upon the placental scar. Parturition is practically bloodless.

RESULTS OBTAINED.

I now submit, shortly, my own interpretation of the following obscure and controverted points.

(1) The origin of the giant cells.

These giant cells arise from epithelial cells, either surface or glandular, (See Figs. 14 and 15), and are found in considerable number in the sub-mucosa, or even lying between the innermost fibres of the circular muscle-layer. They are seen only in the non-placental mucosa, and appearing at the 6th day of gestation they persist until the 14th. As to their function I hazard no hypothesis.

(2) The attachment of the ectoderm to the uterine epithelium.

The thickened ectoderm of the area of placental attachment is altogether *cellular*—large, well-defined cells, with big, round or oval, and active nuclei. This is the condition at the 8th day, (See Figs. 25 and 27), when attachment is just beginning and at the 9th day, (See Fig. 41), when the uterine epithelium has disappeared. It is only at the 10th day that a *plasmoidal change* begins in the ectodermal cells.

(3) The origin of the multinucleate decidual cells.

These multinucleate cells arise by direct division—increase of cell-substance and multiplication of nuclei—from the uninucleate decidual cells of the perivascular sheaths. (See Fig. 45). They are seen first at the 9th day and close to the foetal ectoderm, for it is the thin sheaths of the most superficial capillaries that are first affected. So rapidly do they arise that 24 hours later, at the 10th day, they form a zone in the maternal placenta of considerable thickness—the *intermediary zone*.

(4) The origin and nature of the maternal blood-cavities *swallowed* by the ectoderm.

The foetal ectoderm as it advances, surrounds and includes *swallows*—maternal blood-spaces. These spaces when so treated by the ectoderm, present three varieties.

(a) The maternal capillary, whose thickened endothelial wall is surrounded and replaced by the ectodermal cells. (See Fig. 53.)

(b) Hæmorrhagic cavities, whose ragged walls are composed, in part at least, merely of decidual cells compressed by the hæmorrhage. In such cases the degenerate endothelium has snapped before the capillary has been completely surrounded by the ectoderm. (See Figs. 57 and 58.)

(c) The deep glandular *cul-de-sacs*. These *cul-de-sacs* become at first solid by reason of the enormous hypertrophy of their lining epithelium. (See Fig. 44.) The solid *cul-de-sacs* soon become vacuolated, and so changed into sharply-defined cavities, into which hæmorrhage from a neighbouring weakened capillary subsequently occurs. (See Fig. 64.)

(5) The nature of the so-called "villi."

The essential plan of the rabbit's placenta is most plainly evident between the 10th and 14th days. As seen then in section the foetal placenta may be likened to a row of test-tubes set with their open ends upon the maternal tissue. The walls of the test-tubes are composed of ectodermal cells, and their axes represent maternal blood-spaces. These tubes are set some narrow distance apart, and are separate the one from the other save for a thick collar, cellular like their walls, which binds them together near their open extremity. In this way the set of tubes presents a face to the maternal tissue, interrupted only at the open ends of the tubes which come to abut upon maternal blood-vessels. Now fill in the intervals down to the binding collar between these tubes by mesoderm, vascularised by allantoic vessels, and the scheme is complete. (See Figs. 69 and 75.) Thus there is an inter-digitation of tissues, but only of foetal tissues. The foetal placenta is functionally *the* placenta. Long villi, plunged finger-like into the midst of maternal sinuses, do not exist in the placenta of the rabbit.

(6) The fate of the placental glands.

The gland-channels become solid and stalk-like between 8 and 8½ days (see Figs. 28 and 30), due to the hypertrophy of their lining epithelium. These solid channels disappear at the 9th day (see Fig. 44), leaving their deep *cul-de-sacs*, now likewise solid, completely isolated in the surrounding corium. The fate of these *cul-de-sacs* I have previously indicated. (See point 4.)

(7) The behaviour of the sinus endothelium.

The endothelium of the uterine sinuses at first thickens, its cells remaining distinct. (See Fig. 65.) These cells increase rapidly in size, become globular, and multiply until the lining endothelium is represented by several rows of these large cells. (See Fig. 81.) These cells become detached, fibrin-lamellæ forming beneath them, and they disappear in the blood-stream. (See Fig. 84.) This process continues from the 16th day onward, until at the 24th day the wall of the uterine sinuses is composed solely of fibrin-lamellæ (See Fig. 97.)

(8) The junction of the two tissues, maternal and foetal.

After the 12th day, and owing to the continued growth of its lateral portions, the foetal placenta becomes reniform in shape, with a hilum of maternal tissue. (See Fig. 68.) Further the ingrowth of the foetal ectoderm upon maternal tissue is always somewhat more advanced along the course of the blood-channels. (See Fig. 78.) For these two reasons the *junction* of foetal and maternal tissue is always irregular. But the point I wish to emphasize is, that there is no *intergrowth* of the two tissues; that the foetal ectoderm is laid as a complete covering upon the maternal placenta—a covering interrupted only by the passage of the vessels.

(9) The determination of the zone of separation.

This zone is determined by the depth to which the fibrin-tissue, first seen at the 10th day (see Fig. 63), penetrates along the tracks of the original corium, into the region of the uterine sinuses. The contact of the fibrin-tissue with the perivascular sheaths is co-extensive with the transformation of their uninucleate into multinucleate cells. Thus the penetration-limit of the fibrin-tissue establishes the penetration-limit of the multinucleate decidual cell, and the zone that persists between the multinucleate cells and the musculature is the *zone of separation*. (See Fig. 95.)

(10) The fate of the decidual cells.

These cells, both uni- and multinucleate, pushed further and further away from the lumen of the uterine sinuses by the continual building up of the fibrin-lamellæ, become more and

more compressed between the lamellæ of the neighbouring sinuses. (See Fig. 89.) At the same time there is through these fibrin-walls, a slow extravasation of blood into the midst of these cells with a formation of fibrin-tissue. These cells become further compressed and disintegrated until at the 28th day (see Fig. 111), they appear only as so much chromatic débris embedded in the fibrin-tissue.

The formation at the 12th day of fibrin-tissue, and at the 14th day of fibrin-lamellæ, which subsequently play a part so important that at the 24th day the maternal placenta, save the separation zone, is principally constituted of these, I have not seen elsewhere described.

SECTION B.

GLYCOGEN AS FOUND IN PLACENTA AND FŒTUS.

Method followed. The uterine cornu was removed *en masse* and fixed for twelve hours in absolute alcohol. Transverse slabs of the cornu were then cut with a razor—these slabs being so chosen as to include, at one and the same time, central sections of the placenta, and of the liver of the fœtus. Where this was found impossible slabs of the placenta and of the fœtal liver were cut separately. These slabs were fixed for a further twelve hours in absolute alcohol, after which they were embedded, cut, and mounted in the usual way. The sections were washed in naphtha and absolute alcohol, and cleared in clove oil. They were then immersed in an iodine-chloroform solution—sufficient crystals being added to give a deep claret colour—for twelve hours, and then quickly mounted in Canada balsam. The glycogen is so stained a ruddy brown, while the tissue generally is coloured a light yellow. The above is the method devised by Sheridan Délépine (Proceedings of Phys. Soc., May 10th, 1891), and to him I am personally indebted for "Leaves" from these "Proceedings."

The specimens so prepared are not permanent, for the iodine rapidly fades from the non-glycogenic tissue.

As a control-reagent I have also used the older watery solution of iodine, Lugol's solution. While the two methods were in every case corroborative, the newer method is more delicate, and gives more satisfactory results.

My repeated attempts to counter-stain with hæmatoxylin or alcoholic solution of methylene blue were scarcely successful.

This micro-chemical study of glycogen has in the fœtus been limited to the liver, and this organ, as we have seen, only appears at the 10th day. The study of it in the placenta begins at the 4th day. In either situation negative results will simply be mentioned.

In this description I shall follow, after the 10th day, the same order as in Section (A), viz. :—

- (1) Fœtal tissue—fœtus and fœtal placenta.

- (2) Maternal tissue—placental mucosa or maternal placenta.
 Before the 10th day no reference will be made to (1).
 Gestation sacs of 4, 5, 6, 6½ and 7 days show no glycogen reaction.

GESTATION SAC OF 8 DAYS.—(FIG. 118.)

- (2) Maternal tissue :—placental mucosa.

The first appearance of glycogen is noticed here.

At this date the perivascular sheaths consist of one or two rows of uninucleate decidual cells. (Fig. 119.) These cells are coloured, as is all the tissue, a light yellow by the iodine-chloroform. But within a few of these cells—always those nearest the endothelium of the vessel—there appear one or two ruddy-brown granules.* These lie always within the decidual cells, close against either the cell wall or the nucleus : they are

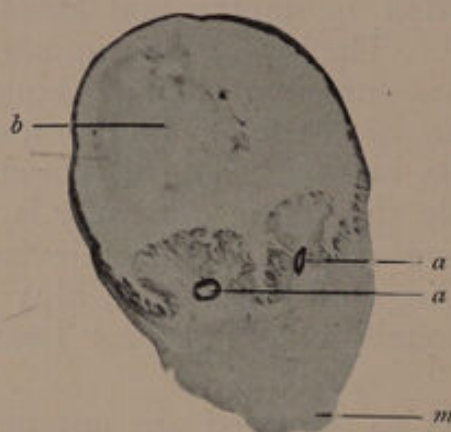


FIG. CXVIII.

(8 days' Gestation showing Glycogen-area.)

Transverse section of gestation sac of 8 days, to show the area in the placental cotyledon where glycogen first appears. Note that the area is in the *deeper* part of the cotyledon.

a, a, areas where glycogen first appears ; *b*, yolk sac ; *m*, mesometrium.
 (Photo.)

angular, show no uniformity in size or shape, and are plainly surrounded by the cell protoplasm.

The sheaths of the vessels, *centrally placed in the uterine cotyledons*, alone show these glycogen granules in their cells ; *the sheaths next the musculature only give a yellow reaction* as do those more superficially placed. The main mass of the corium and its epithelial covering are also of similar uniform colour.

* In tissues fixed in absolute alcohol, the glycogen always appears in the form of *granules*. I have so described it, remembering that the granules are only determined by the fixing agent.

GESTATION SAC OF 9 DAYS.—(FIG. 121.)

(2) Maternal tissue :—placental mucosa.

The perivascular sheaths are considerably thickened and now possess, save the more superficial ones, four or five rows of decidual cells. The glycogen is confined exclusively to these sheaths, and all of these, except the most superficial, show the brown granules, though the sheaths towards the centre of the cotyledons are still the richest therein. (Fig. 122.) While glycogen is present in all the cell-rows of the sheath the innermost rows—those nearest the sinus endothelium—contain it in largest amount. The glycogen granules while larger than at the 8th day, are still angular and irregular in shape. They lie in the midst of

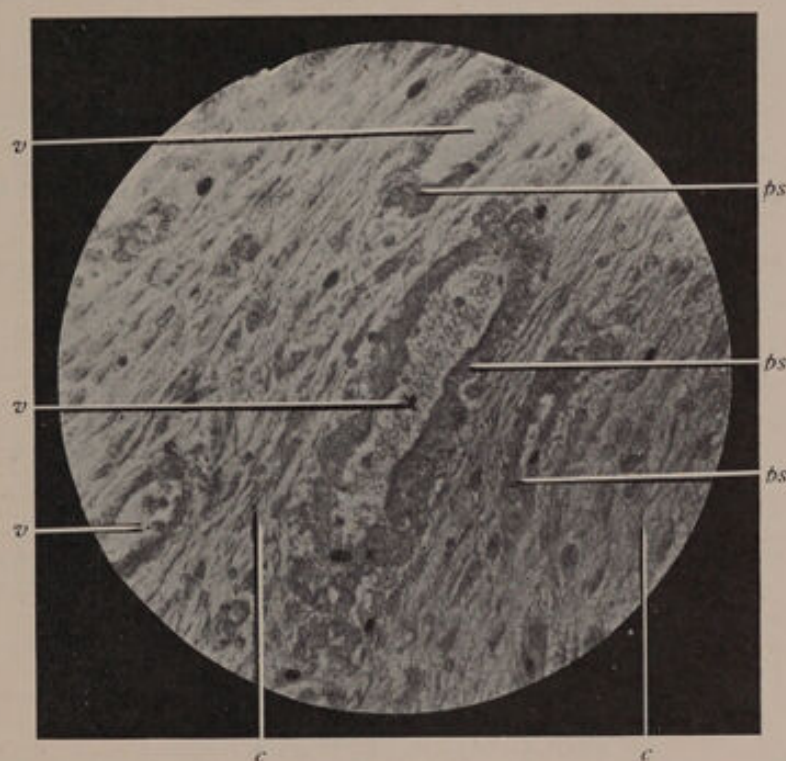


FIG. CXIX.

(8 days' Gestation showing Glycogen.)

Vessels with their sheaths of uninucleate decidual cells, as seen in the central area (*a,a*, Fig. 118) of a placental cotyledon. It is in these perivascular decidual cells that glycogen first appears.

v,v,v, vessels; *ps,ps,ps*, perivascular sheaths of decidual cells; *c,c*, "corium" of cotyledon, formed of connective tissue cells which show no glycogen.

the cell-protoplasm and the larger granules are usually peripherally placed, and at the side of the cell nearest the blood-sinus. (Fig. 123.) The smaller granules form often a perinuclear zone. In the peripheral rows of the sheath the granules are much smaller and more sparse.

The rest of the tissue gives no glycogen reaction.

GESTATION SAC OF 10 DAYS.

(1) Foetal tissue :—foetus and foetal placenta.

The foetal liver has now appeared : it and the foetal placenta show no glycogen.

(2) Maternal tissue :—maternal placenta.

Multinucleate decidual cells, derived as we have seen, from the uninucleate cells, are now found in considerable number immediately underlying the foetal placenta. These multinucleate cells are at their first appearance rich in glycogen (Fig. 125), which shows itself in large, rounded or semi-lunar granules lying in the cytoplasm, usually at one pole of the cell, while the 2, 3 or 4 nuclei occupy the opposite pole. (Fig.



FIG. CXX.

(8 days' Gestation showing Glycogen.)

Drawing of larger vessel shown in Fig. 119. The glycogen-granules are colored brown and the largest of these are found close to the endothelium. They lie always within the decidual cells of the perivascular sheath and oftentimes close to the cell wall.

v, vessel with blood-clot, note thickened endothelium ; *ps*, perivascular sheath of uninucleate decidual cells ; *g,g,g,g,g,g*, glycogen-granules ; *c*, "corium."

126). The granules may also be grouped about the nuclei. The extranuclear areas of the cells not occupied by glycogen appear translucent, clear spaces bounded by the cytomitoma, and the cell-outline remains distinct.

The uninucleated decidual cells of the perivascular sheaths all show now a marked glycogen reaction, but it is evident that the central rows

of the sheath are richest in glycogen. While the glycogen granules have increased in size the cells themselves have also grown and have become in part vesicular. (Fig. 127). There are no glycogen granules between the cells. The perivascular sheaths in the zone next the musculature have added more quickly an increase of glycogen, and are now quite as rich as the sheaths more centrally placed in the placenta. The original corium is glycogen-free.

Upon the large photograph (Fig. 124) I have indicated the general distribution of the glycogen.

GESTATION SAC OF 12 DAYS.—(FIG. 128.)

(1) Foetal tissue :—foetus and foetal placenta.

The foetal liver is now of considerable size, but it contains no glycogen. The foetal placenta likewise gives no glycogen reaction.

(2) Maternal tissue :—maternal placenta.

The intermediate zone of multinucleate decidual cells has greatly increased. From this region, on the one hand, processes of multi-

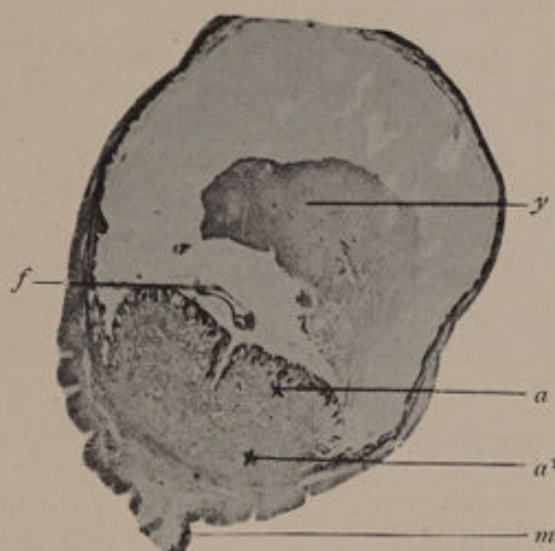


FIG. CXXI.

(9 days' Gestation showing Glycogen-area.)

Transverse section of gestation sac of 9 days, to show area of placenta wherein glycogen is found. (Compare the glycogen-area at the 8th day, Fig. 118).

a, a¹, glycogen-area in one cotyledon ; *m*, mesometrium ; *f*, foetus ; *y*, yolk-sac with yolk. (Photo.)

nucleate cells project into the foetal placenta, owing to the irregular growth of the foetal ectoderm, and on the other hand, areas of multinucleate cells following the fibrin-tissue, are extending deeper, surrounding the perivascular sheaths of the more superficial sinuses. These multinucleate cells wherever found, are rich in glycogen, the areas projecting into the foetal placenta especially so. (Fig. 129).

These areas in so far as they project into the foetal placenta are clothed by the foetal plasmodium, and by this plasmodium, one or two cells in thickness, their glycogen cells are separated on either side from the maternal blood stream. The foetal capillaries have not yet extended down to the depth of these glycogen areas. Within these multinucleate cells the glycogen granules, larger, rounder and more numerous than at the 10th day, lie always in the cytoplasm. Many of

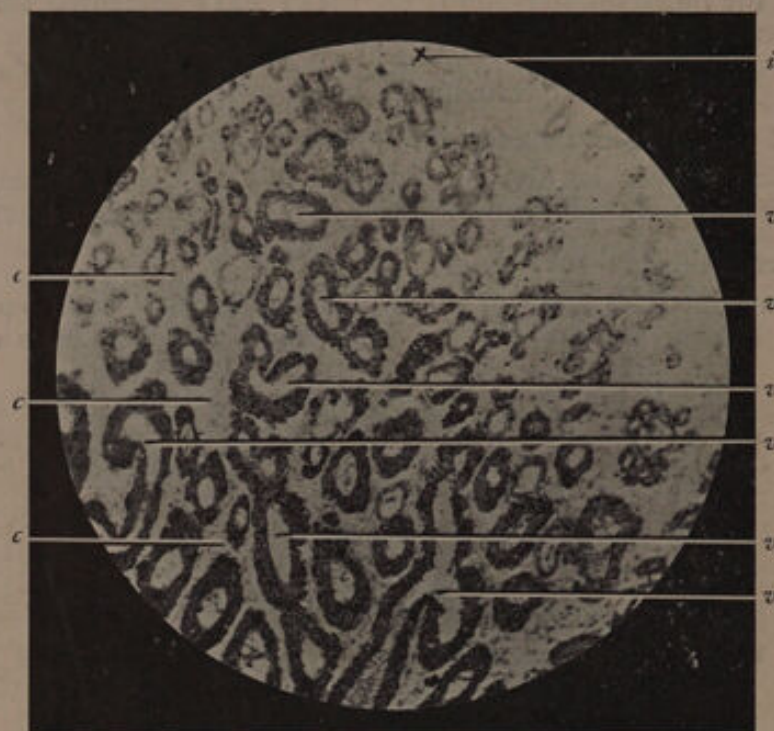


FIG. CXXII.

(9 days' Gestation showing Glycogen.)

Vessels of placental cotyledon with their perivascular sheaths of uninucleated decidual cells. These cells are rich in glycogen. The deeper vessels, those nearer the muscular wall of the cornu, have the thicker sheaths. (This microphotograph is taken from the area a, a^1 , in Fig. 121.)

v, v, v, v, v, v , vessels of placental cotyledon; i , intermediary region close to foetal ectoderm which is not shown. c, c, c , "corium" of connective tissue, no glycogen.

these cells, always those nearest the blood stream, appear entirely occupied by glycogen, the nuclei and cytomitoma being crowded to the periphery. (Fig. 130.)

The uninucleate decidual cells of the perivascular sheaths which have still further thickened, are likewise richer in glycogen than on the 10th day. The granules are now semi-lunar in form and lie against the cell-wall. The remaining cytoplasm of the cell is more distinctly translucent. (Fig. 131.) The narrow strands of original corium which lie

between the perivascular sheaths and the fibrin-tissue contain no glycogen.

I have added a drawing (Fig. 132) to give the general distribution of glycogen at this date.

GESTATION SAC OF 14 DAYS.—(FIG. 133.)

(1) Foetal tissue :—foetus and foetal placenta.

The foetal liver and the foetus itself increase more rapidly in size between the 12th and 14th days than at any other period of intra-uterine

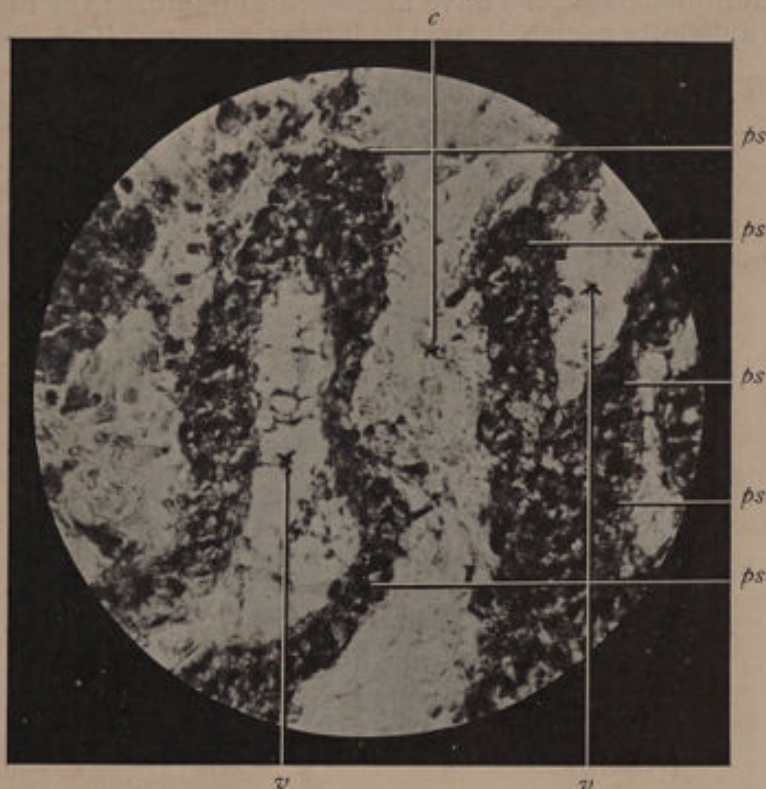


FIG. CXXIII.

(9 days' Gestation showing Glycogen.)

Two vessels in placental cotyledon with their perivascular sheaths. The glycogen-granules appear as dark spots in the uninucleate cells.

v,v, vessels containing blood-clot; *ps,ps,ps,ps,ps*, perivascular sheaths of uninucleate decidual cells; *c*, corium.

life. Compare photographs (Fig. 128) and (Fig. 133) in which this increase is seen to be enormous.

The foetal liver and the foetal placenta give no glycogen reaction.

(2) Maternal tissue :—maternal placenta.

The decidual cells are now extremely rich in glycogen, but the general distribution of this is somewhat changed. At the 10th and 12th days the glycogen in the uni- and multi-nucleate cells was evenly distributed throughout the two regions of the maternal

placenta. But now the uninucleate cells of the region of the uterine sinuses begin to show a loss of glycogen as compared with the multinucleate cells of the intermediary region. It is exactly as if the supply of glycogen in the maternal placenta were moving into a closer neighborhood to the foetal placenta. This appearance will become more and more marked during the later stages. Already it is sufficiently evident to illustrate the ground of Claude Bernard's supposition that the maternal placenta was in part a vascular organ (the deeper part) and in part a secreting organ. (See Part II: Section (B)).

The multinucleate cells have increased in number: the intermediary region as a definite region is now at its maximum. The non-vascular

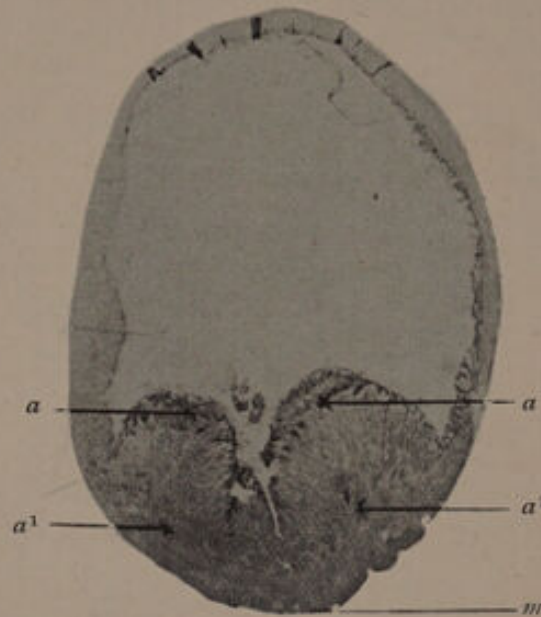


FIG. CXXIV.

(10 days' Gestation showing Glycogen-area.)

Transverse section of gestation sac of 10 days, to show the glycogen-containing areas in the placental cotyledons. The foetal portion of the placenta contains no glycogen.

a, a¹, a, a¹, glycogen areas in the two cotyledons; *m*, mesometrium. (Photo.)

areas which persist at intervals against the advance of the foetal ectoderm are longer and now lie peninsula-like in the foetal placenta; while on the deeper side its cells are everywhere increasing at the expense of the uninucleate cells of the perivascular sheaths.

These multinucleate cells appear loaded with glycogen. It is now the rule to find their cytomitoma crowded to the periphery, and in many cells it is quite lost in the mass of glycogen granules. (Fig. 134.) These granules are smaller and less discrete than at the 12th day.

Microphotograph (Fig. 135) gives a general view of the distal extremity of one of these peninsula-like areas. The foetal ectoderm which clothes it is now only one or two cells in thickness, and the mesodermic

The general distribution of the glycogen remains as at the 14th day. But while the whole deeper region of the maternal placenta is still poorer in glycogen, there remains a narrow zone of uninucleate cells next the musculature which retain their former quantity of glycogen. In consequence this zone appears richer in glycogen.

GESTATION SAC OF 18 DAYS.—(FIG. 140.)

- (1) Foetal tissue :—foetus and foetal placenta.
No glycogen reaction.

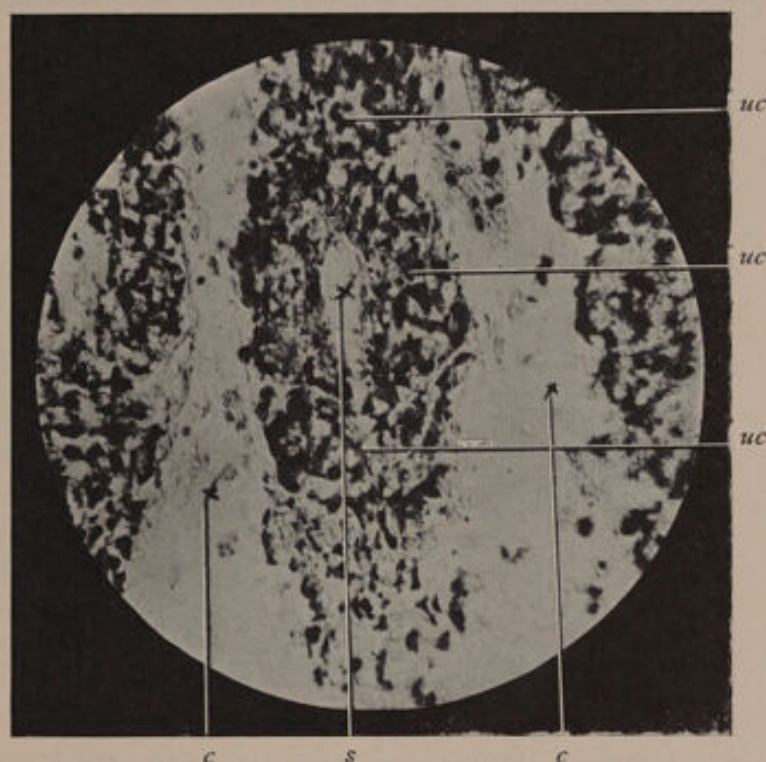


FIG. CXXVII.

(10 days' Gestation, showing Glycogen.)

High-power view of a sinus-capillary and its sheath. The glycogen-granules are larger than at the 9th day and the cells themselves are in part vesicular.

s, sinus-capillary in the region of uterine sinuses; c,c, corium of region; uc,uc,uc, uninucleated decidual cells of perivascular sheath. The black areas are glycogen-granules and are found only in the uninucleate cells of the sheath.

- (2) Maternal tissue :—maternal placenta.

The intermediary zone, as a zone, has disappeared. The multinucleate cells appear now only in irregular tracts, which either project into the foetal placenta or lie between the fragmentary perivascular sheaths of the more superficial sinuses. These sinuses have greatly increased in size, and lie close up to the deep face of the foetal placenta.

The multinucleate cells composing the areas which lie in the foetal placenta are still largely occupied by glycogen. But the granules now are still less discrete, and do not stain so ruddy a brown as formerly, and the remaining cytoplasm is slightly coloured. (Figs. 141 and 142.) The foetal ectoderm clothing these areas is now largely plasmodial and is reduced, in many places, to the thinness of a one-cell layer. This layer still separates the glycogen cells from the blood-channels of the foetal placenta. The region of the uterine sinuses is poorer in glycogen than at the 16th day, though the glycogen granules are still large and numerous in the narrow areas of multinucleate cells. In many places these multinucleate cells containing glycogen granules

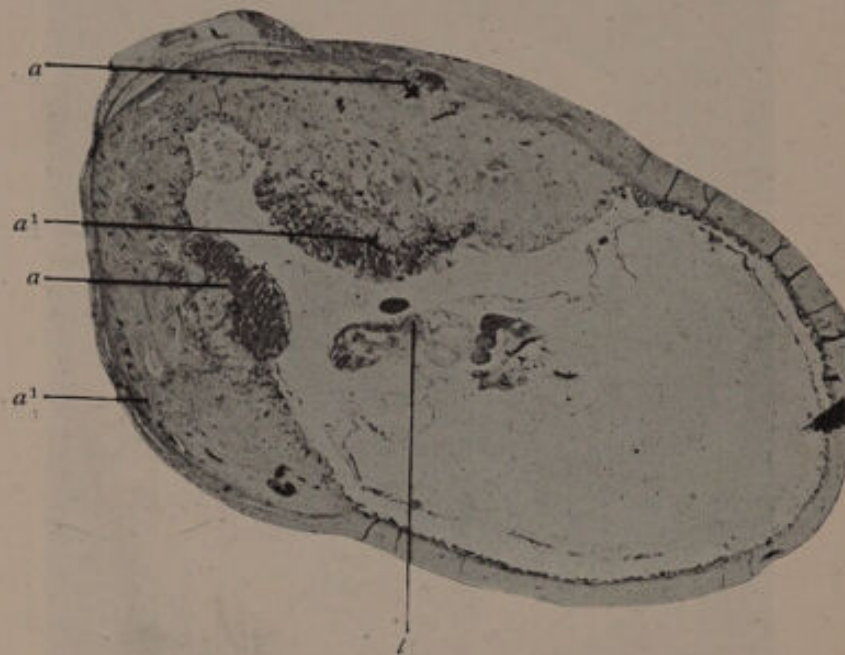


FIG. CXXVIII.

(12 days' Gestation showing Glycogen-area.)

Transverse section of gestation sac of 12 days. The glycogen-containing areas are shown. The foetus is cut longitudinally and the liver can now be seen.

a, a¹, a, a¹, glycogen-containing areas—the whole maternal placenta. The foetal placenta shows no glycogen; *l*, foetal liver. (Photo.)

lie directly against the fibrin-lamellæ which have now formed beneath the detached endothelium of the uterine sinuses. (Fig. 143.) The few remaining endothelial cells give a diffuse glycogen reaction.

The separation zone is still markedly rich in glycogen.

GESTATION SAC OF 20 DAYS.—(FIG. 144.)

(1) Foetal tissue :—foetus and foetal placenta.

No glycogen reaction.

The foetal placenta has now reached its mature stage.

(2) Maternal tissue :—maternal placenta.

The peninsula and island-like areas of multinucleate cells still show the presence of glycogen, though the glycogen granules are small, scarcely discrete, and are distributed throughout the cell. (Fig. 145.) A layer of foetal ectoderm, one cell in thickness, divides these glycogen cells from the blood-channels of the foetal placenta. This layer of ectoderm becomes entirely plasmodial, and persists until the end of pregnancy. The uterine sinuses have increased in size, and their walls

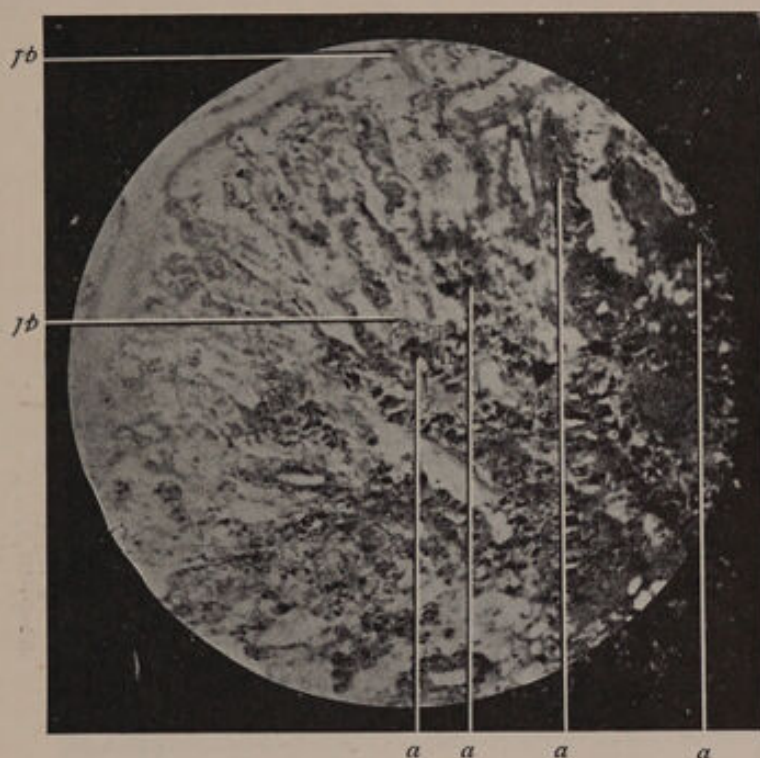


FIG. CXXIX.

(12 days' Gestation showing Glycogen.)

Foetal placenta and intermediary region of maternal placenta are shown. The areas or multinucleate decidual cells lying close to the foetal ectoderm are specially rich in glycogen.

fp,fp, foetal placenta ; *a,a,a,a*, areas of multinucleate decidual cells lying close to foetal ectoderm. The dark granules are glycogen. (See Fig. 130.)

are now definitely formed of fibrin-lamellæ, which are beginning to compress the decidual cells between them. The glycogen is confined exclusively to these decidual cells which are becoming elongated and angular. (Fig. 146.) The multinucleate cells contain larger and more numerous glycogen granules than the uninucleate.

In the zone of separation the glycogen is no longer evenly distributed, for its uninucleate cells near the musculature are now comparatively poor, while its cells near the region of the uterine sinuses are

comparatively rich in glycogen, the granules being larger and more numerous. (Fig. 147.)

GESTATION SAC OF 22 DAYS.—(FIG. 148.)*

(1) Fœtal tissue :—fœtus and fœtal placenta.

The fœtal liver shows its first trace of glycogen. This glycogen does not appear in granules but as a glycogen-brown stain, diffused over small areas in both hepatic and portal zones. At this stage there are no

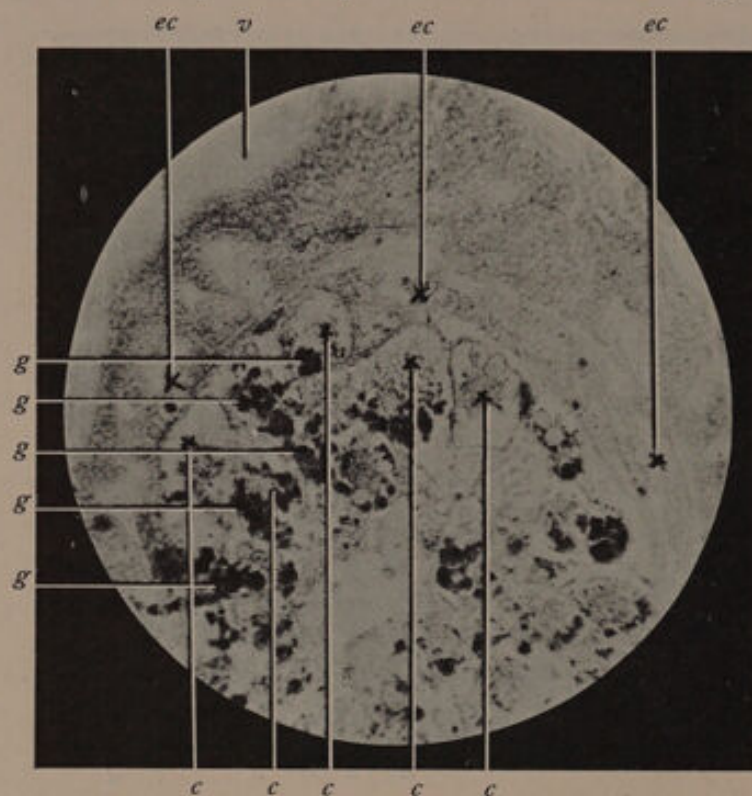


FIG. CXXX.

(12 days' Gestation showing Glycogen.)

An area of multinucleate decidual cells, rich in glycogen projecting somewhat into the fœtal placenta; the fœtal vessels have not as yet penetrated to this depth.

ec, ec, ec, fœtal ectoderm; *v*, maternal blood space lying in fœtal ectoderm; *c, c, c, c, c*, multinucleate decidual cells; *g, g, g, g, g*, glycogen granules lying within the multinucleate cells.

very definite liver columns, the intercolumnar spaces are wide and filled with blood. The liver cells are round or oval in shape and giant cells are numerous.

* As the general distribution of the glycogen continues, throughout the remainder of gestation, as it is indicated in Fig. 148, the large photographs of the series need not be further reproduced.

(2) Maternal tissue :—maternal placenta.

The areas of multinucleate cells lying peninsula- or island-like in the foetal placenta show now only a faint, diffuse brown colouration. Glycogen-granules are no longer found, and this dirty brown discolouration is the only indication of its presence. The cells are oedematous, and their cytomitoma is in part disintegrated.

In the region of the uterine sinuses the decidual cells are becoming more and more compressed by the ever-thickening fibrin-lamellæ. They still contain glycogen but the granules are small. (Fig. 149.)

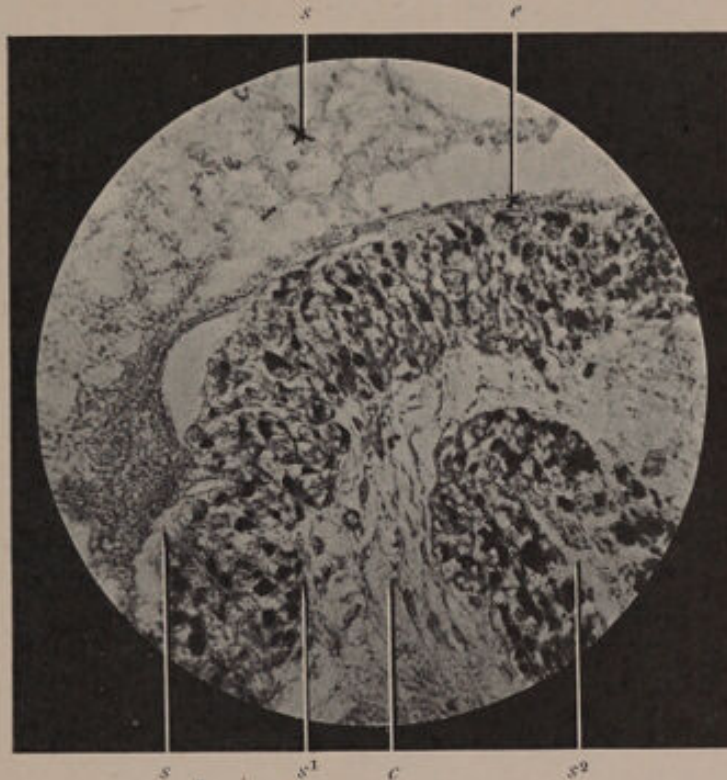


FIG. CXXXI.

(12 days' Gestation showing Glycogen.)

Region of uterine sinuses. A high-power view of sinus with its perivascular sheath of uninucleate decidual cells rich in glycogen. The "corium" shows no glycogen.

s, uterine sinus containing blood-clot; *e*, thickened endothelium; *s*, *s*¹, perivascular sheath, the dark granules of glycogen are distinct and lie always within the cells; *c*, "corium"; *s*², a second sinus with its sheath.

In the zone of separation the glycogen persists in considerable quantity, there being only few of the uninucleate cells which do not contain at least one granule. The cells next the region of the uterine sinuses contain the largest granules. (Fig. 150.)



FIG. CXXXII.

(12 days' Gestation showing Glycogen.)

Drawing giving the general distribution of glycogen at this date of gestation. The thickness of the entire placenta is shown from the muscular wall of the uterine cornu below to the foetal surface above. The foetal placenta shows no glycogen.

fp, fp¹, foetal placenta; *ir, ir¹*, intermediary region of maternal placenta; *rs, rs¹*, region of uterine sinuses of maternal placenta; *m*, muscular wall; *s, s¹*, uterine sinuses; *ec, ec, ec*, "ectoplacental columns," the axes of which are hollow and filled with maternal blood; *vm*, vascular mesoderm (nucleated foetal blood); *g, g, g, g*, glycogen-granules in the multinucleate decidual cells; *ps, ps¹*, perivascular sheaths of uninucleate decidual cells rich in glycogen.

GESTATION SAC OF 24 DAYS.

(1) Foetal tissue :—foetus and foetal placenta.

The glycogen brown colouration is now more intense in the hepatic and portal zones. In addition, in both zones, and grouped closely about the vessels, there are evident, small, sharply-outlined, ruddy-brown glycogen granules. These lie always in the liver cells in the meshes of the cytomitoma, and usually near the periphery of the cell. (Fig. 151.)

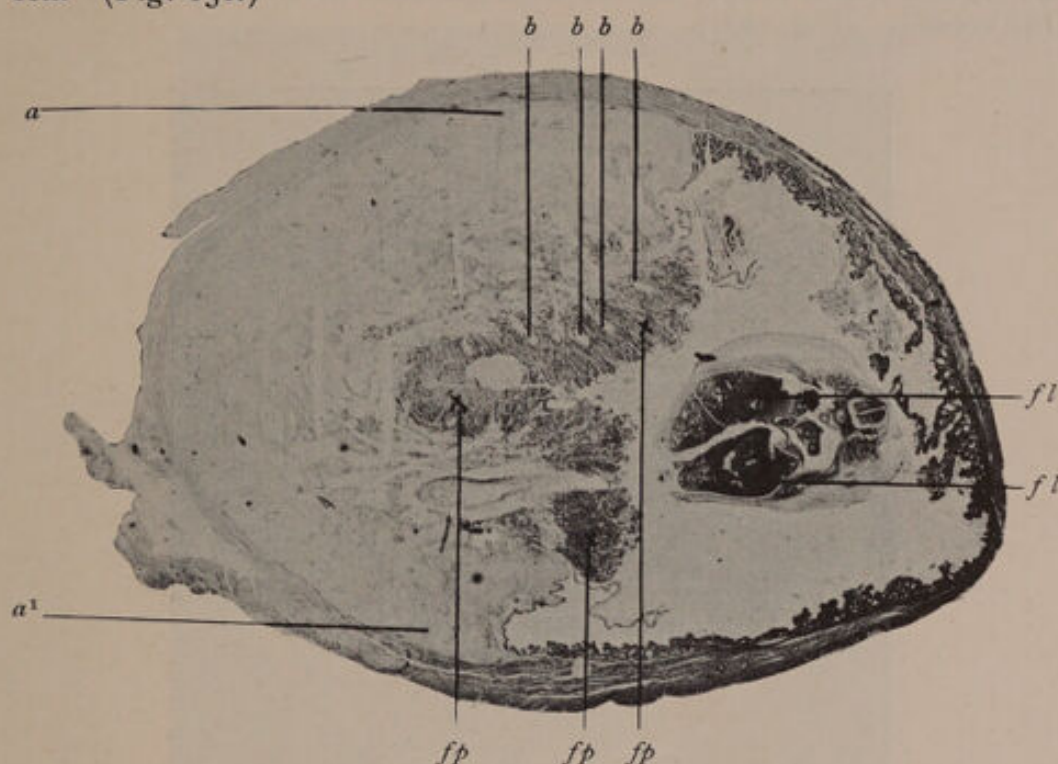


FIG. CXXXIII.

(14 days' Gestation showing Glycogen-area.)

Transverse section of gestation sac of 14 days. The foetal placenta shows no glycogen; the maternal placenta is now especially rich in glycogen.

a, a¹, glycogen-containing area—the whole maternal placenta; *fp, fp, fp*, foetal placenta (no glycogen); *b, b, b, b*, areas of multinucleate cells lying peninsula-like in the foetal placenta. These cells are rich in glycogen (See Fig. 135); *fl, fl*, foetal liver, no glycogen. (Photo.)

(2) Maternal tissue :—maternal placenta.

The areas of multinucleate cells lying in the foetal placenta show now no trace of glycogen.

In the region of the uterine sinuses the decidual cells are crowded so closely that their identity is becoming lost. In their midst are a few scattered glycogen granules.

In the zone of separation the glycogen granules are still large and numerous. (Fig 152.)

GESTATION SAC OF 26 DAYS.

(1) Foetal tissue :—foetus and foetal placenta.

The liver cells are larger and they are more definitely arranged in columns. The mesodermic septa are thinner and less vascular. The hepatic and portal vessels can now with more certainty be distinguished.

The glycogen granules are large and sharply defined. Very constantly they lie at the periphery close up to the cell-wall. They are of no regular size or shape, but the large granules invariably lie closer to the vessels. (Fig. 153.)

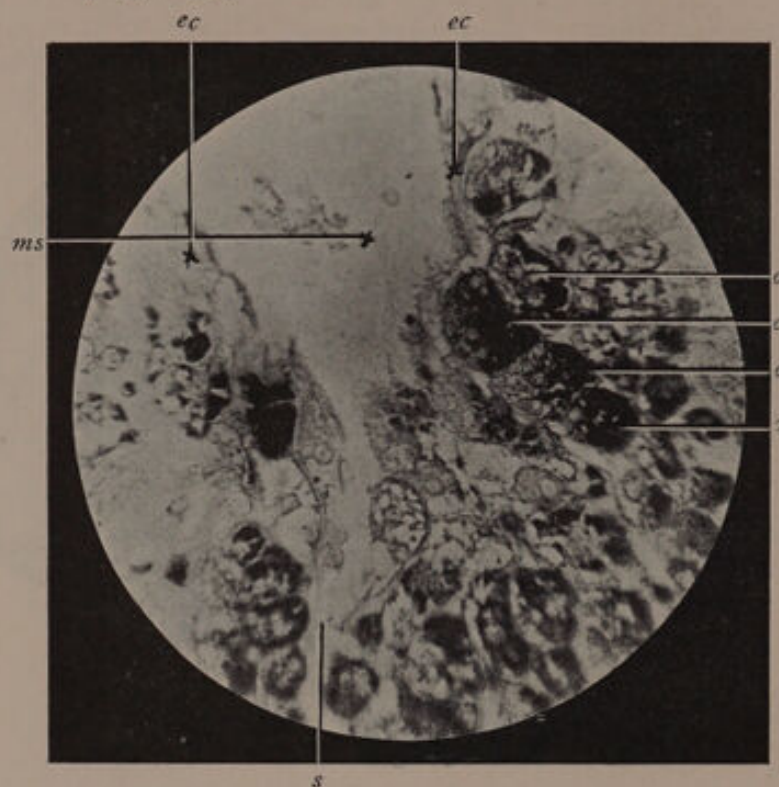


FIG. CXXXIV.

(14 days' Gestation showing Glycogen.)

Multinucleate decidual cells of intermediary region almost completely filled with glycogen. These cells immediately underlie the foetal placenta. Note the maternal capillary (*s*) with its degenerate endothelium.

s, sinus-capillary with ragged endothelium; *ms*, maternal blood space; *ec,ec*, foetal ectoderm; *c,c,c,c*, glycogen-granules almost filling the multinucleate decidual cells.

(2) Maternal tissue :—maternal placenta.

In the region of the uterine sinuses the outlines of the decidual cells can only be in places distinguished, for the greater part they form a conglomerate mass. There are scattered glycogen granules in the midst of this mass. The separation zone is finely retiform in appear-

ance. Many of its cells are glycogen free, but those next the uterine sinuses exhibit the granules in considerable size and number.

GESTATION SAC OF 28 DAYS.

(1) Foetal tissue :—foetus and foetal placenta.

The glycogen-granules now occupy more or less definitely the hepatic and portal zones. The drawing (Fig. 154) shows the appearance of the granules and their arrangement within the liver cells.

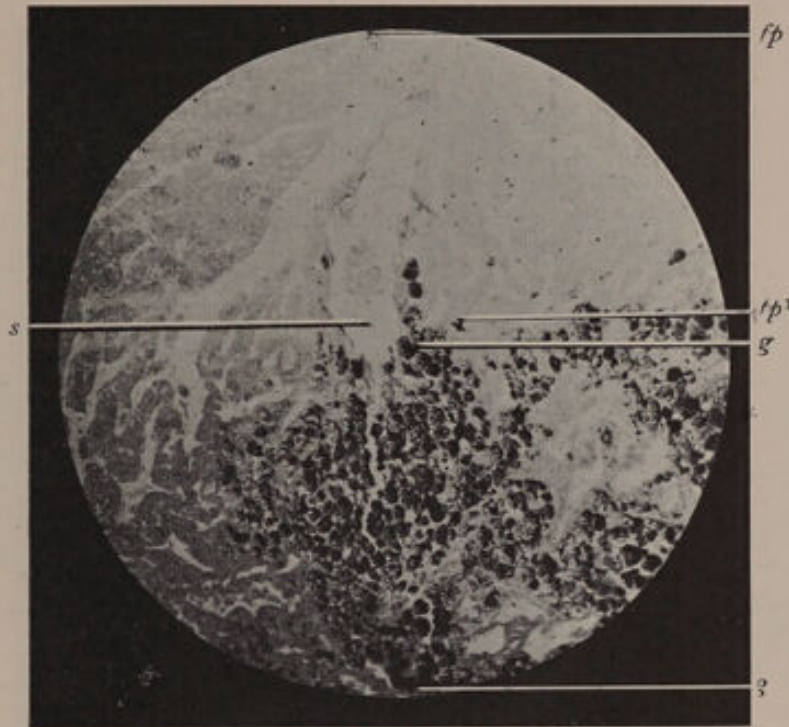


FIG. CXXXV.

(14 days' Gestation showing Glycogen.)

Shows the general distribution of the glycogen-containing multinucleate decidual cells immediately underlying the foetal placenta. (See *b,b,b,b*, Fig. 133.) The glycogen is most abundant along the course of a maternal capillary.

fp,fp¹, foetal placenta (no glycogen); *s*, maternal blood space in foetal placenta in direct communication below with a maternal capillary; *g,g*, glycogen-granules lying in multinucleate decidual cells.

(2) Maternal tissue :—maternal placenta.

The glycogen granules are small, and are scattered throughout the conglomerate areas of decidual cells between the fibrin-lamellæ. (Fig. 155.) The uninucleate cells of the separation zone still retain their identity and glycogen-granules. At this date there is only a comparatively small quantity of glycogen in the placenta, and the greater part of this is found in the zone of separation.

GESTATION SAC OF 30 DAYS.

(1) Foetal tissue :—foetus and foetal placenta.

The foetal liver is rich in glycogen which is confined, for the most part, to the hepatic and portal zones, though there a few granules found in the cells of the intermediary zone.

The glycogen-granules are large and lie always within the cell, very constantly occupying the peripheral area of the cell. The remainder of the cytoplasm often appears translucent.

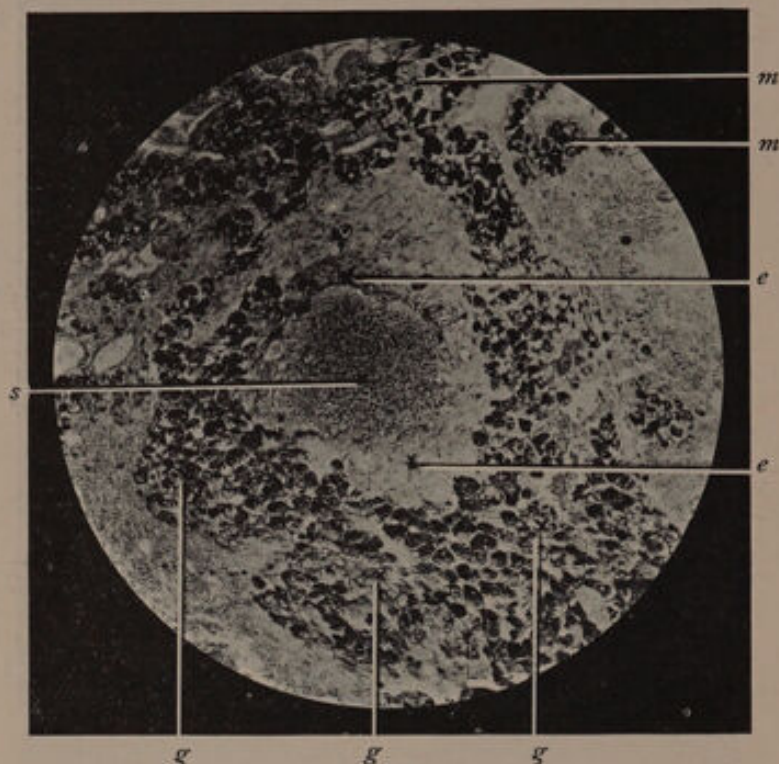


FIG. CXXXVI.

(14 days' Gestation, showing Glycogen.)

A sinus, from the region of uterine sinuses. Note the perivascular distribution of the glycogen and the thick wall of degenerated endothelium.

s, uterine sinus with blood-clot; *e,e*, thickened endothelium (its cells have multiplied); *g,g,g*, glycogen-granules lying in the uninucleate decidual cells of the perivascular sheath; *m,m*, multinucleate decidual cells rich in glycogen.

(2) Maternal tissue :—maternal placenta.

A few small glycogen-granules are scattered throughout the region of the uterine sinuses, lying in the conglomerate remains of the decidual cells. The granules do not lie in the cells, for now there are really no cells for them to occupy, they are found simply in the midst of the conglomerate mass. In the zone of separation there are still present in the attenuated cells some small glycogen granules.

LIVER OF YOUNG RABBIT.

Liver of young rabbit 24 hours after birth. It had suckled.

The liver is still very vascular, the cell-columns are irregular, and the lobules indistinct. The liver now shows a maximum amount of glycogen. This is gathered in greatest amount about the vessels, both hepatic and portal, but it is found in varying quantity throughout the whole extent of the lobule. (Fig. 156.) These glycogen-granules are largest near the vessels where they often occupy the whole cell. For

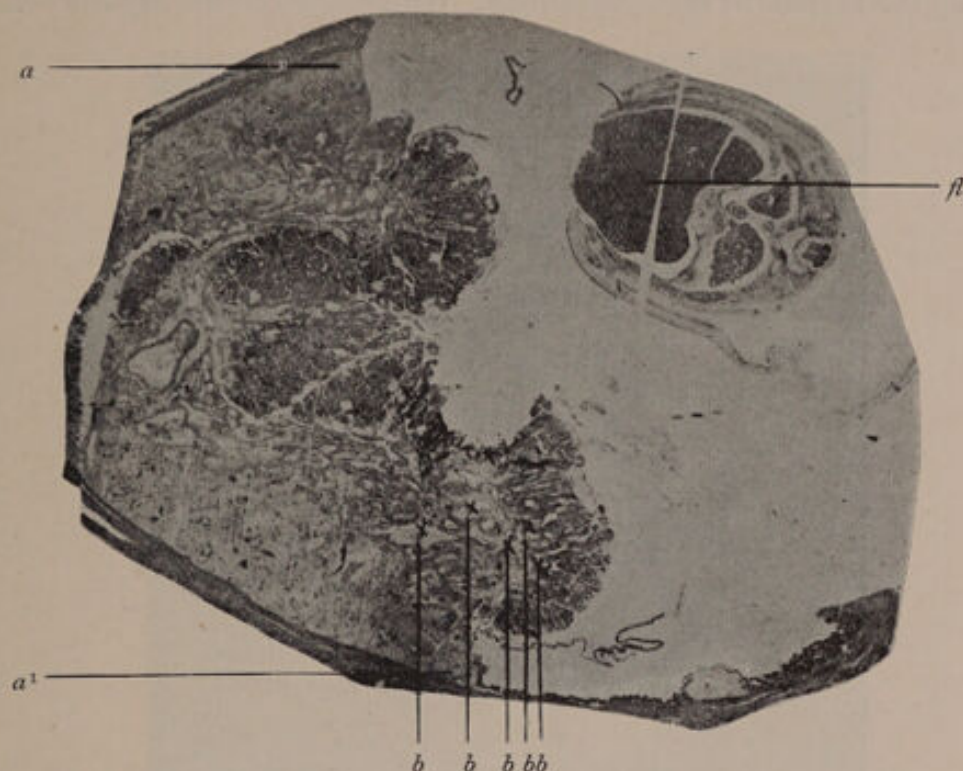


FIG. CXXXVII.

(16 days' Gestation showing Glycogen-area.)

Transverse section of gestation sac of 16 days. The foetal placenta and foetus (foetal liver) show no glycogen. The whole maternal placenta is rich in glycogen.

a, a¹, glycogen-containing area—the whole maternal placenta; *a¹*, foetal liver; *b, b¹, b, b¹, b b, b b b*, areas of multinucleate decidual cells specially rich in glycogen. (See Fig. 138.) (Photo.)

the most part however only a portion of the cell is thus occupied, the glycogen being accumulated at the periphery or about the nucleus. In these cases the remaining portions of the cell appear vacuolated—well-defined translucent spaces in the cytoplasm. These spaces may have previously been occupied by a serous fluid, (Sheridan Délépine Contribution to the study of the vertebrate liver: Proc. Roy. Soc.: Dec. 17th, 1890) or by fat, in either case rendered empty by the absolute alcohol.

As the liver at this date is loaded with fat (see Section (C)) these spaces have been probably so occupied.

ADULT LIVER—5 HOURS AFTER A MEAL.

The lobules are comparatively distinct, the cell columns are regular and the cells themselves large and well-defined. As has been shown by Lauder Brunton and Délépine (Proc. Roy. Soc.: Oct. 22nd, 1891) during digestion, glycogen accumulates in the liver cells, and gradually fills up the meshes of the cytomitoma. This begins in the *hepatic zone*,

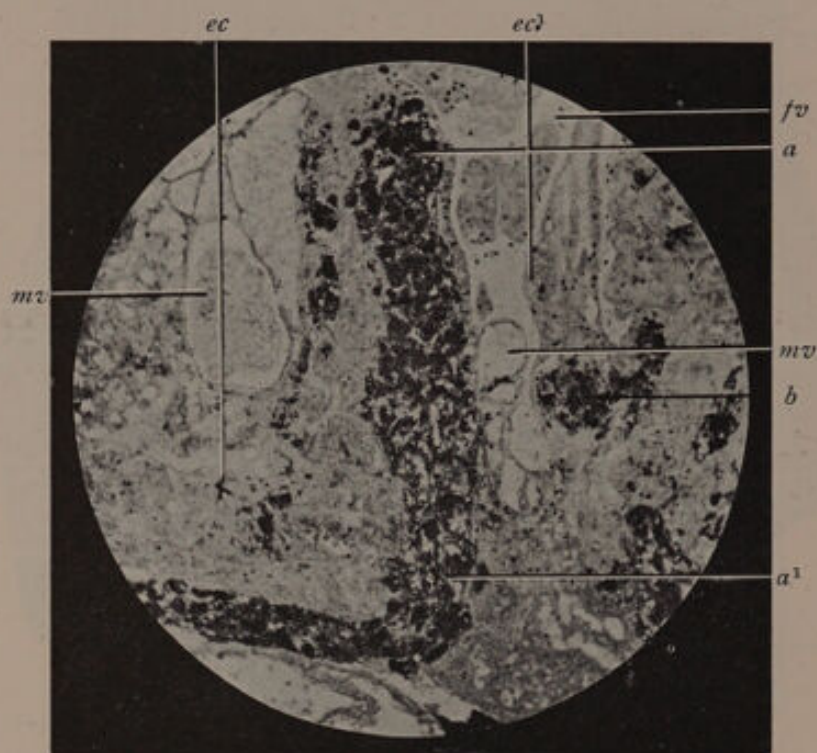


FIG. CXXXVIII.
(16 days' Gestation showing Glycogen.)

Area of multinucleate decidual cells lying peninsula-like in the foetal placenta. The larger maternal blood-channels are seen and also at one place the foetal vessels which are now approaching these glycogen-areas.

ec, ec1, foetal ectoderm; *a, a1*, area of multinucleate decidual cells, rich in glycogen; *b*, island-like area of decidual cells, rich in glycogen; *mv, mv*, maternal blood-channels; *fv*, foetal vessels.

almost immediately after the beginning of a meal, attains its maximum from the 3rd to the 8th hour, and gradually diminishes, till at the 12th hour only a few granules are left in the hepatic zone, *which is thus the first and the last to be infiltrated with glycogen.*

The appearances 5 hours after a meal are shown in the drawing. (Fig. 157.)

SUMMARY OF GLYCOGEN.

Glycogen is never found in the foetal placenta.

In the maternal placenta it appears first at the 8th day in the uninucleate decidual cells of the perivascular sheaths of the centrally-placed sinuses. It increases rapidly in amount, and in 24 hours is found in the sheaths of all the sinuses, lying always in the decidual cells, the granules being



FIG. CXXXIX.

(16 days' Gestation showing Glycogen.)

Superficial uterine sinus with surrounding multinucleate decidual cells, rich in glycogen. The endothelium of the sinus is degenerate.

s, sinus with blood-clot; *e,e*, degenerate endothelial cells *g,g,g,g,g,g*, large granules of glycogen lying within the multinucleate decidual cells.

larger and more numerous close to the sinus-endothelium. The multinucleate decidual cells, from their first appearance at the 9th day contain glycogen, and in them the granules are always larger than in the uninucleate decidual cells. The glycogen is confined exclusively to these decidual cells, and is always most abundant in the cells next the blood-stream.

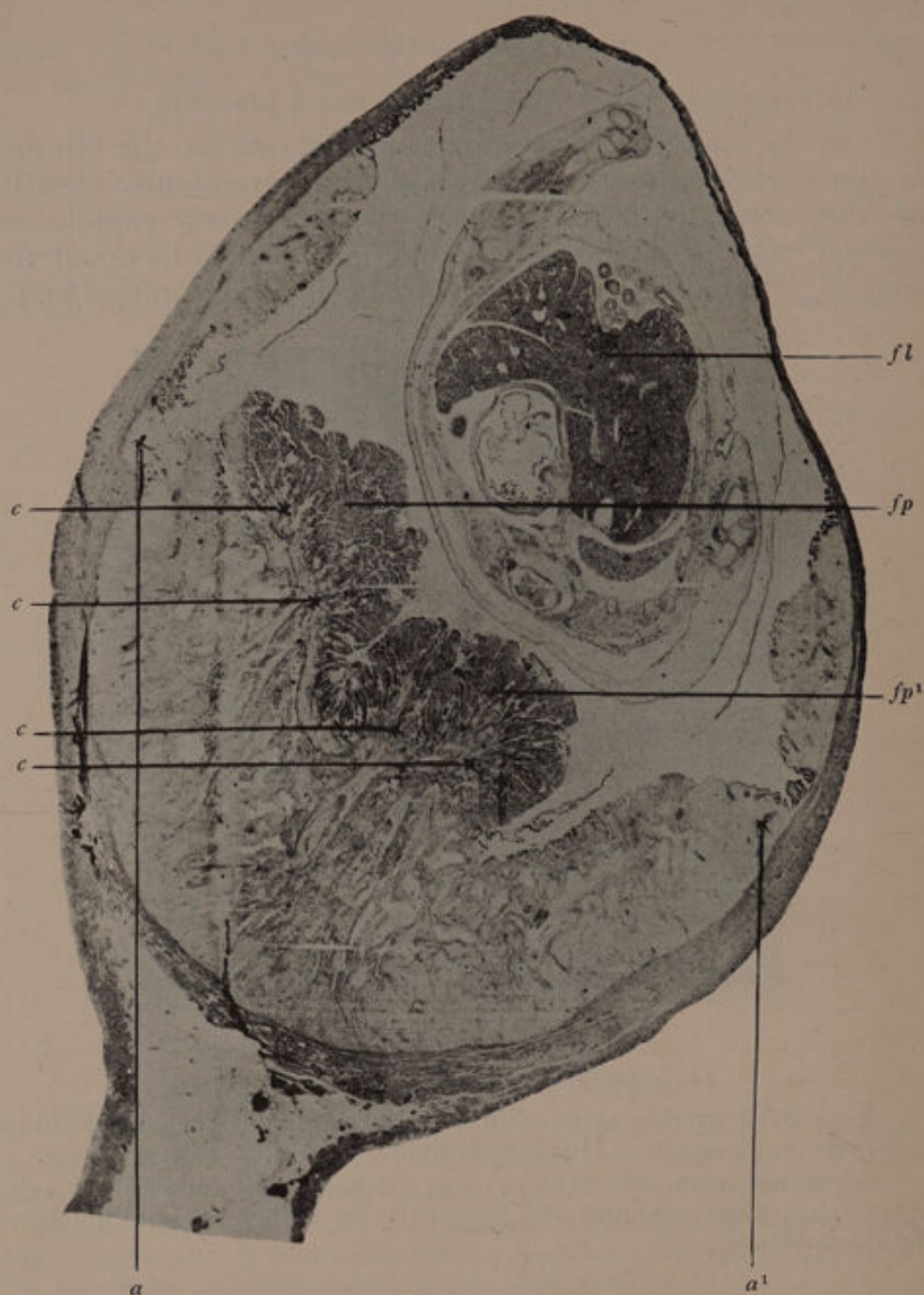


FIG. CXL.

(18 days' Gestation showing Glycogen-area.)

Transverse section of gestation sac of 18 days. The foetus and foetal placenta show no glycogen; the maternal placenta is rich in glycogen.

a, a¹, glycogen-containing area, the whole maternal placenta *fp, fp¹*, foetal placenta; *fl*, foetal liver; *c, c, c, c*, areas of multinucleate decidual cells specially rich in glycogen. (Photo.)

At the 10th and 12th days the glycogen is evenly distributed throughout the regions of the maternal placenta, for while the granules are larger in the multinucleate cells of the intermediary region, they are more numerous in the uninucleate cells of the region of the uterine sinuses. The amount of glycogen in the maternal placenta reaches a maximum

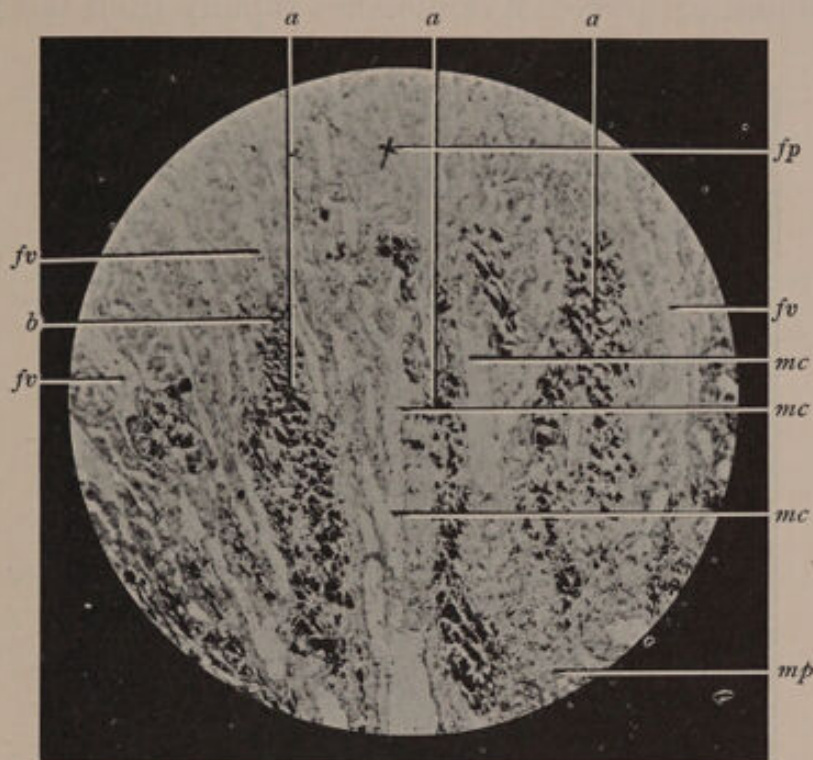


FIG. CXLI.

(18 days' Gestation showing Glycogen.)

Areas of glycogen-containing multinucleate decidual cells lying peninsula-like in the foetal placenta. These areas are always completely clothed by the foetal ectoderm.

a,a,a, areas of multinucleate decidual cells containing dark glycogen-granules; *fp*, foetal placenta; *mp*, maternal placenta; *mc,mc,mc*, maternal blood-channels; *fv,fv,fv*, foetal vessels which now lie close to glycogen containing cells; *b*, area shewn in Fig. 142.

between the 12th and 16th days, and at the same time the region of the uterine sinuses begins to show a loss of glycogen as compared with the intermediary region.

The glycogen-containing cells, multinucleate, are always separated by a layer of foetal ectoderm from the blood-channels of the foetal placenta, and in the maternal placenta the

glycogen cells, uni- or multinucleate, are separated from the blood-stream either by a thickened endothelial wall or by the subsequently formed fibrin lamellæ. The zone of separation always exhibits glycogen in its uninucleate cells, the granules being specially plentiful about the small sinuses, and these persist here in considerable number until the end of gestation. The amount of glycogen diminishes rapidly from the 16th to

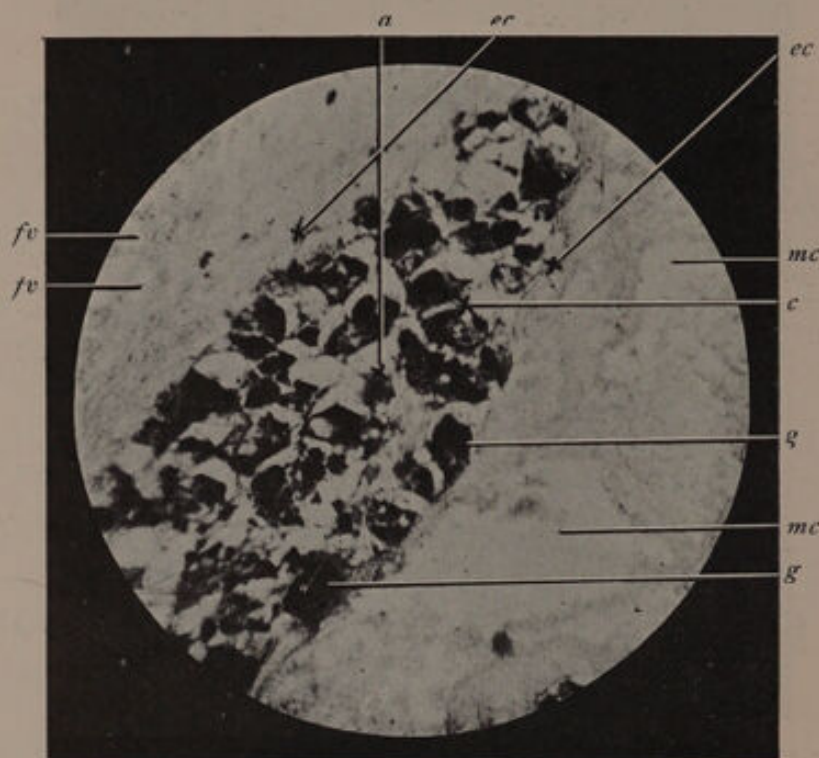


FIG. CXLII.

(18 days' Gestation showing Glycogen.)

High-power view of one peninsula-like area of multinucleate decidual cells. (See Fig. 141.) The cells are largely occupied by the dark glycogen-granules, and the *area* is surrounded by a complete layer of ectoderm.

a, peninsula-like area ; *ec,ec*, foetal ectoderm ; *c*, multinucleate cell half-filled with glycogen ; *g,g*, glycogen-granules ; *mc,mc*, maternal blood-channels ; *fv,fv*, foetal vessels.

the 22nd day. After this date till the end of gestation there are found only small glycogen-granules scattered in the midst of the conglomerate masses of uni- and multinucleate cells, save in the separation zone where the cells remain distinct and retain their glycogen granules.

Glycogen appears in the foetal liver at the 22nd day. It increases rapidly and steadily in amount till the end of gestation. It is confined chiefly to the hepatic and portal zones, and lies always in the liver cell. 24 hours after birth the liver is specially rich in glycogen, and in the adult liver the maximum glycogen reaction is obtained between 5 and 6 hours after a meal.

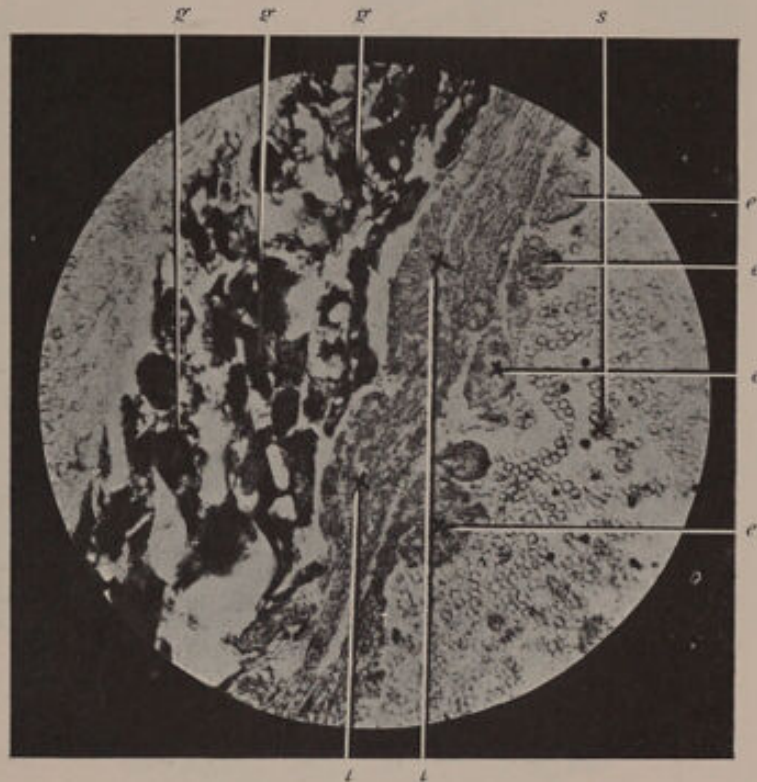
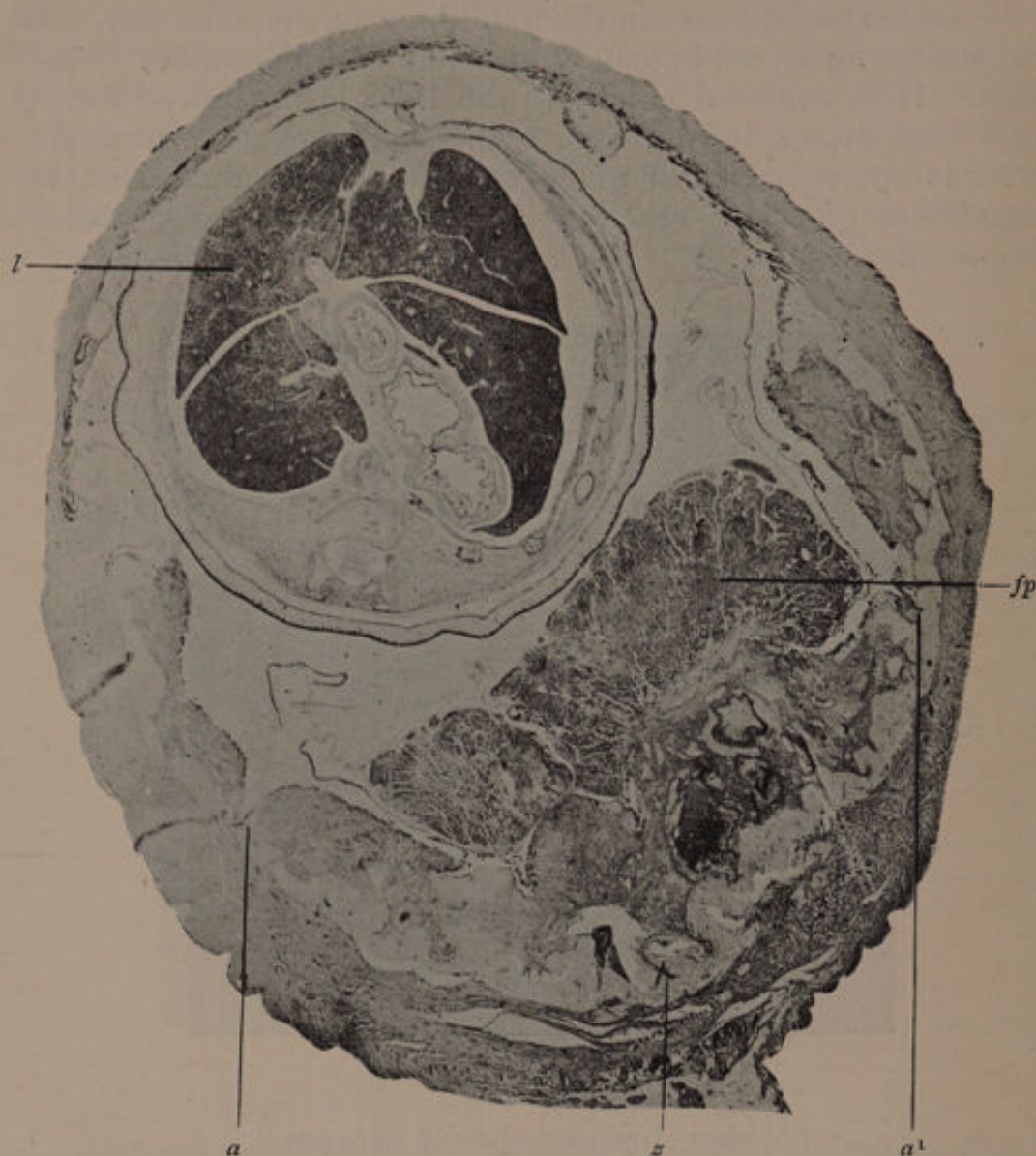


FIG. CXLIII.

(18 days' Gestation showing Glycogen.)

Uterine sinus in maternal portion of placenta. The endothelium is largely detached, the wall of the sinus being composed of fibrin-lamellæ outside which lie the decidual cells occupied by the dark glycogen-granules.

s, uterine sinus with blood-clot ; *e,e,e,e*, detached endothelial cells ; *l,l*, fibrin-lamellæ ; *g,g,g*, large glycogen granules within decidual cells whose outline is becoming indistinct.



(20 days' Gestation showing Glycogen-area.)

Transverse section of gestation sac of 20 days. The foetal liver cut at such a level as to show its five lobes contains as yet no glycogen ; in the foetal placenta is no glycogen. The maternal placenta gives everywhere the glycogen reaction even in the "zone of separation."

a, a', glycogen-containing area ; *s*, "zone of separation ;" *fp*, foetal placenta ; *l*, foetal liver. (Photo.)

SECTION C.

FAT AS FOUND IN PLACENTA AND FŒTUS.

Method followed. The smaller gestation sacs were isolated, incised along their ventral border, and submitted practically intact to the osmic acid. The larger gestation sacs, after the 10th day, were hardened first in a 10 % solu-

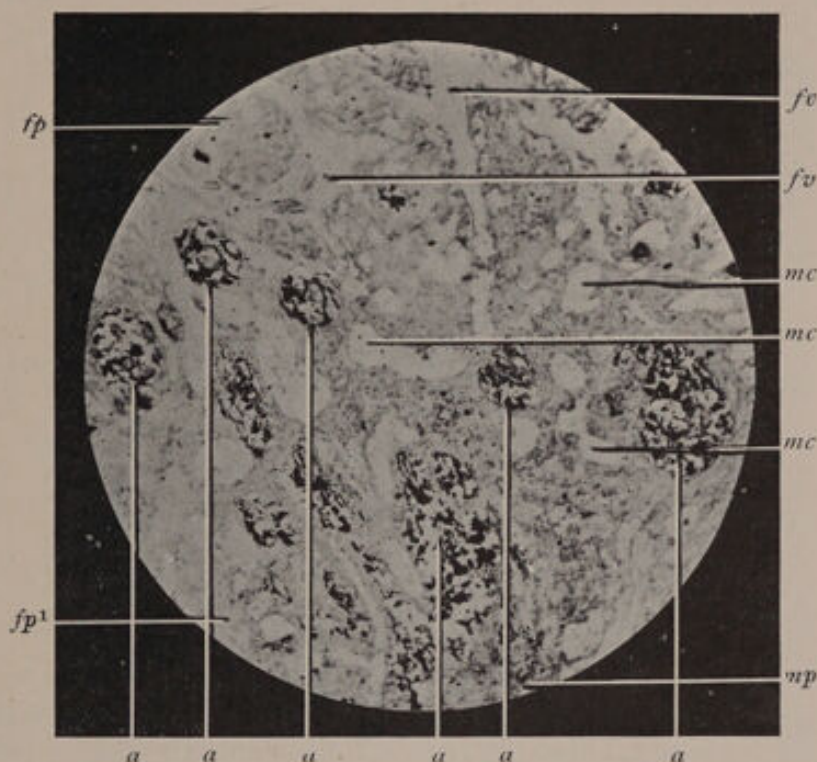


FIG. CXLV.

(20 days' Gestation showing Glycogen.)

Areas of multinucleate decidual cells, rich in glycogen, lying some distance within the fœtal placenta (they appear isolated by reason of the plane of section. See Fig. 141.) The glycogen granules are small and fragmented.

fp, fp¹, fœtal placenta; *mp*, maternal placenta; *a, a, a, a, a, a*, areas of multinucleate decidual cells showing the dark glycogen granules; *fv, fv*, fœtal mesoderm with its vessels; *mc, mc, mc*, maternal blood channels.

tion of formalin (formalin does not dissolve but fixes fat) for 12 hours. Then slabs were cut through the central portion of the placenta and the liver of the fœtus, and these slabs submitted to the osmic acid.

A 1 % solution of osmic acid freshly prepared was always used, and the specimens were left in this for 24 hours. To increase the penetrative power I found it advisable to place the bottle containing the specimens, tightly stoppered, upon the top of the incubation-oven for 12 hours.

The specimens were then washed in running water for 24 hours, dehydrated, cleared, embedded and cut in the usual way. After fixation to the slide the sections were simply washed in naphtha and mounted in balsam.



FIG. CXLVI.

(20 days' Gestation showing Glycogen.)

A uterine sinus in maternal placenta. Its endothelium has disappeared and its wall is now formed by fibrin lamellæ outside which lie uninucleate decidual cells containing glycogen granules. (Compare Fig. 143.)

s, sinus with blood-clot; *l*, fibrin-lamellæ; *c,c,c*, uninucleate decidual cells; *g,g,g*, glycogen-granules.

The above method gives satisfactory results, even the minute droplets of the embryo's fat appearing discrete and of a definite blackness. I also employed Sudan III., following the method given by H. Rieder. (Dents. Arch. f. Klin. Med. Bd. L.I.X., p. 444-450, 1897.) Sudan III. stains the fat a bright crimson but its use involves the employment of a freezing microtome, and the thick sections which alone can be cut by this; while, where the fat occurs in small droplets, its action is not discriminate. Where fat occurs in consider-

able quantity and occupies definite cells Sudan III. gives a very pretty result, but even though counterstained with hæmatoxylin these sections do not photograph at all well, those stained with the osmic acid being immeasurably better in this respect.

Note :—Pure palmitic and stearic acids and their glucosides do not reduce osmic acid, while on the other hand osmic acid is a very sensitive re-agent for the detection of *oleic acid* and *olein*. (Carl Handwerck, Beiträge zur Kenntniss vom Verhalten der Feilkörper zu Osmiumsäure und zum Sudan. Zeits. f. Wissench, Mikr., Oct., 1898.

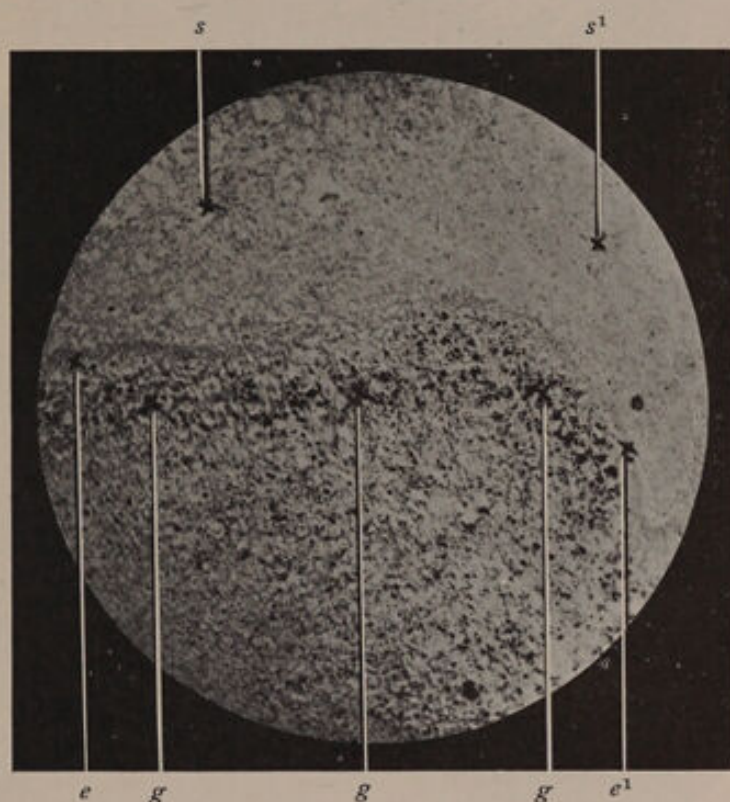


FIG. CXLVII.

(20 days' Gestation showing Glycogen.)

Blood vessel in the "zone of separation," its endothelium is thickened. The surrounding decidual cells are attenuated with branching processes, while the dark glycogen-granules within these cells are small and more numerous near the vessel.

s, s¹, vessel with blood-clot; *e, e¹*, endothelium; *g, g¹*, glycogen-granules.

While the micro-chemical study of fat in the placenta will be conducted exactly in the same way as in the study of glycogen, in the fœtus it will include both the sub-cutaneous tissue and liver.

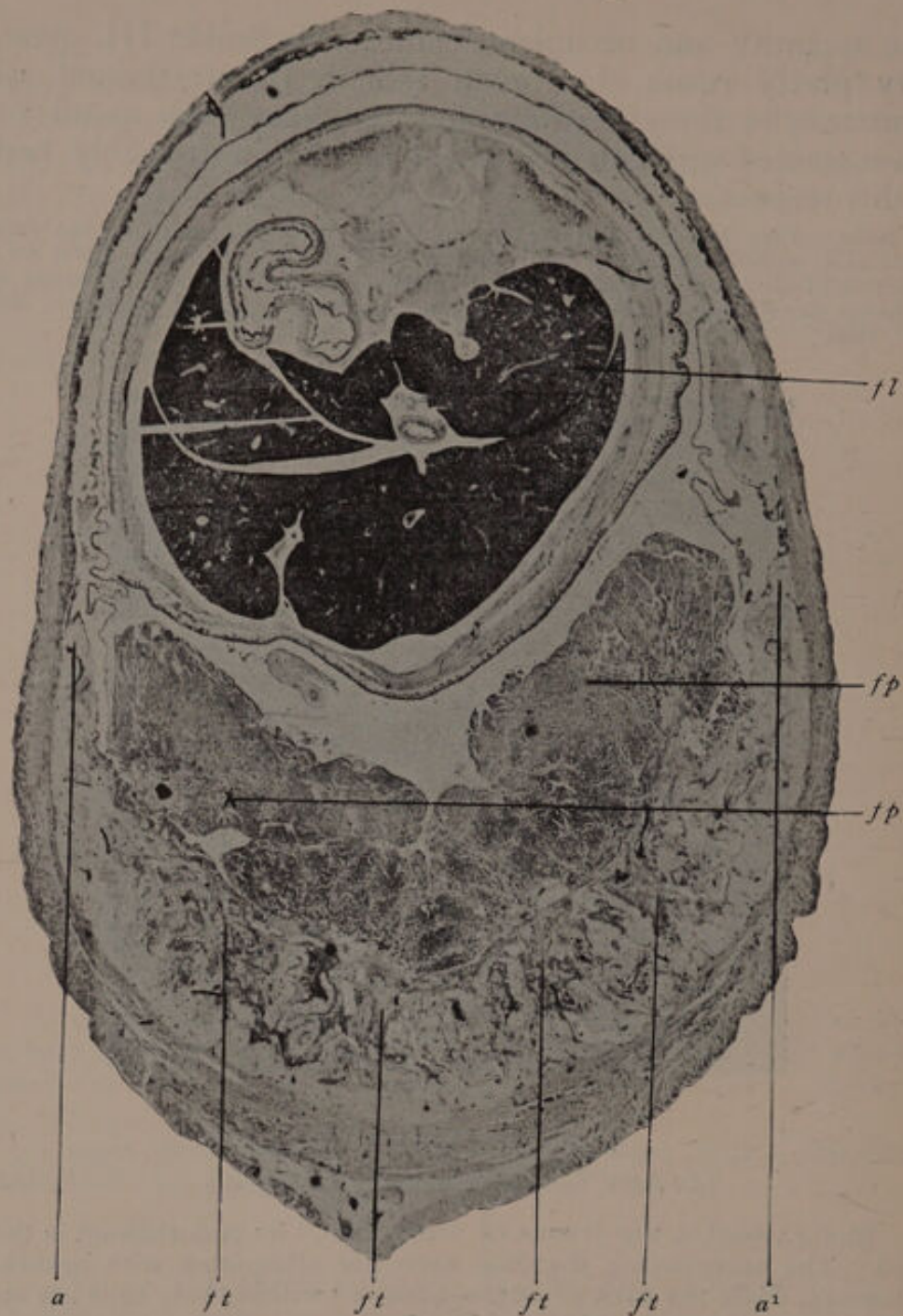


FIG. CXLVIII.

(22 days' Gestation showing Glycogen-area.)

Transverse section of gestation sac of 22 days. Large tracts of fibrinous tissue, containing no glycogen, are seen in the maternal placenta; the foetal liver shows now the first trace of glycogen; the foetal placenta now, as always, shows no glycogen.

a, a¹, glycogen-containing area; *ft, ft, ft, ft*, fibrinous-tissue tracts which contain no glycogen; *fp, fp*, foetal placenta; *fl*, foetal liver.
(Photo.)

In the following descriptions I shall maintain the same order as in Sections (A) and (B), viz:—

- (1) Foetal tissue—foetus and foetal placenta.
- (2) Maternal tissue — placental mucosa or maternal placenta.

As before negative results will simply be mentioned.

Gestation sacs of 4, 5, 6, 6½, 7, 8 and 9 days show no fat reaction.

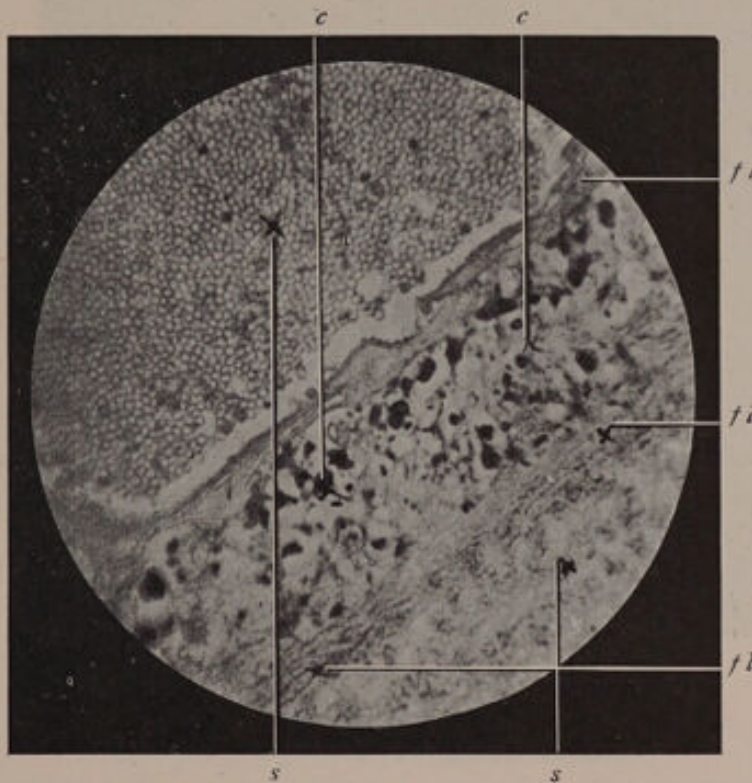


FIG. CXLIX.

(22 days' Gestation showing Glycogen.)

Two neighbouring uterine sinuses in maternal placenta. Their walls are composed of fibrin-lamellæ and between them are remains of decidual cells with scattered dark glycogen-granules.

s,s, sinuses with blood-clot; *fl,fl*, fibrin-lamellæ; *c,c*, decidual cells with dark glycogen-granules.

GESTATION SAC OF 10 DAYS.

- (1) Foetal tissue :—foetus and foetal placenta.

Fig. 158 shows a transverse section of the foetus which passes through the newly-formed liver. Very minute droplets of fat or of a

substance stained black by osmic acid are seen in the liver, the heart-walls, the wall of the mid-gut and in the endodermal cells of the vascular area of the umbilical vesicle. These droplets are most numerous in the wall of the mid-gut, while in the endodermal cells of the umbilical vesicle they are of a larger size. They lie as far as can be observed always within the cells. These droplets are probably fat.

It will be remembered that at this date the vitelline circulation has reached its maximum activity. With the immediate establishment of the

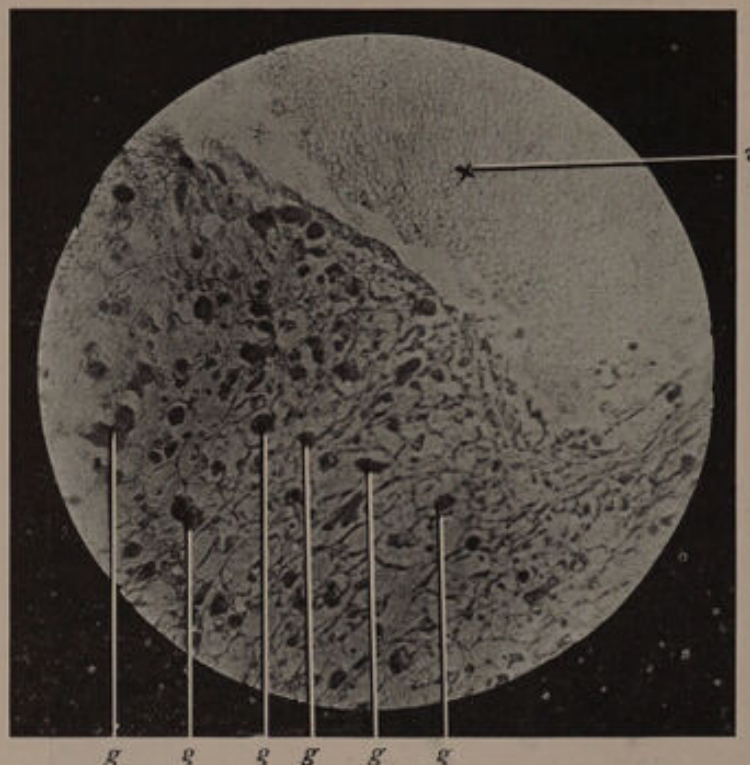


FIG. CL.

(22 days' Gestation showing Glycogen.)

Vessel in the "zone of separation." The dark glycogen granules are in the attenuated decidual cells, often around the nucleus.

v, vessel with blood clot ; *g,g,g,g,g,g*, glycogen-granules within the cells. The granules are always larger and more numerous near the vessel.

allantoic circulation my observations show that fat disappears from the foetus and does not reappear until the 16th day, and then only in the liver and in drops of much larger size.

The foetal placenta shows no fat.

(2) Maternal tissue :—maternal placenta.

No fat reaction.

GESTATION SAC OF 12 DAYS.

(1) Foetal tissue :—foetus and foetal placenta.

The foetus itself shows no fat, but numerous minute drops are seen in the membranes. These droplets are found in the endodermal cells of the vascular area of the umbilical vesicle, especially near the sinus terminalis at either extremity of the vascular area. They are also numerous in the extra-placental ectodermal cells, especially near the placental margins. The mesodermic cells show no fat. In the large photograph (Fig. 159) where the membranes are shown I have indicated the areas where fat occurs, and in microphotograph (Fig. 160) which shows the chorionic layers of ectoderm and mesoderm near the placental margin, the fat droplets in the ectoderm are numerous and large.



FIG. CLI.

(24 days' Gestation showing Glycogen.)

Foetal liver—hepatic vessel (vein) and surrounding liver cells. The perivascular distribution of the glycogen is shown.

v, portal vein ; *c, c, c, c*, liver cells showing no glycogen ; *g, g*, glycogen granules occupying part of liver cells ; *g¹*, cell entirely filled with glycogen.

It is important to remember that these fat-bearing cells, both ectoderm and endoderm, have shown signs of marked degeneration since the 10th day, and that previous to that time they gave no fat reaction.

The foetal placenta is now divided into columns, and is rapidly extending deeper into the intermediary region of the maternal placenta. The deep surface of the ectoderm is plasmodial, and this plasmodium extends into processes reaching deeper along the maternal blood-channels.

The plasmodium shows numerous droplets of fat. These droplets are very minute, are scattered in groups, and appear in greatest number in the deeper-reaching processes. They have no special arrangement in regard to the blood-channels. (Fig. 168.)

The cellular ectoderm reveals no fat.

(2) Maternal tissue :—maternal placenta.

Gives no fat reaction

GESTATION SAC OF 14 DAYS.—(FIG. 162.).

(1) Foetal tissue :—foetus and foetal placenta.

The foetus shows no fat.

The membranes are still rich in fat droplets. The deep plasmodial margin of the foetal placenta is thicker and more irregular. In this plas-



FIG. CLII.

(24 days' Gestation showing Glycogen.)

Section of a vessel in the "zone of separation" (maternal placenta.) The glycogen granules lie within the decidua cells in a perinuclear zone. The endothelium is thickened.

v, vessel with blood-clot; *e*, endothelium; *g,g,g,g,g*, glycogen-granules in the uninucleate decidua cells.

modium the fat droplets are larger than at the 12th day and much more numerous. These droplets often lie in rows along the very edge of the plasmodium and close to the multinucleate cells, also they occur in greater number near the maternal blood-channels. (Fig. 163.)

The main mass of the foetal placenta reveals no fat.

(2) Maternal tissue :—maternal placenta.

Fat appears now for the first time in the maternal placenta and in two situations. The multinucleate decidua cells which lie close to the

plasmodial edge of the foetal ectoderm show small fat-droplets. These droplets lie in the cytoplasm scattered irregularly through the cell. (See Fig. 163.) Only the cells that lie close to the foetal plasmodium contain fat, and these cells show no signs of degeneration. The endothelium of the superficial uterine sinuses has multiplied, and at this date, as we have shown in Section (A), consists of several layers of large, round or oval cells.

These endothelial cells contain fat. The droplets here also lie in the cytoplasm, but they are small, segregated and with blurred outline.

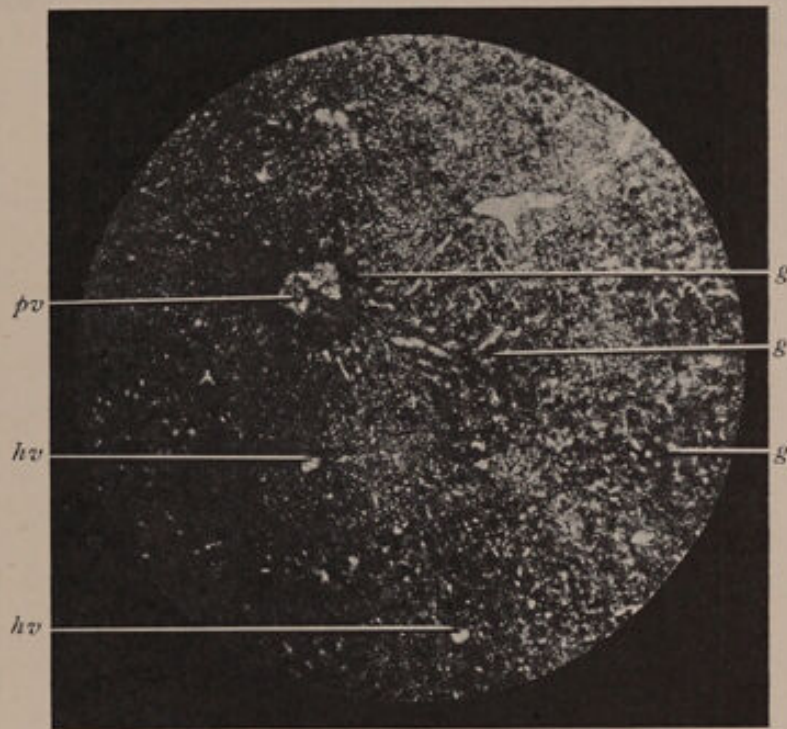


FIG. CLIII.

(26 days' Gestation showing Glycogen.)

Foetal liver. The darker areas are due to the glycogen granules. The glycogen is more abundant close to the vessels, both portal and hepatic, and the larger granules lie closer to the vessels.

pv, portal vein; *hv*, *hv*, hepatic vein; *g*, *g*, *g*, granules of glycogen.

(Fig. 164.) These endothelial cells are in process of degeneration and are already being detached from the sinus wall. The main body of the maternal placenta shows no fat, in all the uninucleate decidual cells there is no trace of it.

GESTATION SAC OF 16 DAYS.

(1) Foetal tissue:—foetus and foetal placenta.

The foetal liver shows now the first appearance of fat since the establishment of the allantoic circulation. The droplets are numerous,

they are of uniform size, and are found evenly distributed throughout the liver substance. The fat lies in the liver cells, but is not collected in any way about the liver vessels, all the zones showing a more or less equal number of droplets. (Fig. 165.)

The foetal placenta is rich in fat, which now is found throughout the inner (distal) third of the ectodermal tubes. The droplets are gathered for the most part into numerous clusters of varying size and well-defined outline which lie within the foetal ectoderm, but are especially numerous close to the blood-channels or along the deep margin of the plasmodium in near relation to the multinucleate decidual cells. (Fig. 166.) These



FIG. CLIV.

(28 days' Gestation showing Glycogen.)

Foetal liver, portal zone. The portal vein is shown with columns of liver cells on either side. The cells nearest the vessel are entirely filled with glycogen.

v, portal vein; *g,g*, two liver cells filled with glycogen; *c,c,c*, semi-lunar deposit of glycogen close to the periphery of three cells.

clusters of fat droplets are often gathered about the persisting nuclei of the plasmodial ectoderm, and are contained within a sharply-defined, more or less translucent, area in the midst of the plasmodium. All stages of this translucency can be observed up to complete vacuolisation where distinct vacuoles appear in the plasmodium containing a greater or less amount of fatty debris. As far as I can observe this aggregation of fat droplets in the foetal plasmodium seems always to determine sooner or later the formation of a vacuole. (Fig. 167.) These vacuoles often arise in the plasmodial wall of a maternal-blood channel, ultimately

communicate with this channel, and so give to the plasmodial wall a dentate appearance.

In the central portions of the ectodermal tubes the fat is scattered in single droplets, while in the proximal or foetal third no fat appears. The "mesodermic villi" show no trace of fat.

(2) Maternal tissue : maternal placenta.

The areas of multinucleate decidual cells which lie island-like or peninsula-like in the foetal placenta, all contain fat. The droplets here are minute, numerous, and scattered regularly throughout the cell. (See Fig. 167.) The nuclei and cell outline of these cells is still distinct.

The multinucleate cells of the intermediary region proper also contain a few sparsely-scattered, very minute fat droplets.



FIG. CLV.

(28 days' Gestation showing Glycogen.)

Two neighbouring uterine sinuses in the maternal placenta with walls of fibrin-lamellæ. Between them is a conglomerate mass of the remains of decidual cells with brown granules of glycogen scattered throughout.

s,s, sinuses walled with fibrin and filled with blood-clot m, mass ; of decidual cells, the brown granules are glycogen.

The large, multiplied endothelial cells which still remain here and there attached to the sinus walls, show numerous clusters of fat droplets. In the more superficial of the uterine sinuses where the detachment is more advanced fibrin-lamellæ are found beneath these endothelial cells.

These fibrin-lamellæ also show the presence of fat, numerous scattered drops which are often gathered, here and there, between the lamellæ, into regular clusters.

The *uninucleate decidual cells* which lie outside these fibrin-lamellæ now contain fat. The droplets are small and not numerous, and only the cells that lie near the fibrin-lamellæ contain them.

Thus we see that fat is found much deeper in the maternal placenta than at the 14th day, though the deeper area of the intermediary region, and the great body of uninucleate cells of the region of the uterine sinuses contain no fat.

GESTATION SAC OF 18 DAYS.—(Fig. 168.)

(1) Fœtal tissue :—fœtus and fœtal placenta.

In the fœtal liver the amount of fat is only slightly increased; the droplets have no arrangement in regard to the blood-vessels. Fat

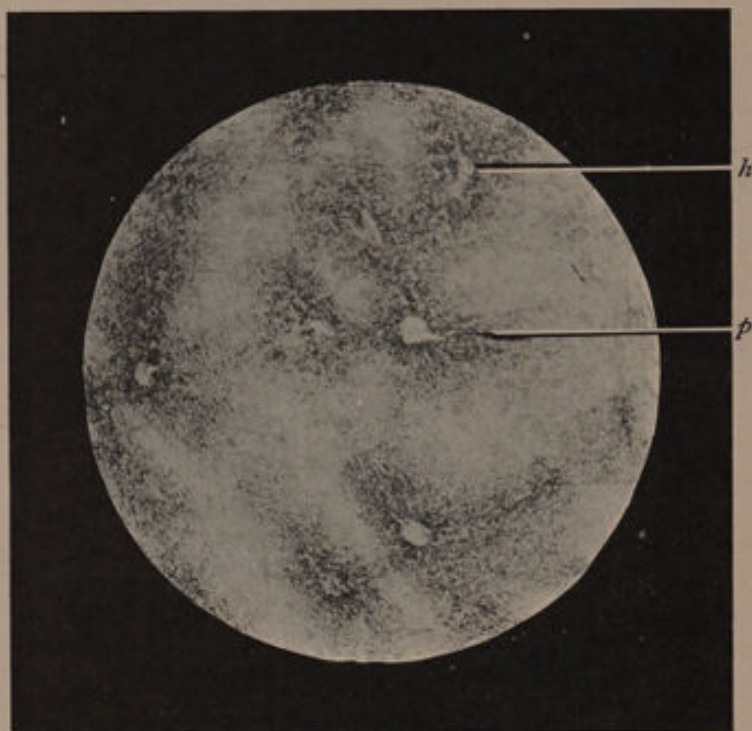


FIG. CLVI.

Liver of rabbit 24 hours old, to show glycogen. The darker areas represent the glycogen and correspond anatomically to the hepatic and portal zones of the liver lobule. The intermediary zones show fainter shadings of glycogen.

p, a portal zone; *h*, an hepatic zone.

droplets are still to be found in the non-placental chorionic ectoderm, especially near the placental margins.

In the fœtal placenta the fat is now more completely confined to the maternal extremities of the *ectodermal tubules*, for the central course of these tubules no longer show the singly-scattered droplets. In these

maternal, or distal, extremities the fat is still found especially abundant close to the margin of the blood-channels and close to the decidual cells, but the droplets are no longer discrete, and are grouped into irregular ill-defined clusters. Many of these clusters appear made up of *fatty granules*, rather than of fat drops. The plasmodial walls which clothe the maternal blood-channels and the peninsula-like areas of decidual cells are thinner and appear pitted. (Fig. 169.) In some of these pits are to be found minute traces of fat, and the appearance would seem to justify the hypothesis that the fat was gradually disappearing from these plasmodial walls, and the small rounded spaces where the fat droplets lay were becoming emptied of their fat, and that thus there is given to the plasmodium this pitted or honey-combed appearance.

The "mesodermic villi" now reach in close to the multinucleate decidual cells, but they show no fat.



FIG. CLVII.

Liver of adult rabbit five hours after a meal to show the glycogen reaction. The glycogen granules are larger and more numerous near the vessels and they lie for the most part close to the nucleus of the cell.

c,c,c, columns of liver cells; *v*, hepatic vein; *g,g,g*, glycogen granules.

(2) Maternal tissue :—maternal placenta.

The multinucleate decidual cells are richer in fat than at the 16th day. The droplets are larger and more numerous, especially in the *areas* lying in the foetal placenta. (See Fig. 169.) The outline of these cells is no longer sharp and distinct. The greater number of the multinucleate cells of the intermediary region show the presence of fat.

In the region of the uterine sinuses fat has also increased in quantity, traces of it being found down to the zone of separation. The drops lie between the fibrin-lamellæ which now wall the sinuses, and in a narrow zone of uninucleate decidual cells which lie immediately outside the lamellæ.

GESTATION SAC OF 20 DAYS.—(FIG. 170.)

(1) Fœtal tissue :—fœtus and fœtal placenta.

In the fœtal liver the fat drops are little larger, but they are more numerous than at the 18th day. The liver cells are now more distinct,

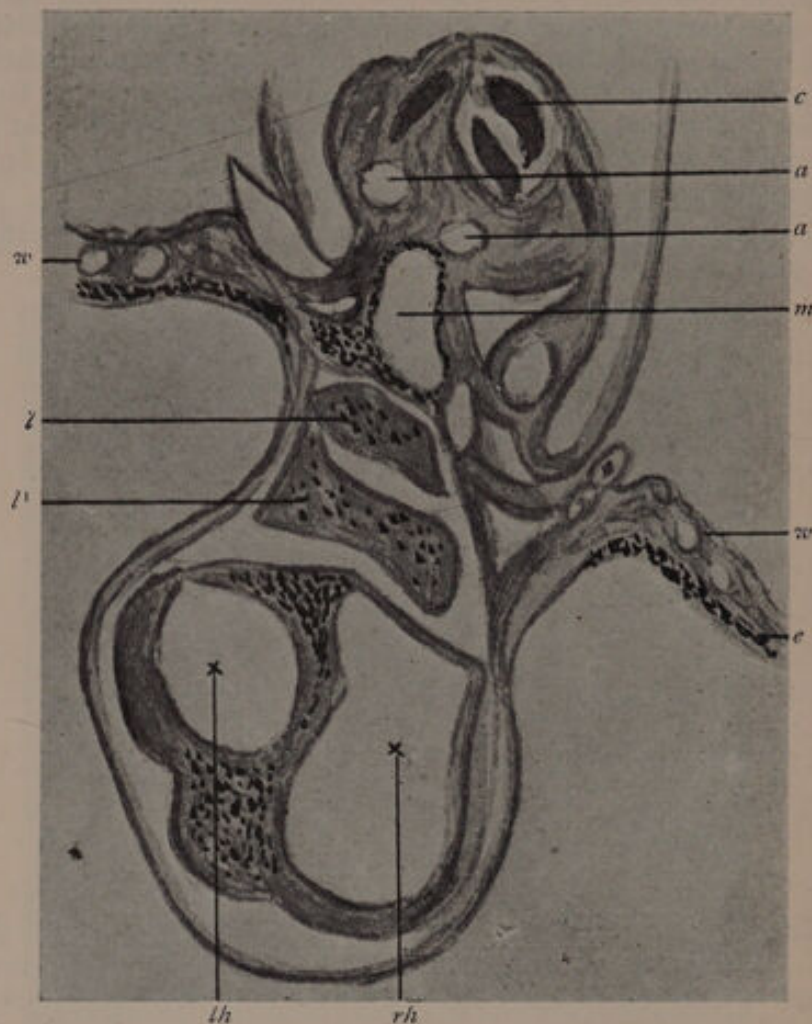


FIG. CLVIII.

(10 days' Gestation showing Fat.)

Drawing of transverse section of fœtus at the level of the newly-formed liver. Minute black droplets (fat?) are seen in the walls of the mesenteron, in the heart and liver and in the endodermal cells of the vascular wall of the yolk-sac. This is the first appearance of fat in the fœtus.

w, w, vascular wall of yolk-sac; *e*, endodermal cells with minute fat droplets; *m*, mesenteron; *lh*, left side of heart; *rh*, right side of heart; *l*, liver; *a, a*, aortæ; *c*, spinal cord.

and the droplets lie within them. The tubules of the fœtal placenta are now almost entirely plasmodial, but they are free of fat, save at their

maternal or distal extremities. Indeed the fat drops which are large and of irregular size are found in a very narrow zone along the deep margin of the plasmodium. (Fig. 171.) The plasmodial walls of the tubules are thin and at their distal extremities, where fat has previously been present their edges are still pitted and ragged. At this date there is very little fat in the foetal placenta.

(2) Maternal tissue :—maternal placenta.

In the maternal placenta fat shows itself in maximum quantity at this date.

The multinucleate decidual cells, both in the areas which lie *island- and-peninsula-like* in the foetal placenta, and in the areas which are

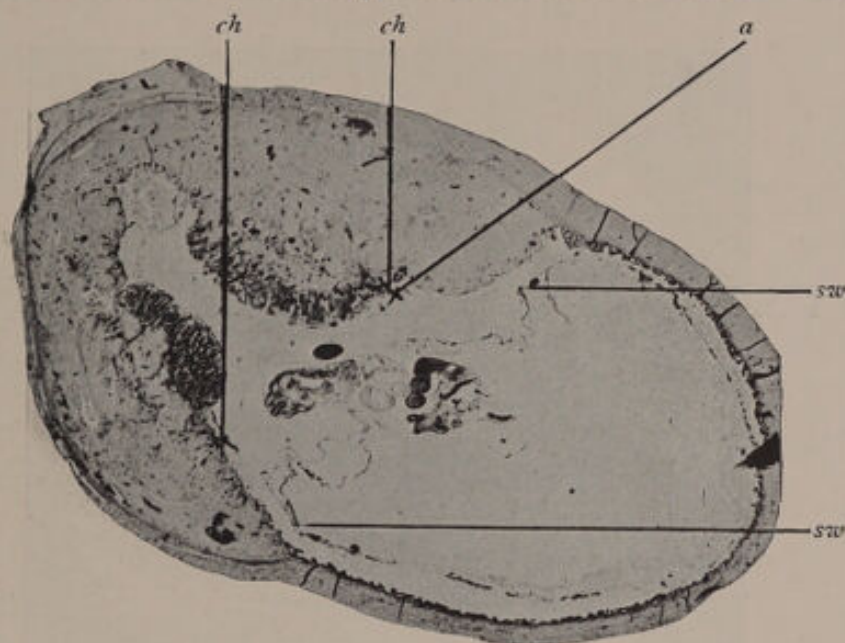


FIG. CLIX.

(12 days' Gestation showing Fat-area.)

Transverse section of gestation sac of 12 days showing the membranes wherein are found fat droplets.

ch, ch, extra-placental chorion (See Fig. 160); *a*, area shown in Fig. 160; *sw, sw*, superior (vascular) wall of yolk-sac, the endodermal cells contain many fat droplets. (Photo.)

found between the uterine sinuses, contain many and large fat droplets. (See Fig. 171.)

These cells are beginning to show signs of degeneration, their cytomitoma is swollen and indistinct and their contents appear granular. In the midst of this granular cytoplasm the fat droplets lie, while also there are found here irregular and large fat-bearing granules, a fatty debris.

The large uterine sinuses now lie close to the deep surface of the foetal placenta, and are walled by thick layers of fibrin-lamellæ. Fat

droplets are plentiful between these lamellæ, while in the uni- and multi-nucleate decidual cells, crowded together outside these, granules and droplets of fat abound. (Fig. 172.) This fat has no specified distribution, and all the tissues of the maternal placenta now contain it. It is found throughout the whole depth of the region of the uterine sinuses, but the *separation zone* reveals no trace of it.

GESTATION SAC OF 22 DAYS.

(1) Foetal tissue :—foetus and foetal placenta.

¹¹⁸³₁₇₃ The foetal liver is richer in fat than at the 20th day, but the droplets are less evenly distributed throughout the lobule. (Fig. 173.)

In the sub-cutaneous tissue fat now appears for the first time. The

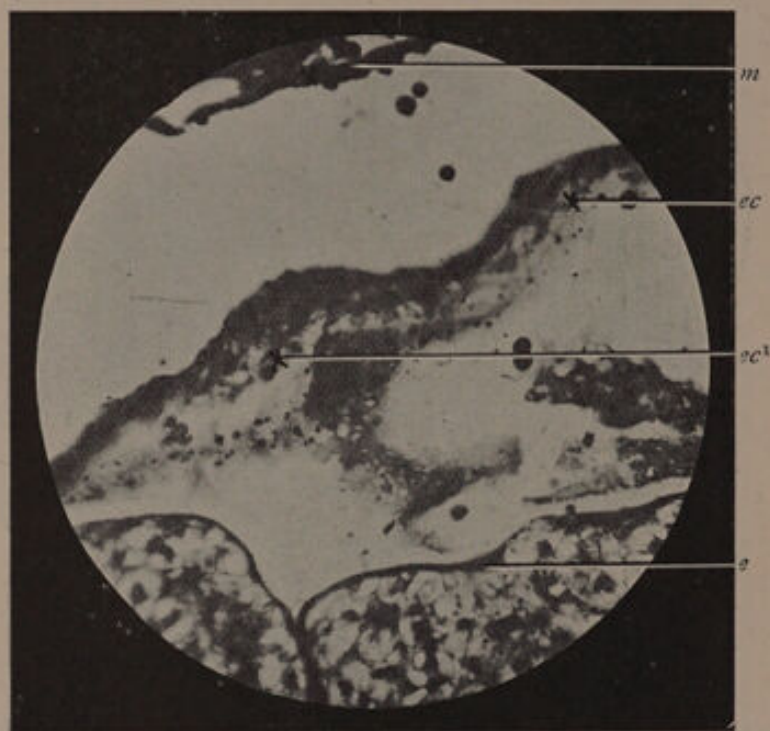


FIG. CLX.

(12 days' Gestation showing Fat.)

Extra-placental chorion near the placental margin. The ectodermal cells are degenerating and show fat droplets. The mesoderm shows no fat.

e, thinned epithelium (maternal) covering the placental cotyledon just beyond the attachment of the placenta; *ec*, *ec¹*, ectodermal cells with numerous fat droplets; *m*, mesoderm.

fat cells are very few, and are found grouped round the small vessels close to the underlying muscle. (Fig. 174.)

The foetal placenta is now almost free from fat, only a few minute droplets being found in the plasmodial margin close to the maternal placenta.

The maternal placenta contains a large quantity of fat, its character, droplets and granules, and its distribution are the same as at the 20th day. The multinucleate decidual cells are now markedly degenerate, their cytoplasm being definitely granular and cell-outline lost. I give a microphotograph (Fig. 175) of an area of these cells, lying island-like in the midst of the foetal placenta. The degeneration is evident, and also the large quantity of fat as droplets or granules, which these areas

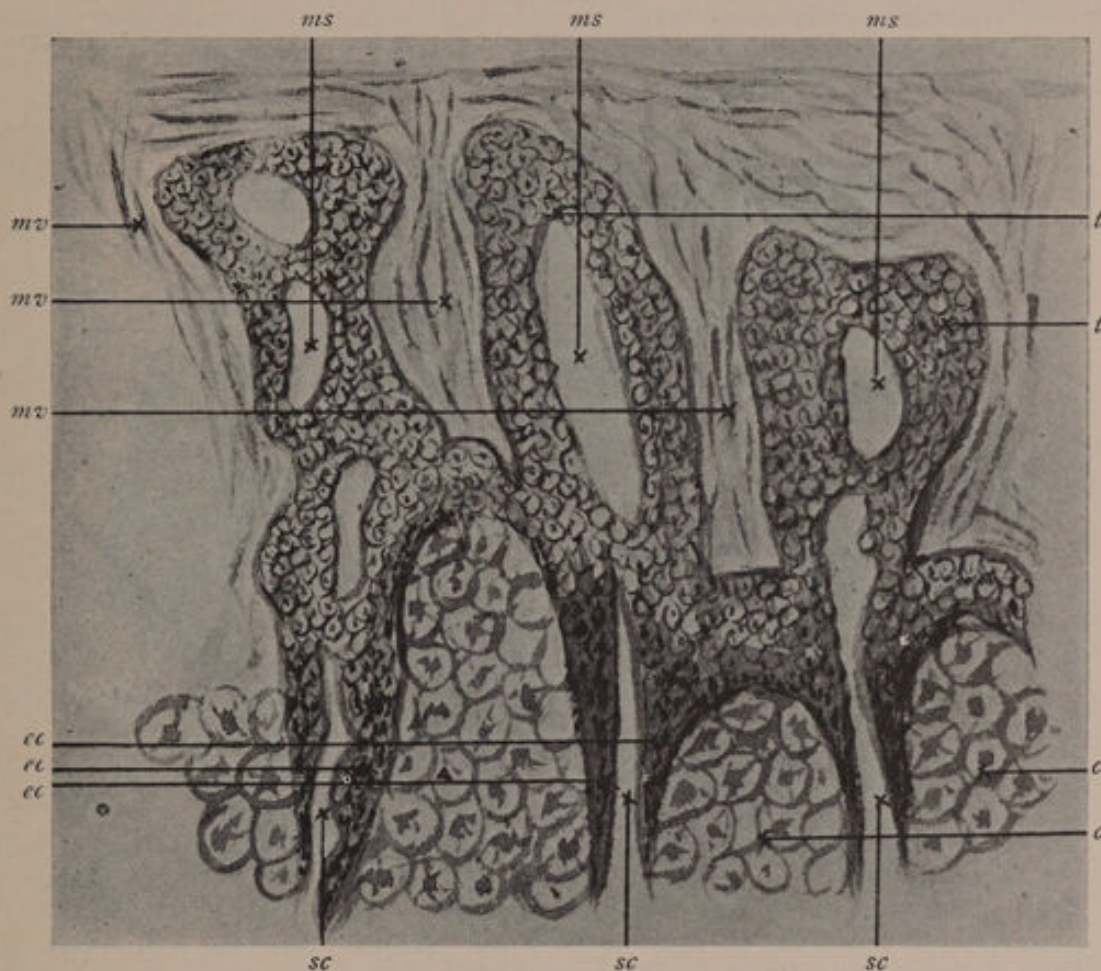


FIG. CLXI.
(12 days' Gestation showing Fat.)

Foetal placenta with part of the intermediary region of maternal placenta. Fat droplets are found in the plasmodial edge of the ectoderm and are more numerous near the blood-channels.

c,c, multinucleate decidual cells (maternal); *t,t*, ectodermal tubes or columns of the foetal placenta; *ms,ms,ms*, maternal blood spaces in the axes of the columns; *mv,mv,mv*, mesodermic villi; *ec,ec,ec*, plasmodial edge of ectoderm with fat droplets; *sc,sc,sc*, maternal sinus-capillaries.

contain. In the region of the uterine sinuses the fat is less abundant, but is distributed as at the 20th day, while the separation zone still remains entirely free.

GESTATION SAC OF 24 DAYS.

(1) Foetal tissue :—foetus and foetal placenta.

In the foetal liver the quantity of fat is increasing but there is no definite distribution.

In the sub-cutaneous tissue the fat cells are found in large definite clusters round the vessels and close to the parietal muscle. (Fig. 176.)

The corium shows no fat.

The foetal placenta is now entirely free of fat, even its plasmodial margin showing no droplets.

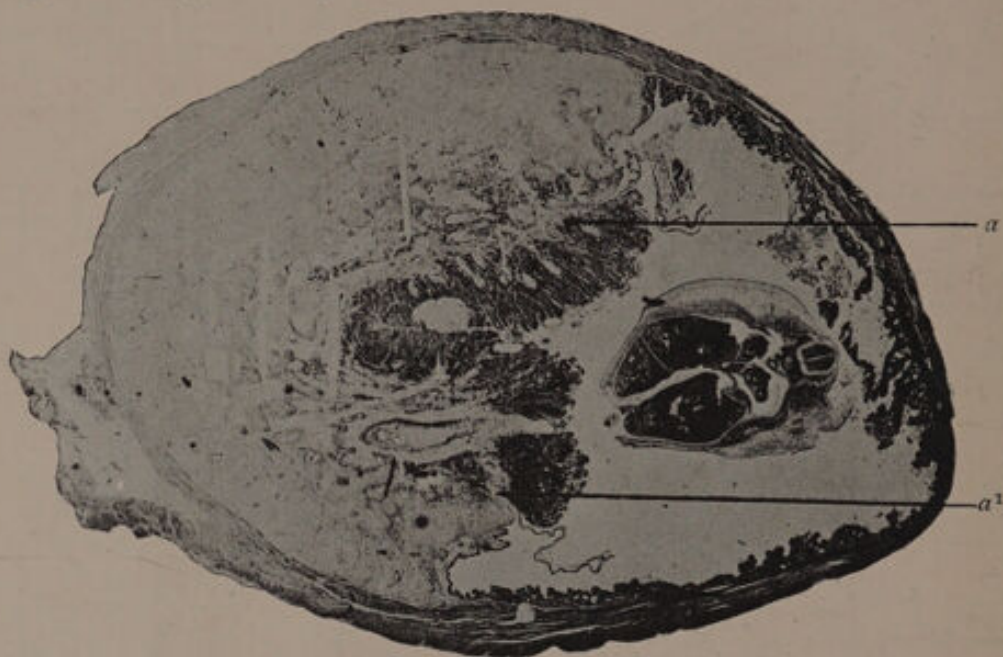


FIG. CLXII.

(14 days' Gestation showing Fat-area.)

Transverse section of gestation sac of 14 days. Fat is found in the deep plasmodial margin of the foetal placenta. (See Fig. 163.) In the maternal placenta fat is present in small quantity in two situations. (See Figs. 163 and 164.)

a, a¹, plasmodial edge of foetal ectoderm.

(Photo.)

(2) Maternal tissue :—maternal placenta.

The maternal placenta now consists of large sinuses surrounded by fibrinous tissue, in the midst of which appears the debris of the decidual cells with numerous granules and droplets of fat.

The separation zone now also shows fat. It occurs as droplets which are found in the swollen endothelial cells of the small sinuses. The surrounding decidual tissue is fat free.

GESTATION SAC OF 26 DAYS.

(1) Foetal tissue : foetus and foetal placenta.

In the foetal liver the fat has increased and while the droplets are

scattered throughout the lobule, for the first time they appear larger and more numerous close about the vessels.

In the sub-cutaneous tissue the fat is more abundant than at the 24th day, and now it makes its first appearance in the corium or true skin. In the corium the droplets lie about the hair follicles. The foetal placenta shows no fat.

(2) Maternal tissue :—maternal placenta.

Microphotograph (Fig. 177) shows the cellular debris of the decidual cells and fibrinous tissue, found between the uterine sinuses. The fat

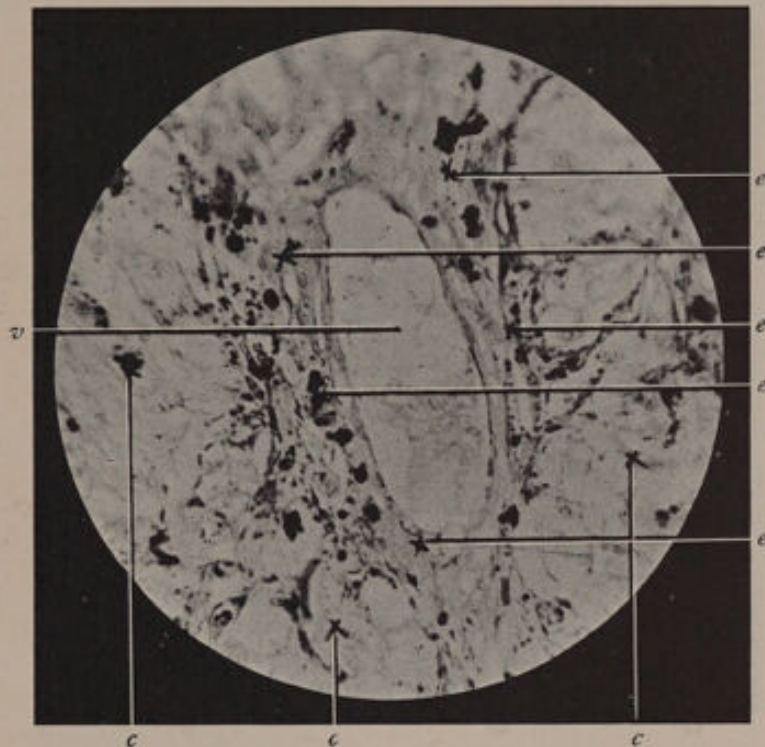


FIG. CLXIII.

(14 days' Gestation showing Fat.)

Shows plasmodial edge of ectoderm containing numerous fat drops. This foetal ectoderm has completely surrounded a maternal vessel from which the endothelium has disappeared. Multinucleate decidual cells of the maternal placenta show few fat droplets.

v, maternal vessel surrounded by foetal ectoderm ; e,e,e,e,e, advancing plasmodial edge of ectoderm ; black fat drops are numerous and large ; c,c,c, decidual cells with small fat droplets.

occurs here for the most part in the form of granules. In the zone of separation the sinus-endothelium shows an increased number of fat droplets.

GESTATION SAC OF 28 DAYS.

(1) Foetal tissue :—foetus and foetal placenta.

The foetal liver is rich in fat, and there is a certain perivascular distribution of the droplets.

The skin and sub-cutaneous tissue show an increase of fat which is distributed in the same manner as at the 26th day.

In the foetal placenta fat is absent.

(2) Maternal tissue :—maternal placenta.

The amount of fat in the maternal placenta is greatly diminished, though numerous granules and droplets of fat are found in the cellular debris between the uterine sinuses. The sinus-endothelium of the zone of separation shows many small droplets.

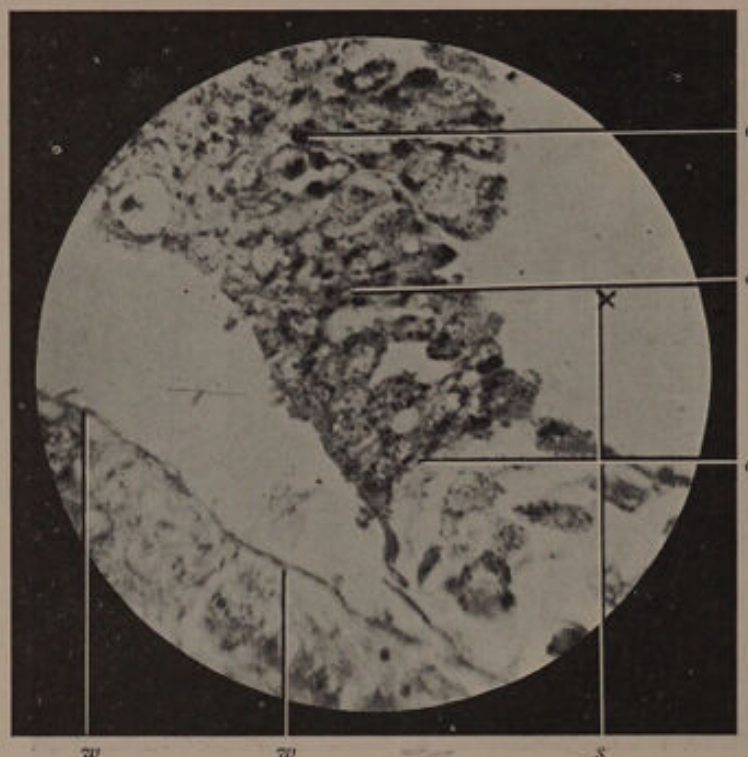


FIG. CLXIV.

(14 days' Gestation showing Fat.)

Superficial sinus in maternal portion of the placenta. The multiplied endothelial cells are degenerate and detached; they contain numerous fat droplets.

s, uterine sinus; *w,w*, sinus-wall from which the endothelium is detached; *c,c,c*, detached endothelial cells, with indistinct cell-outline and minute fat droplets. (cf. fat droplets in Fig. 163.)

GESTATION SAC OF 30 DAYS.

(1) Foetal tissue :—foetus and foetal placenta.

In the foetal liver there is a marked increase of fat since the 28th day, and the droplets are now definitely grouped about both portal and hepatic vessels. (Fig. 178.)

In the skin and sub-cutaneous tissue, especially in the latter, the fat has increased, while maintaining its former distribution. (Fig. 179.)

The foetal placenta is fat free.

(2) Maternal tissue :—maternal placenta.

The fat in the maternal placenta is found now almost entirely in the form of a fatty débris scattered between the large sinuses. A few fat droplets are also found here. The total amount of fat is comparatively small.

In the separation zone the sinus endothelium is greatly swollen, and the cells are rich in minute fat droplets.

RABBIT 24 HOURS OLD.

Rabbit 24 hours old : it had suckled. The liver is exceedingly rich in fat, the cells of the hepatic and portal zones being simply

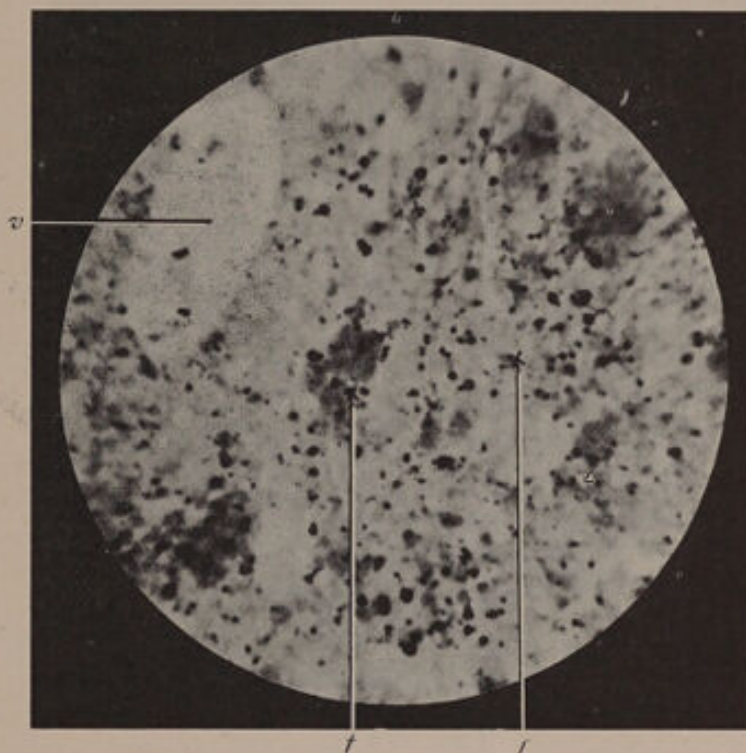


FIG. CLXV.

(16 days' Gestation showing Fat.)

Fœtal liver, showing numerous fat drops which lie within the cells and are evenly distributed throughout the liver lobule.

v, hepatic vessel ; f, fat drops.

crowded with the droplets. As far as my observations have gone, the rabbit's liver at, or about, this time gives a maximum fat-reaction.

The skin and sub-cutaneous tissue are richer in fat than at any period during intra-uterine life. (Fig. 180.)

ADULT RABBIT.

Adult rabbit : five hours after a meal. The liver shows only a few scattered droplets which lie in the cells near the vessels.

The sub-cutaneous tissue is rich in fat (the rabbit was a fat one) and the increased size of the fat cells as compared with those of a rabbit 24 hours old is evident.

The corium also contains a large number of fat cells, still arranged about the hair follicles.

SUMMARY OF FAT.

The fœtus. Liver. At the 10th day minute droplets of fat (or of a substance stained black with osmic acid) are found

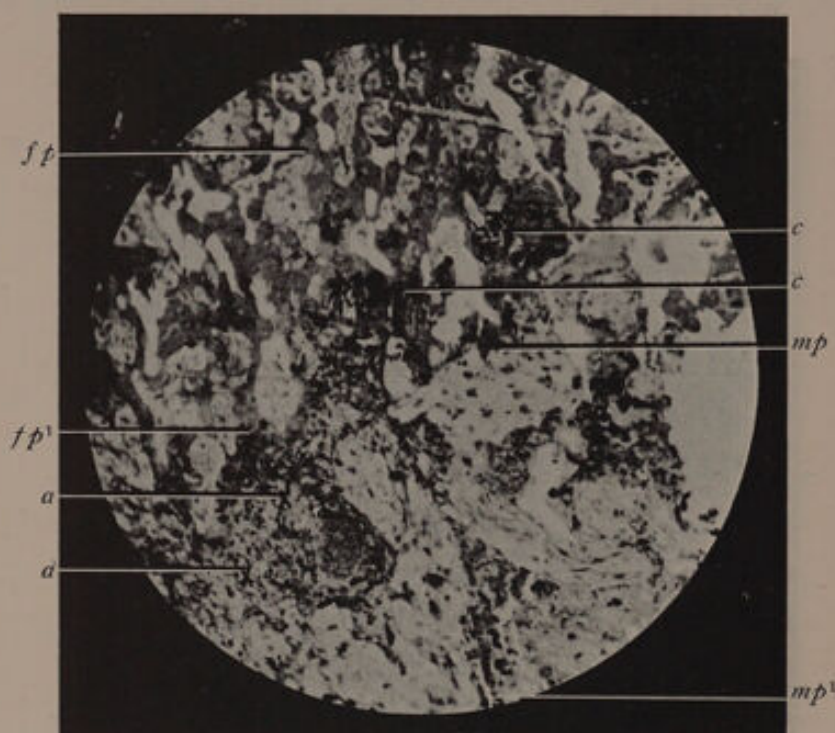


FIG. CLXVI.

(16 days' Gestation showing Fat.)

Distal extremities of ectodermal "tubes" of fœtal placenta and their junction with maternal placenta. In these "tubes" the fat lies in clusters close to the blood-channels. The multinucleate decidual cells of maternal placenta show some fat.

fp, fp¹, fœtal placenta; *mp, mp¹*, maternal placenta; *c, c*, clusters of fat in ectodermal "tubes"; *d, d*, droplets of fat in decidual cells.

in the viscera of the fœtus. These droplets are not visible at the 12th day and fat does not reappear until the 16th day, 6 days after the establishment of the allantoic circulation, and then only in the liver. In the liver the fat droplets are at first scattered evenly throughout the liver substance, lying always

in the liver cells. From its appearance at the 16th day the fat in the liver increases steadily in amount, and at the 26th day it first shows a certain perivascular distribution, being gathered about both portal and hepatic vessels. At the 30th day the liver is richer in fat than at any other period of intra-uterine life, while in the liver 24 hours after birth, there is a further increase in the amount of fat. The adult liver is comparatively poor in

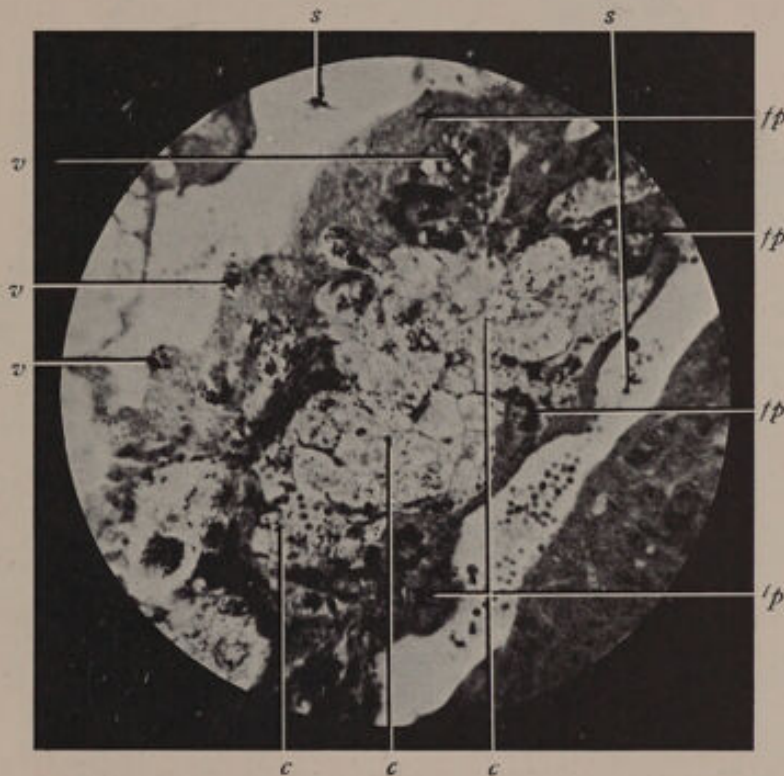


FIG. CLXVII.

(16 days' Gestation showing Fat.)

Area of multinucleate decidua cells projecting peninsula-like into the foetal plasmodium ; both it and the decidua cells contain fat.

c,c,c, area of decidua cells with droplets of fat ; *fp,fp,fp,fp*, foetal ectoderm (plasmodial) showing clusters of fat drops ; *s,s*, maternal blood-channels ; *v,v,v*, vacuoles in foetal plasmodium.

fat, and the amount is much more constant in relation to meals, than is that of glycogen.

Sub-cutaneous tissue: cutis vera. Fat first appears in the sub-cutaneous tissue at the 22nd day, the fat cells occurring in groups about the vessels and close to the parietal muscular layer. The number of these fat cells steadily

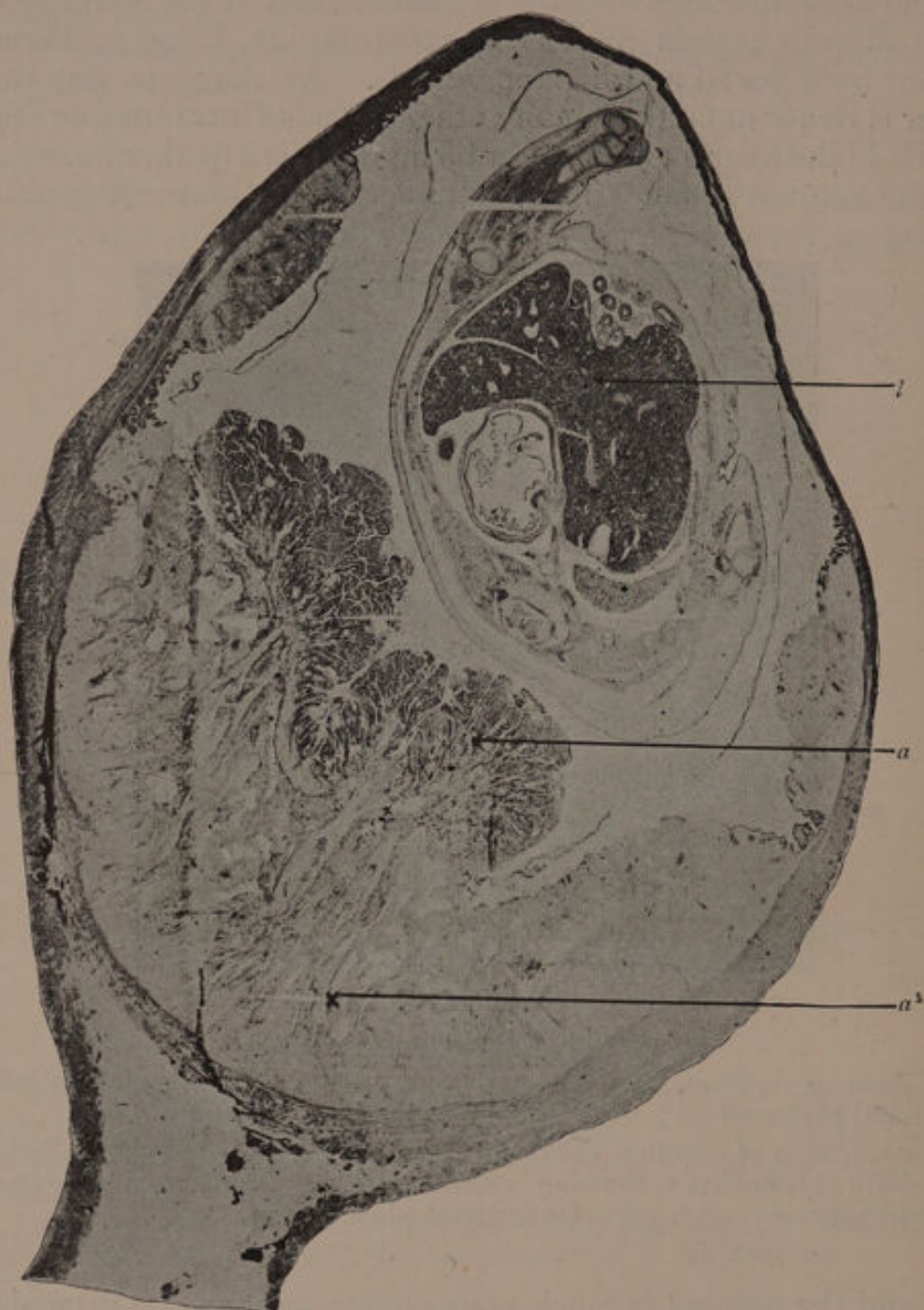


FIG. CLXVIII.

(18 days' Gestation showing Fat-area.)

Transverse section of gestation sac of 18 days. The fat-containing areas are indicated.

a, a', area of placenta where fat is found; *l*, foetal liver richer in fat than at the 16th day. (See Fig. 165.) (Photo.)

increases, and at the 26th day they appear also in the cutis vera lying in small clusters about the hair follicles. In both situations the fat cells become more numerous and increase in size up to the close of intra-uterine life. 24 hours after birth they have further increased, while in the adult rabbit (plump ones were always examined) the fat cells of the sub-cutaneous tissue form a definite stratum and are of much larger size.

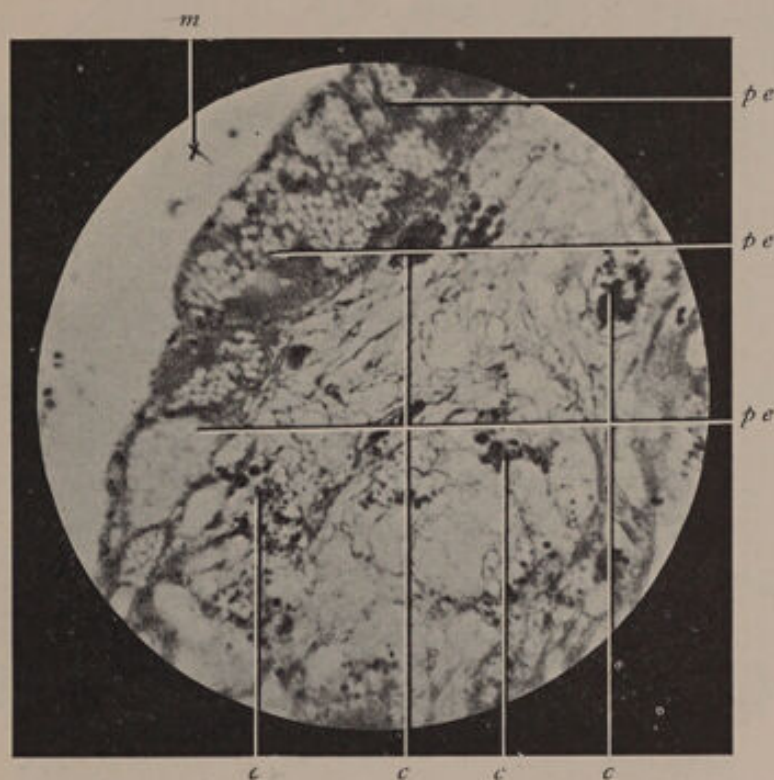


FIG. CLXIX.
(18 days Gestation showing Fat.)

A peninsula-like area of decidual cells with a covering of plasmodial ectoderm—the junction of the foetal and maternal portions of the placenta near a maternal blood-channel. The plasmodium has a pitted appearance and shows few fat droplets. The decidual cells have lost their cell-outline and the fat drops are gathered into groups.

m, maternal blood-channel; *pe, pe, pe*, plasmodial ectoderm; *c, c, c, c*, clusters of fat in the midst of decidual cells.

The Foetal Placenta. Fat first appears here at the 12th day, small droplets showing themselves in the deep plasmodial margin of the ectoderm, next the maternal placenta. These droplets have no special relation to the blood-channels, for they are quite as numerous opposite the non-vascular areas

of multinucleate decidual cells. At the 14th day the droplets are larger and more numerous, and at the 16th day they are

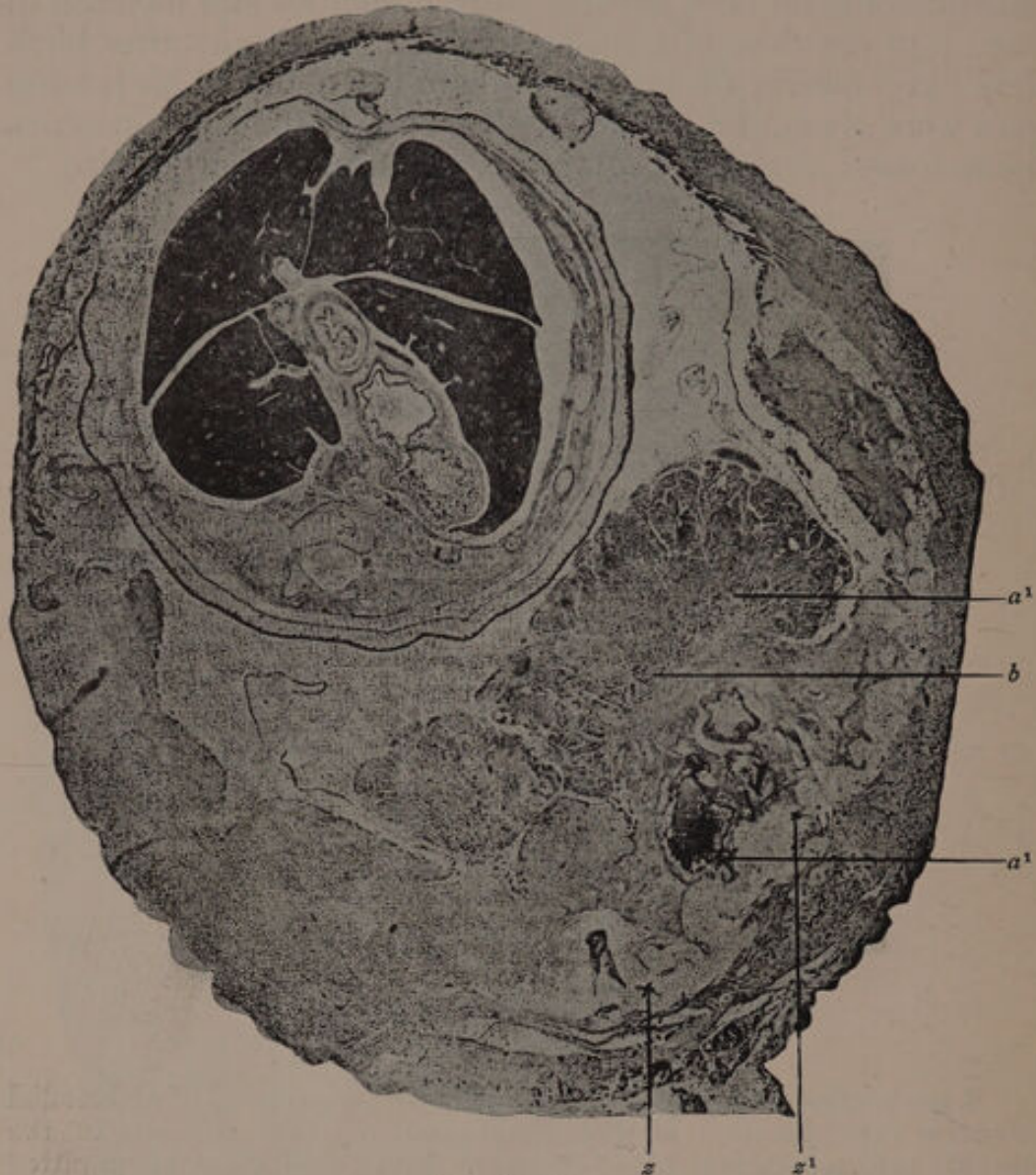


FIG. CLXX.

(20 days' Gestation showing Fat area.)

Transverse section of gestation sac of 20 days. The fat-containing area is shown, viz. : the maternal extremities of the foetal tubules and the whole of the maternal placenta down to the "separation zone."

a, a', fat-containing area ; *b*, area shown in Fig. 171 ; *s, s'*, separation zone. (Photo.)

found throughout the inner or distal third of the ectodermal tubes. The maximum quantity of fat is found at this date,

and the droplets are gathered into clusters, which lie for the most part close to the blood-channels of the foetal placenta. From this time onward the droplets are less numerous, they lose their regular outline, and appear more of the nature of granules, while they become steadily fewer and more and more closely restricted to the distal extremities of the ectodermal tubules. At the 24th day all trace of fat disappears from the foetal placenta.

The "mesodermic villi" never show fat.

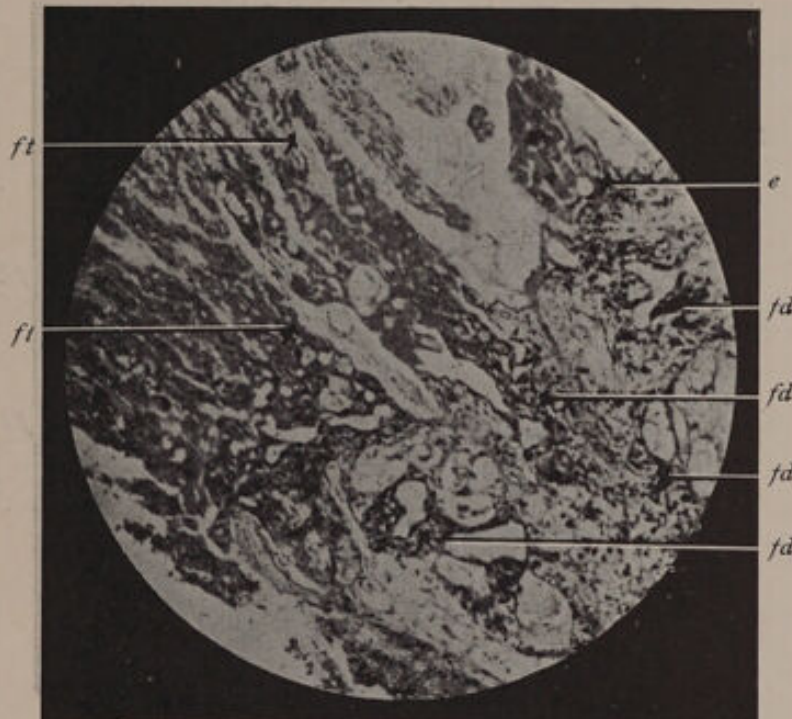


FIG. CLXXI.

(20 days' Gestation showing fat.)

Junction of foetal and maternal portions of the placenta. Fat is seen in the maternal extremities of the foetal "tubules" and in the intermediary region, lying in clusters about the maternal blood spaces.

ft, ft, foetal "tubules" (no fat); *e*, maternal extremity of "tubule" which contains fine fat droplets; *fd, fd, fd, fd*, clusters of fat drops, more numerous near vessels and lying in the uninucleate cells of intermediary region.

The Maternal Placenta. Fat first appears here at the 14th day, and in two situations, viz. :—in the multinucleate decidual cells lying close to the deep surface of the foetal placenta, and in the proliferating endothelial cells of the

superficial uterine sinuses. I have drawn attention to the differences of the appearance of the fat in the two situations (see Page 131 : Section (C)). At the 16th day a large number of the multinucleate decidual cells contain fine fat droplets, especially those areas which lie island- or peninsula-like in the foetal placenta. The fibrin-lamellæ of the superficial uterine sinuses and the uninucleate decidual cells immediately outside them now also contain fat. The amount of fat

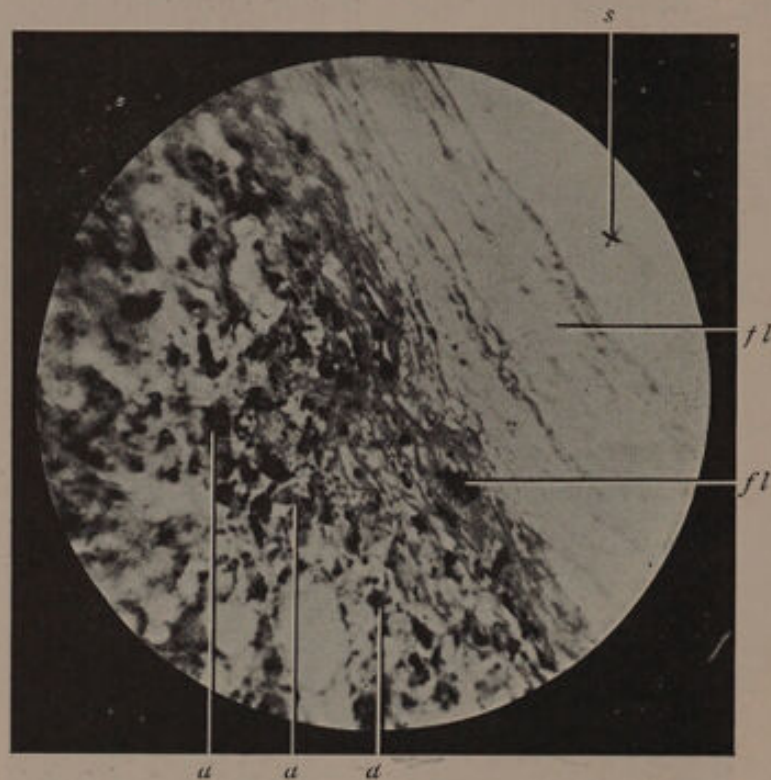


FIG. CLXXII.

(20 days' Gestation showing Fat.)

Maternal placenta—section of uterine sinus. Fat drops lie among the more external of the fibrin-lamellæ and in the midst of the multi- and uninucleate decidual cells.

s, uterine sinus, its endothelium has disappeared; *fl, fl*, fibrin-lamellæ; *d, d, d*, fat drops in the midst of uni- and multinucleate decidual cells.

steadily increases, and the droplets which were only found at first close to the foetal placenta come to occupy the deeper regions of the maternal placenta. At the 20th day the maternal placenta is richest in fat; the droplets lie in the multinucleate and uninucleate decidual cells, and between the fibrin-lamellæ, and are arranged in definite zones about the

uterine sinuses. With the subsequent atrophy of the decidual cells the fat, while maintaining its definite distribution gradually decreases in amount, and at the end of gestation it appears no longer in well-formed droplets but merely as a fatty débris.

The separation zone remains free from fat, save the thickened endothelial cells of its narrow sinuses, where minute droplets appear at the 24th day, and persist till the end of gestation.

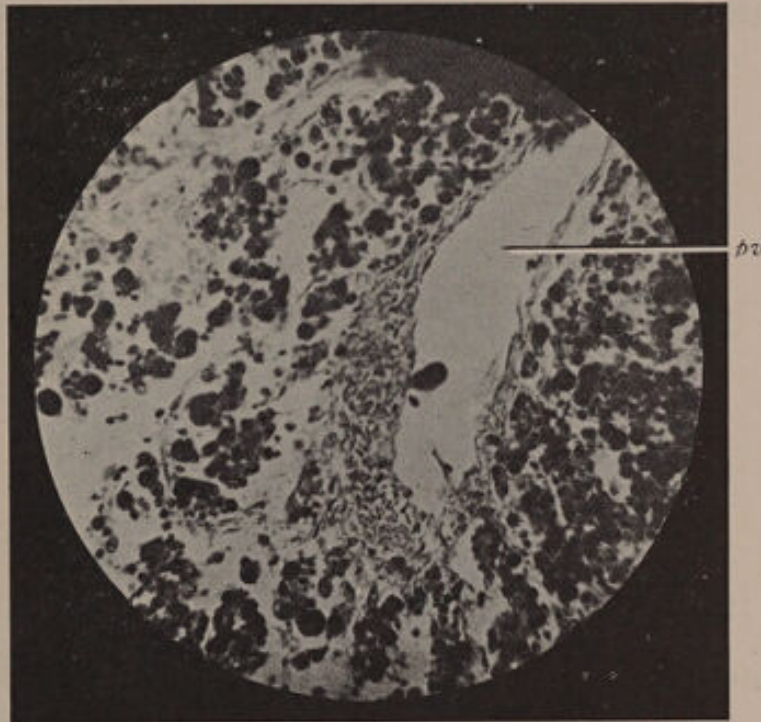


FIG. CLXXIII.

(22 days' Gestation showing Fat.)

Fœtal liver showing fat ; a portal vessel and zone are shown. The fat drops are larger and more numerous near the vessels.
pv, portal vessel.

The following is the sequence of the appearance of fat in the placenta and fœtus after the establishment of the allantoic circulation :—

Fat appears in the fœtal placenta at the 12th day.

Fat appears in the maternal placenta at the 14th day.

Fat appears in the fœtal liver at the 16th day.

Fat appears in the sub-cutaneous tissue of the fœtus at the 22nd day.

SECTION D.

IRON AS FOUND IN PLACENTA AND FŒTUS.

Method followed. The gestation sacs were incised and treated in the same way as the glycogen preparations (section B), and the specimens afterwards fixed for a further 12 hours in absolute alcohol. In the subsequent treatment I have employed in every case two methods: the hæmatoxylin method of Macallum (*Journ. Phys.*, Vol. XXII, page 92, Sept. 1897) and the acid ferrocyanide method of Tizzoni (*Outlines*

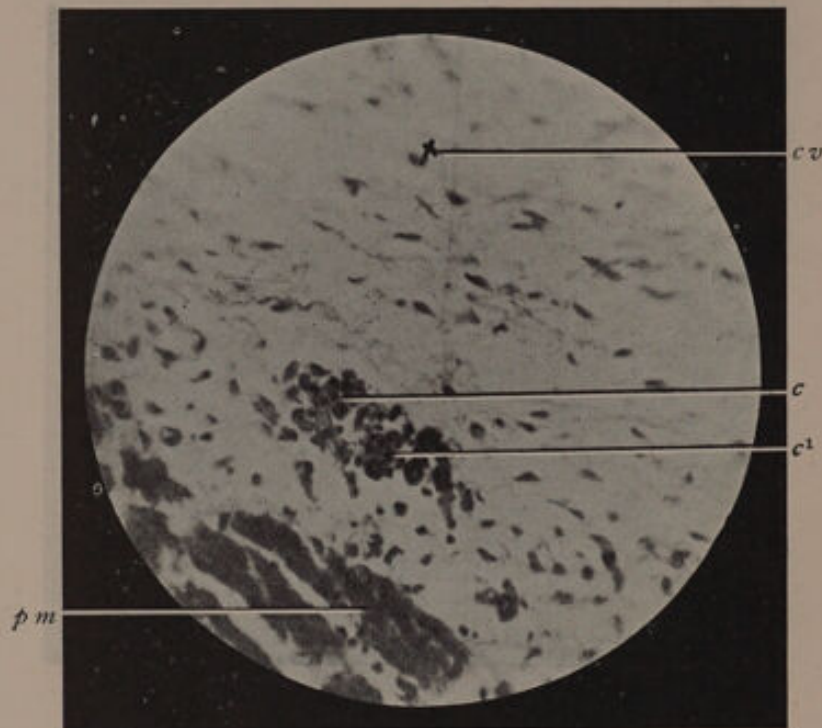


FIG. CLXXIV.

(22 days' Gestation showing Fat.)

Sub-cutaneous tissue of foetus; the first appearance of fat-cells in the somatopleure.

cv, cutis vera; *pm*, parietal muscle; *c, c¹*, cluster of fat cells.

of Practical Histology; Stirling, page 243; 1890) as somewhat modified by Sheridan Délepine (*Proc. Phys. Soc.*, May 10, 1891). In both methods great care was taken to avoid all contamination of the specimens, no iron or steel instrument, and only the purest solutions being used. The results of the two methods I have always found corroborative, but

in neither are the specimens available for microphotography. In the hæmatoxylin method the iron appears in distinct granules, which can be always accurately localised, while with the acid ferrocyanide, if the granules be not abundant, the iron reaction appears merely as a wash diffused through the tissues.

Macallum's method. After being fixed in absolute alcohol the specimens were embedded, cut and mounted in

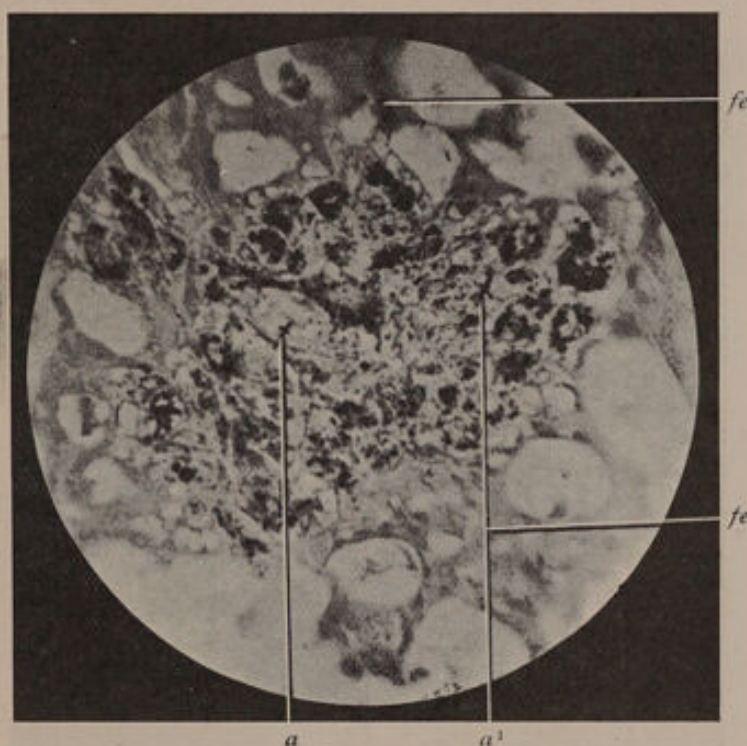


FIG. CLXXV.

(22 days' Gestation showing Fat.)

Area of multinucleate decidual cells lying island-like in the foetal placenta. Cell-outline is indistinct and the fat is found in clusters of droplets and granules throughout the area.

fe, fe, foetal ectoderm with numerous blood-channels, no fat ; *a, a¹*, area of decidual cells (degenerate) with numerous fat droplets.

the usual way. The paraffine was washed off with naphtha, and this in its turn with alcohol. The sections were then placed in a 0.5% watery solution of hæmatoxylin "for a few minutes"—(I found it advantageous to stain in the solution for 12 hours)—and afterwards were cleared in clove oil and mounted in balsam.

This method is very delicate, and the results are permanent; the iron is stained a blue-black and the tissues a brownish-yellow.

With this method, as above described, the *inorganic* iron compounds alone appear. I have used the hæmatoxylin for the detection of the organic compounds, previously steeping the section for from 1-12 hours in a 4% solution of sulphuric acid in alcohol, in order to convert the organic iron into an inorganic form. Though I have closely followed

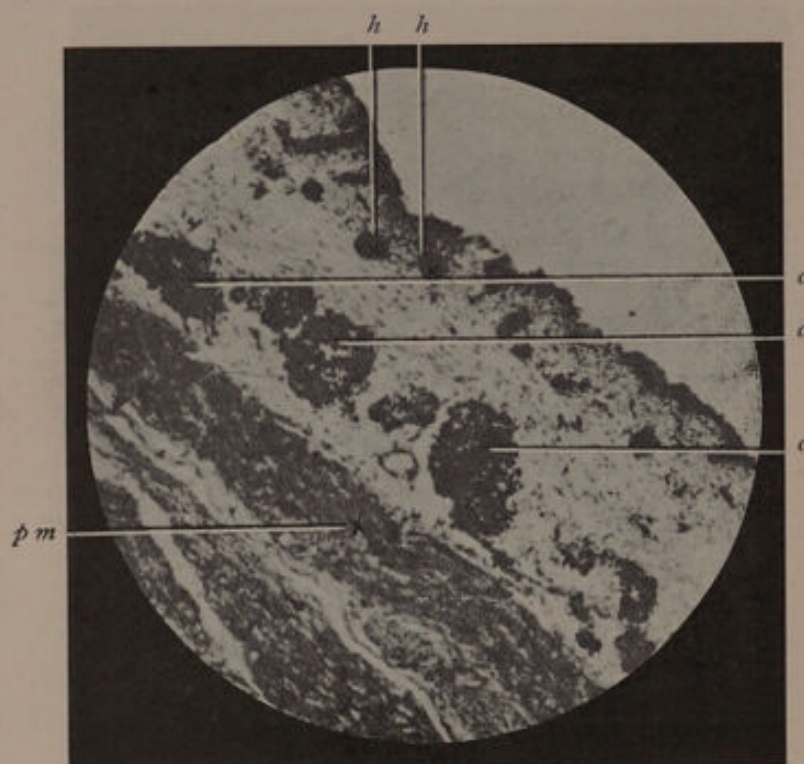


FIG. CLXXVI.
(24 days' Gestation showing Fat.)

Fœtal skin and subcutaneous tissue. The fat cells are in clusters about the vessels of the subcutaneous tissue. The cutis vera is fat-free; the hair follicles are distinct.

p, m, parietal muscle; *c, c, c*, clusters of fat cells; *h, h*, hair follicles.

Macallum's directions here, the results obtained have not been satisfactory, and in the present study it is the inorganic compounds alone that I shall describe.

Tizzoni's method slightly modified by Délépine.

Délépine claims (*loc. supra*) that if fresh tissues be soaked for several days in a mixture of equal parts of glycerine

and alcohol they will give a brighter iron reaction. I have found that an immersion of even one day renders the tissue so brittle that it can scarcely be cut at all with the Cambridge rocker, and the iron reaction is always decisive where as fixing agent the absolute alcohol alone is used.

After the naphtha has been washed off with methylated spirit the slide is placed for from five minutes to half an hour in a 5% watery solution of ferrocyanide of potash. It is then washed in water and placed in a .85-1% solution of

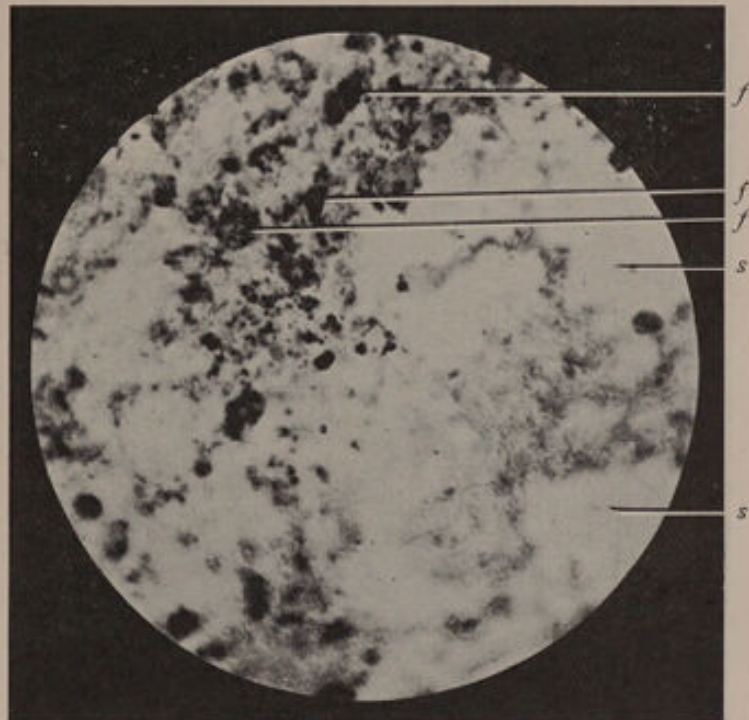


FIG. CLXXVII.

(26 days' Gestation showing Fat.)

Region of uterine sinuses. Fat drops and granules in the midst of a conglomerate tissue composed of fibrin, uni- and multinucleate decidual cells.

s,s, uterine sinuses ; f,f,f, fat granules and droplets.

hydrochloric acid for five minutes. Again wash in water (the sections may now be advantageously stained in alum carmine), dehydrate, clear and mount in balsam. The iron gives the reaction of prussian blue.

This method is perhaps not so delicate a test as Macallums' and the specimens are not permanent.

In the following study of iron I shall simply mention all negative results, and in the descriptions I shall maintain the same order as in Sections (A), (B) and (C), viz.:—

(1) Foetal tissue—foetus and foetal placenta.

(2) Maternal tissue—placental mucosa or maternal placenta.

In illustration of my observations I have been obliged to employ drawings only, for I have not succeeded by any

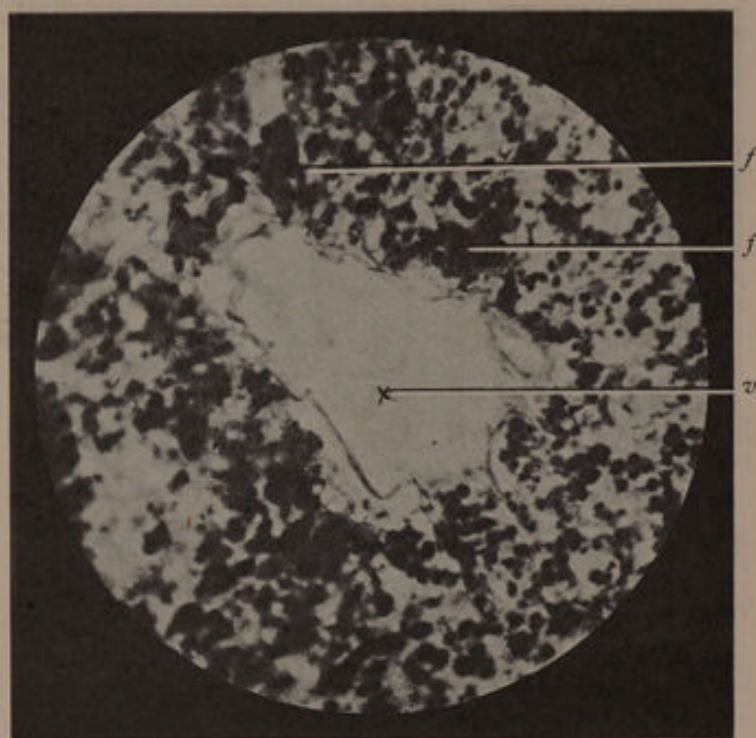


FIG. CLXXVIII.

(30 days' Gestation showing Fat.)

Foetal liver,—portal vein and zone. The fat drops are large and more numerous in the hepatic and portal zones.

v, portal vein ; *f*, *f*, fat droplets.

method of counterstaining in bringing out in a microphotograph the small iron granules. Both the description and the drawings are made from the specimens stained with hæmatoxylin.

Gestation sacs of 4, 5, 6, 6½, 7, 8, 9, 10 and 12 days show no iron reaction.

GESTATION SAC OF 14 DAYS.

(1) Foetal tissue :—foetus and foetal placenta.

In this study of iron in the foetus I have confined my attention to the foetal liver, and at this time it shows no iron. In the foetal placenta iron makes its first appearance at this date as small blue-black granules, irregularly distributed throughout the mesodermic partitions which separate the ectodermal *tubes*. These granules lie always within the mesodermic cells, and while they are few in number, and are found

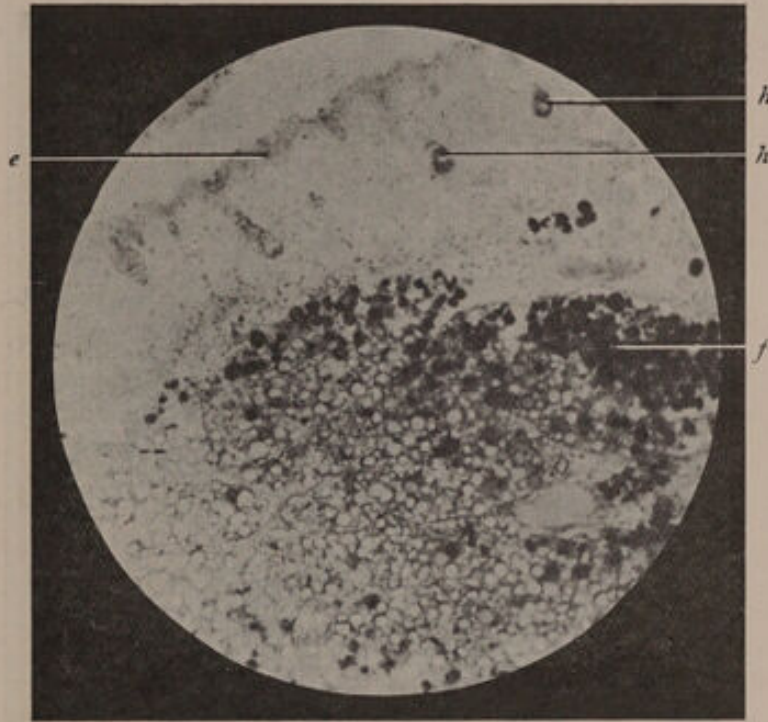


FIG. CLXXIX.

(30 days' Gestation showing Fat.)

Skin and subcutaneous tissue of foetus. Fat cells are numerous and are found in the true skin as well as in the subcutaneous tissue.

h, h, hair follicles; *f*, fat cells (out of many of them the fat has been dissolved); *e*, epidermis.

throughout the entire length of the "mesodermic villi," they are most numerous at the distal or maternal end of these villi, and are often grouped about the small allantoic vessels. (Fig. 181.) The ectodermal wall of the tubes show none of these granules.

(2) Maternal tissue :—maternal placenta.

The maternal placenta shows no trace of iron.

GESTATION SAC OF 16 DAYS.

(1) Foetal tissue :—foetus and foetal placenta.

The foetal liver reveals no iron.

In the foetal placenta while the distribution of the iron granules is the same as at the 14th day, the number is considerably increased. These granules are of very irregular size, and the larger ones are often grouped about the nucleus of the fusiform mesodermic cells. The increase in the iron has occurred chiefly at the distal or maternal ends of the "mesodermic villi." The ectodermal walls of the placental tubes now show a few of the blue-black granules. These lie in the ectodermal cells, often close to the nucleus, and only, though not always, opposite the iron deposit in the mesoderm. (Fig. 182.)

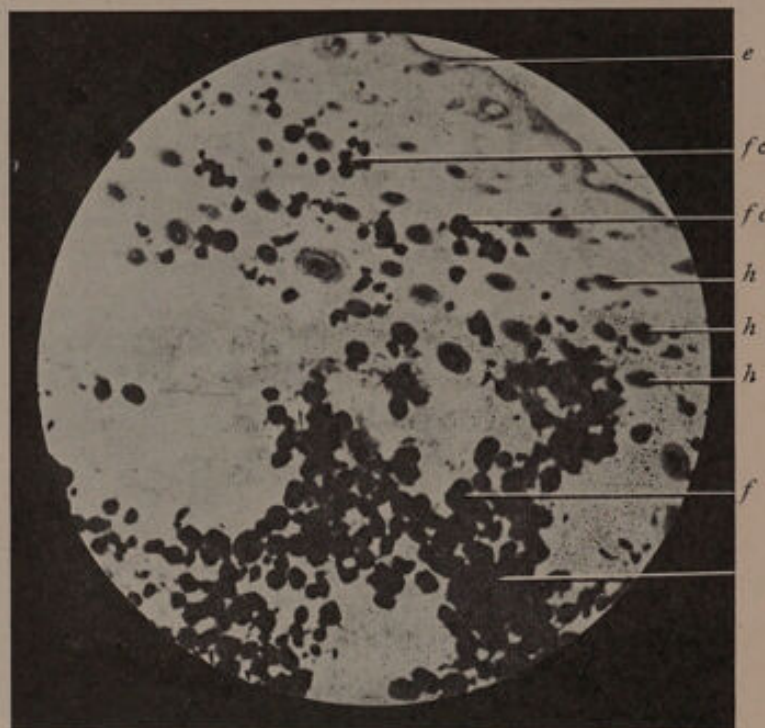


FIG. CLXXX.

(*Skin and Subcutaneous Tissue of a Rabbit 24 hours old.*)

The fat cells of the subcutaneous tissue are much the larger.

f, fat cells in subcutaneous tissue; *h,h,h*, hair follicles; *fc,fc*, fat cells in cutis vera; *e*, epidermis.

(2) Maternal tissue :—maternal placenta.

The areas of multinucleate decidual cells which lie island- or peninsula-like in the foetal placenta, show in a few cases a trace of iron. Usually those *areas* which directly underlie the iron deposit in the mesodermic villi are the areas which reveal the presence of iron, while the others are quite iron free.

The iron granules are minute and lie within the multinucleate cell, often grouped round the nucleus or spread along the threads of the cytomitoma. The cells nearest the foetal plasmodium contain the greatest number of granules. (See Fig. 182.)



FIG. CLXXXI.

(14 days' Gestation showing Iron.)

Drawing of foetal placenta and portion of intermediary region of maternal placenta. The iron in the form of small granules (blue-black) is shown in the vascular mesoderm of the foetal placenta ("mesodermic villi") often grouped round the foetal vessels. The ectodermal tubes are quite free of iron and also the maternal placenta.

ir, ir, ir, intermediary region of maternal placenta; *v*, maternal vessel with plasmodial ectoderm advancing along the walls; *g, g, g, g, g*, granules of iron; *t, t, t, t, t*, ectodermal tubes, their axial cavities are maternal blood spaces; *vm, vm, vm, vm*, vascular mesoderm ("mesodermic villi").



FIG. CLXXXII.

(16 days' Gestation showing Iron.)

Drawing of foetal placenta and portion of intermediary region of maternal placenta. Shows distribution of iron. The granules are found in the "mesodermic villi" and in the apposing walls of the ectodermal "tubules." Iron is present in small quantity in the multinucleate cells of the intermediary region of the maternal placenta, but only close to foetal ectoderm.

c,c,c, iron granules in multinucleate decidual cells of maternal placenta; *v,v*, maternal vessels along whose walls the plasmodial ectoderm is advancing; *b,b*, iron granules in ectodermal "tubules"; *fv,fv*, foetal vessels; *ss*, maternal blood spaces in "tubules"; *aa,aa*, iron granules in mesodermic villi.

GESTATION SAC OF 18 DAYS.

(1) Fœtal tissue : fœtus and fœtal placenta.

The fœtal liver shows for the first time the presence of iron. The iron granules are few and small; they lie in the liver cells, often scattered throughout the cell, and often gathered into a peri-nuclear zone, and the cells nearest the liver vessels contain these granules in greatest number. (Fig. 183.)

In the fœtal placenta my observations show that the maximum amount of iron is found at this date. While at former periods many of the "mesodermic villi" showed no trace of iron, it is now the exception to see one wherein a greater or less number of granules are not to be observed. The distribution of the iron is the same as at the 16th day, and the increase is only evident toward the distal or maternal ends



FIG. CLXXXIII.

(18 days' Gestation showing Iron.)

Fœtal liver—First appearance of iron. The iron granules are in the liver cells, often in a perinuclear zone and are more numerous in the perivascular cells.

v, hepatic vessels, g,g,g,g,g,g,g,g, iron granules.

of the allantoic partitions. In the ectodermal walls of the *tubules* the granules are also somewhat more numerous. (Fig. 184.) It will be observed that this period of greatest deposit of iron in the fœtal placenta is coincident with its first appearance in the fœtal liver.

(2) Maternal tissue ; maternal placenta.

The distribution of the iron granules is similar to that of the 16th day, only these granules are larger and more numerous in the multinucleate cells close to the fœtal plasmodium, and a greater number of the deeper multinucleate cells contain them. (See Fig. 184.)



FIG. CLXXXIV.

(18 days' Gestation showing Iron.)

Fœtal placenta and portion of intermediary region of maternal placenta. The iron is abundant in the "mesodermic villi" and the number of granules in the ectodermal "tubules" has increased. In the multinucleate decidual cells of the intermediary region (maternal placenta), the iron has increased since the 16th day.

bbbb, iron granules in multinucleate decidual cells; *aaa*, iron granules in "mesodermic villi;" *gg*, iron granules in ectodermal "tubules;" *tttt*, ectodermal "tubules."

GESTATION SACS OF 20 AND 22 DAYS.

(1) Foetal tissue :—foetus and foetal placenta.

The foetal liver becomes steadily richer in iron during this period, and always the greatest number of the granules are found in the peri-vascular liver cells.

The foetal placenta shows a gradual diminution in the amount of its iron. The granules are still found throughout the entire length of the



FIG. CLXXXV.

(24 days' Gestation showing Iron.)

Foetal liver. Portal and hepatic zones. The iron granules lie always within the liver cells and are confined definitely to the hepatic and portal zones of the lobule.

ps, portal space ; *ps*, *ps¹*, portal zone (the iron is seen in the blue-black granules) ; *hs*, *hs¹*, hepatic zone ; *v*, hepatic vessel ; *cc*, giant cells.

inter-tubular mesodermic partitions, but they everywhere appear in smaller numbers.

(2) Maternal tissue :—maternal placenta.

The distribution of the iron, and its quantity, so far as I am able micro-chemically to estimate it, show no appreciable change.

GESTATION SAC OF 24 DAYS.

(1) Fœtal tissue :—fœtus and fœtal placenta.

The fœtal liver reveals its iron distributed throughout the portal and hepatic zones ; in the intermediary zone there are very few granules. The total number of the granules has greatly increased. (Fig. 185.)

In the fœtal placenta there is little change in the amount of iron since the 22nd day, and its distribution is the same.

(2) Maternal tissue :—maternal placenta.

The multinucleate decidual cells are now markedly degenerated, and their island- or peninsula-like areas have a granular and sodden appearance. One or two of these areas are stained a diffuse-black by the hæmatoxylin, no granules are to be seen in these areas, and the inference is that the iron compounds with the degeneration of the multinucleated cell, have become diffused throughout the conglomerate mass of cell débris. In no other form or situation does iron appear in the maternal placenta at this date.

GESTATION SAC OF 26 DAYS.

(1) Fœtal tissue : fœtus and fœtal placenta.

In the fœtal liver the iron granules are more numerous, and in the fœtal placenta less numerous than at the 24th day. In both cases the distribution remains the same. (See Fig. 186.)

(2) Maternal tissue :—maternal placenta.

There are now numerous areas stained diffusely a blue-black. These are found not only in the "peninsulas" and "islands" of what were formerly multinucleate decidual cells, but also in the tissue between the uterine sinuses. Drawing (Fig. 186) gives a representation of the distribution of the iron at this period. It will be remembered that the tissue of the region of the uterine sinuses is made up of fibrin-lamellæ, and the remains of the uni- and multinucleate decidual cells. Close to a few of the sinuses, lying often between the fibrin-lamellæ, there are seen also large iron granules.

GESTATION SAC OF 28 AND 30 DAYS.

(1) Fœtal tissue :—fœtus and fœtal placenta.

The iron steadily increases in the fœtal liver, until at 30 days it shows the maximum amount found during intra-uterine life. The granules are present in all three zones of the lobule, though the hepatic and portal zones possess it in much larger quantity. In the fœtal placenta the amount of iron remains, as far as I can judge, undiminished. The distribution of the granules is not so uniform, as they often appear gathered in cluster, and in other places singly scattered ; they lie always in the fine mesodermic partitions which separate the tubules.

(2) Maternal tissue :—maternal placenta.

The only evidence of iron now found are a few scattered areas stained a diffuse blue-black. These areas lie in the midst of the remains



FIG. CLXXXVI.

(26 days' Gestation showing Iron.)

Drawing of the placenta. In the maternal portion of the placenta the iron appears as a few granules clustered round the more superficial uterine sinuses and as diffusely-stained, blue-black areas close to the deep surface of the foetal placenta. In the foetal portion of the placenta the "mesodermic villi" alone show a few small granules.

fp,fp', foetal placenta; *mp,mp'*, maternal placenta; *ss*, uterine sinuses; *w*, muscular wall; *bbb*, iron granules near sinuses; *aaaa*, areas diffusely stained a blue-black; *ggggg*, iron granules in "mesodermic villi."

of the degenerated decidual cells, and for the most part close to the foetal placenta.

RABBIT 24 HOURS OLD.

Rabbit 24 hours old ; it had suckled. The liver is very rich in iron, much richer than at any period of intra-uterine life. The distribution of the iron is unmistakeably perivascular, though the cells in all the zones contain the granules. The portal zone is especially rich, the cells near the vessels being simply crowded with the small uniform blue-black granules.

ADULT RABBIT.

Adult rabbit : 5-12 hours after food. The amount of iron in the liver of the adult rabbit is comparatively small. The granules which are never very distinct are found more numerous in the hepatic and portal zones. So far as my observations go (3 rabbits with an interval of from 5-12 hours after food) the amount of iron in the liver, under average food conditions, remains fairly constant.

SUMMARY OF IRON.

The foetal placenta. Iron first appears in the foetal placenta and at the 14th day of gestation. With Macallum's method it is found in the form of blue-black granules, irregularly distributed throughout the mesodermic partitions which separate the ectodermal tubes. These granules lie always in the mesodermic cells, and are most numerous at the distal end of the "mesodermic villi."

At the 16th day the amount of iron has increased, its distribution remains the same, save that occasionally the ectodermal cells of the tubes which immediately appose the iron deposit in the mesoderm, contain a few of the granules.

At the 18th day the granules have increased both in number and in size, and my observations show that at this date the maximum amount of iron is found in the foetal placenta. The distribution is that of the 16th day. I have remarked that this period of the greatest deposit of iron in the foetal placenta is coincident with its first appearance in the foetal liver.

During the 20th and 22nd days the amount of iron shows a gradual diminution, and the granules disappear entirely from the ectodermal walls of the tubules.

Iron continues to be found in the mesodermic partitions until the close of gestation.

The maternal placenta. Iron appears in the maternal placenta at the 16th day of gestation. The granules are minute and discrete, and are found here and there in the multinucleate decidual cells of the intermediary region, which lie close against the foetal placenta. Only a few of the multinucleate cells show the iron granules, and these cells are always those which immediately underlie the iron-containing "mesodermic villi," and the cells nearest the foetal plasmodium always contain the greatest number of granules. The granules lie in the cytoplasm, ranged round the nucleus, or along the cytomitoma.

At the 18th day a greater number of these multinucleate cells reveal the presence of iron, and the granules themselves are larger and more numerous. The island- and peninsula-like areas of multinucleate cells are often specially rich.

During the 20th and 22nd day there is little change, but at the 24th day the multinucleate decidual cells are degenerated, and the iron therein no longer appears in the form of discrete granules, but as irregular patches of a diffuse blue-black staining. These patches of diffuse staining lie close to the foetal placenta, but at the 26th day they are found also in the tissue between the deeper uterine sinuses. They are distributed always in the areas of degenerated decidual cells, and they represent with little change in character or distribution the iron as found in the maternal placenta at the end of gestation.

In the foetal liver. Iron appears in the foetal liver at the 18th day. The granules are few and small, lie in the liver cells, and are often gathered into a perinuclear zone. A few cells close to the liver vessels are the first to show these iron granules.

The foetal liver becomes steadily richer in iron, the cells in either hepatic or portal zones showing always the greatest number of granules. At the 24th day the cells of the intermediary zone show for the first time a few scattered granules, and, at 30 days, is reached the maximum amount of iron found in the liver during intra-uterine life.

Twenty-four hours after birth the liver is much richer in iron than at any period of intra-uterine life, and while the iron granules are found scattered throughout the lobule the main distribution is perivascular, and the portal zone is specially rich in iron.

In the liver of the adult rabbit the amount of iron is comparatively small, and under average food conditions this remains fairly constant.

PART II.

STATEMENT AND DISCUSSION OF THE RESULTS OF OTHERS.

A SUMMARY of the papers which have appeared during the last ten years only is given.

At the conclusion of each summary a critical comparison will be established between its results and my own.

In the appended bibliography there will be found a complete list of the papers which I have consulted, and their place therein is indicated by a parenthetical number in the text.

I shall follow the same order in this discussion as in Part I., namely:—

- A. Histology and histogeny of placenta and foetus.
- B. Glycogen as found in placenta and foetus.
- C. Fat as found in placenta and foetus.
- D. Iron as found in placenta and foetus.

The bibliography is likewise classified.

SECTION A.

HISTOLOGY AND HISTOGENY OF PLACENTA AND FŒTUS.

By reason of its resemblance in shape to the human placenta the placenta of the rabbit early attracted the attention of anatomists. In 1842 Bischoff in his monograph (1) on the development of the rabbit, and speaking of the work of his predecessors Eschricht (2) de Baer (3) and Coste (4), states that no light had yet been thrown upon the structure of the rabbit's placenta. (Page 137.) In the years immediately succeeding, de Graaf, Malphigi and Haller studied the placenta of the rabbit, but only at, or after mid-term, and in respect of showing therein a maternal and foetal portion.

It is only since the year 1868 that microscopic researches have been conducted upon the placenta of the rabbit. Among the first of these researches are notably those of Ercolani, Mauthner, Godet and Turner.

Ercolani (5) in 1868 described the gravid uterus of a rabbit between the 9th and 10th day of gestation. This description, correct in many of its observations, was written in the conception of that great synthesis with which the name of Ercolani will always be associated, whereby all

placentæ "are formed of two distinct portions: the foetal portion vascular and absorbing, the maternal portion glandular and secreting." (Page 501). His four later treatises, 1870-1883, and upon the placenta of different mammals, wherein rodents are included, though they evince a change of view in regard to the origin of the placental tissues, still support this conception.

Mauthner (6) in 1873, was the first to describe the ecto-placental tubes, with their plasmodial wall, and their cavities containing maternal blood. "These plasmodial walls are due to a fusion of the foetal epithelium covering apposing chorionic villi."

Godet (7) in 1877, supports Mauthner as regards the structure of villi, but calls the epithelial tissue which surrounds them epithelioid, and considers it not epithelium at all. (Page 34.)

Turner's work (8) ranges from 1871-1889, and includes researches upon the placenta of the several orders of mammalia. I have been privileged to see the original drawings representative of his work upon the placentation of rodents. This work has been largely macroscopic: the care and skill with which his dissections have been executed, and the faithfulness with which these have been depicted and described, establish a limit beyond which it is scarcely possible to go. His work upon the foetal membranes is especially valuable, and his many contributions have indicated and determined the lines of subsequent research.

In 1879 appeared the "Mémoire" of Masquelin and Swaen, dealing with the early phases of the maternal placenta of the rabbit. This study was carried out by means of microscopic sections, and upon uteri of 8 and 10 days' gestation. When one reads the following conclusion: "L'épithélium superficiel de la muqueuse utérine et l'épithélium des glands, après avoir subi différentes modifications, finit par se transformer en globules, imprégnés d'hémoglobine et identiques aux corpuscles rouges du sang," it is scarcely astonishing that Kölliker (10), writing in the same year, says that: "New researches are necessary in order thoroughly to comprehend the complicated structure of the placenta of the rabbit."

In 1887 Mathias Duval began his work upon the placenta of the rabbit, and in the July of that year he presented to the Société de Biologie a preliminary note thereon in order, as he confesses, to establish a claim of priority. At this time there was only one mémoire upon the development of the placenta of the rabbit—that of Masquelin and Swaen.

In 1888 Strahl (13) published a short thesis upon the placenta of the rabbit and of the mole. Strahl argues that in the rabbit, as in the dog, cat and fox, he finds that the uterine epithelium takes a share in the formation of the placenta.

It was not till 1889-90—ten years ago—that Duval's completed work on the rabbit's placenta was published. I shall now give a short summary of this and of all papers that have subsequently appeared. As I have previously intimated, after each summary a critical comparison will be established between my own and the author's results.

Duval's able monograph (11) gives the life-history of the rabbit's placenta from the 7th to the 30th days inclusive. The time-interval in

this series is from 24-48 hours. In each instance serial sections have been cut and excellent drawings made from these. He divides this 30-day gestation cycle, in accordance with definite histogenetic changes which he describes in the placenta, into 3 periods:—

- A. Origin and formation of the ectoplacenta—up to the 10th day.
- B. Period of "remaniement" of the ectoplacenta—from the 10th to the 25th day.
- C. Period of "achèvement" of the ectoplacenta—from the 25th to the 30th day.

A. Origin and formation of the ectoplacenta. (Page 323.)

Duval begins his age-series with a gestation sac of 7 days. (Fig. (1): Pl. (1).) He describes the already-formed placental cotyledons, embracing this opportunity to quote Bischoff (1) and Hollard (12) in respect of the normal arrangement of the uterine mucosa. The growth of the cotyledons is attributed to a hyperplasia of the corium, and their covering epithelium is described as transformed into a thick homogeneous couch, with loss of all cell-outline and fragmentation of nuclei. (Fig. (4): Pl. (1).) The vessels of these cotyledons are described as capillaries, and about the deeper of these appear now slight perivascular sheaths, composed of uninucleate decidual cells. Duval agrees with Masquelin and Swaen, who first described these perivascular sheaths, in attributing the origin of these uninucleate decidual cells to the star-shaped and fusiform connective tissue cells of the surrounding corium. The blastosphere lies free within the cavity of the gestation sac, and the embryonic pole is already outlined, and is directed towards the placental cotyledons.

Embryos of $7\frac{1}{2}$, 8 and 9 days. During this period the attachment of the blastodermic vesicle to the thickened mucosa of the two cotyledons takes place: this attachment is anticipated by a pronounced thickening of crescent-shaped areas, the "croissants ectoplacentaires," of the ectoderm, one on either side of the embryo. These "croissants" come to be composed of many layers of cells. The superficial layers soon assume a plasmodial disposition, "couche plasmodiale," while the deep layers remain formed of distinct cells, "couche cellulaire." These "croissants" so formed, constitute the "ectodermal laminæ," the "ectoplacenta," and they soon arrive in contact with the homogeneous epithelial couch covering the two placental cotyledons. The "couche plasmodiale" becomes attached to the thickened maternal epithelium which gradually diminishes in thickness, and is absorbed. Vegetative bud-like processes from this "couche" penetrate the uterine mucosa, notably at the level of the gland-mouths, and at the end of the 9th day come to surround the superficial maternal capillaries. At the same time all trace of the uterine epithelium has disappeared over the areas of placental attachment, and the only remains of it are in the glandular cul-de-sacs.

Embryo of $9\frac{1}{2}$ days. In Duval's own words, "the essential fact that we have to observe at $9\frac{1}{2}$ days (or 10 days about) marks a stage of first importance in the evolution of the ectoplacenta: that is, in effect, the investment of the superficial capillaries of the maternal cotyledons by the shoots from the plasmodial couch of the ectoplacenta, the disappearance of the endothelial wall of these capillaries, and the reduction of

these vessels to the state of lacunæ, hollowed out in the ectoplacenta tissue of embryonic origin, lacunæ containing maternal blood"—"lacunes sangui—maternelles de l'ectoplacenta" (pages 336-7). The maternal cotyledons have greatly increased in size, their many and large capillaries retain their endothelial lining, outside which are now gathered thicker perivascular sheaths of decidual cells. These cells have become vesicular. There persist now but few and isolated remains of the uterine glands. The connective-tissue cells, the most superficial (those nearest the ectoplacenta), commence to acquire a vesicular structure and multiple nuclei.

The foregoing constitute the changes which Duval describes as occurring during the period of formation of the ectoplacenta. With the immediate arrival of the allantoic vessels, the disc-like aspect of this ectoplacenta will be completely modified, changes which Duval describes under :

B. Period of "remaniement" of the ectoplacenta—from the 10th to the 25th day.

At the beginning of the 10th day the allantoic vessels arrive, penetrate and divide the ectoplacental lamina into a series of territories, in the form of columns, each of which represents a future lobe; these columns subsequently divide into a "complexus tubulaire," which represents this lobe, and of which each tube responds to a future lobule, for finally each of these tubes divides into "canalicules" and forms a "complexus canaliculaire" or lobule. This description Duval gives as the basis for the following elaborate and somewhat fanciful sub-classification (page 596).

- (a) the subdivision of the ectoplacenta into lobes and the columnar character of these lobes.
 - (b) the passage of the columnar lobes to the state of the complex tubule.
 - (c) the division of the tubes into canaliculi and the formation of the complex conalculus which represents a lobule.
- (a) Subdivision of the ectoplacenta into lobes; columnar state of these lobes, from the 10th to the 12th day.

(1) Uterine Cotyledons. These are still further increased in size and are now distinctly divided into two regions, a "région intermédiaire," next the ectoplacenta—where the capillaries have no perivascular sheaths and wherein arises the multinucleate decidual cell—and the "région des sinus utérins," the larger mass of the cotyledon. In this latter region the perivascular sheaths of uninucleate vesicular cells increase rapidly in thickness, and at the 12th day begin to impinge upon one another. Duval here describes (Page 598) and figures (Fig. 29) a distinct layer of lax connective tissue, next the musculature. He states that though this layer comes to be composed entirely of uninucleate decidual cells, that it always retains its present dimension, and at parturition, determines the line of separation of the placenta. This is our zone of separation: it is called by Duval "couche vésiculeuse protectrice ou permanente."

The multinucleate decidual cells of the intermediary region arise directly from the star-shaped or fusiform connective tissue cells of the corium.

The vessels of the intermediary region remain until the 11th day simple capillaries, no mention is made of even a thickened endothelium, and as previously stated, Duval finds here no perivascular sheaths. At the 11th day the walls of the vessels of this region are formed by a continuous lamina, sown with nuclei. "Does this protoplasmic lamina result from a transformation of the endothelium?" Duval answers this question in the negative, and after a lengthy review of his sections upon the placenta of the guinea-pig he decides that "these laminae are derived from the ectoplacenta, that they glide in along the walls of the maternal capillaries substituting themselves for the endothelial lining, which they cause to atrophy and disappear." These laminae are called "*couche plasmodiale endovasculaire*," and reach and clothe the walls of the uterine sinuses and extend up to the "*couche vésiculeuse protectrice*." (Figs. 30, 31, 32: Pl. III.)

(2) Ectoplacenta. (Page 606.) At $9\frac{1}{2}$ days areas of mesoderm begin to gather in the folds on the foetal face of the ectoplacenta, and these, reinforced at the 10th day by the arrival of the allantoic vessels, plunge into the midst of the ectoplacental lamina and divide it into a series of columns. This is the first indication of the "*état colonnaire*" of the ectoplacenta, and each of these columns corresponds to a future lobe. The "*lacunes sangui-maternelles*" occupy the axis of these columns and communicate directly with the maternal vessels of the intermediary region, lined by the "*couche plasmodiale endovasculaire*." The vascular mesodermic partitions never completely divide the ectoplacenta, that is, they never reach altogether through it; between their deepest penetration and the maternal tissue intervenes always a lamina of the ectoplacenta—the "*lame limitante ectoplacentaire*." (Fig. 31.) The walls of these ectoplacental columns possess a cellular and a plasmodial layer.

(b) Passage of the columnar lobes—ectoplacental columns—to the state of the complex tubule, from the 12th to the 14th day.

(1) Ectoplacenta. The ectoplacental columns begin to present irregularities of contour, processes from their plasmodial wall extend into their lumen, the "*lacune colonnaire sangui-maternelle*" fuse with other similar processes and so come to divide the lacune into a number of smaller lacunes or tubes. At the same time processes of vascular mesoderm, invaginate the wall of these columns, opposite the points of origin of these former plasmodial processes, extend inward in these, and so come to occupy the axes of these plasmodial processes. This process of division is prosecuted in a plane parallel to the long axis of the column, and so each column comes to be divided into a number of tubes, and so to represent a "*complexus tubulaire*" or lobe. (Figs. 32, 33: Pl. III.)

(2) Uterine cotyledons. The uterine sinuses are larger and their perivascular sheaths are thicker. The vessels of the intermediary region are provided with a "*belle couche plasmodiale endovasculaire*," and this "*couche*" has passed already into the more superficial of the uterine sinuses. (Page 617.)

(c) Division of the tubes into canaliculi, and the formation of the complex canaliculus or lobule, from the 15th to the 25th day.

(1) Uterine cotyledons. The intermediary region becomes a much narrower zone, due to the growth of the ectoplacenta on the one hand and the dilation of the uterine sinuses on the other. In the region of the uterine sinuses the perivascular sheaths begin to come in contact, and at the same time the sinuses increase enormously in size. The 'couche vésiculeuse protectrice' comes to be formed of vesicular vaso-adventitious cells, and its sinuses come to be narrowed. (Fig. 40.) The uterine sinuses are now entirely lined by the 'couche plasmodiale endovasculaire,' for their endothelium thus replaced has disappeared. This endovascular plasmodium reaches only to the 'couche vésiculeuse protectrice,' and thus in all the vascular canals which lie beyond this couche the maternal blood circulates within walls formed by embryonic elements.

(2) Ectoplacenta. The ectoplacental tubes are divided into smaller tubes or canaliculi, in the same way as previously the columns were divided into tubes (Figs. 51, 53: Pl. V.), and the number of canaliculi derived by division from one tube remains grouped, and constitutes the complexus canaliculaire or lobule. But there is this difference that whereas the tubes were separated from one another by both foetal capillaries and mesodermic cells, the canaliculi are separated only by foetal capillaries; so that now the tissues that divide the maternal from the foetal blood are only the plasmodial canalicular wall and the endothelium of the foetal capillary. (Fig. 54: Pl. V.) The lobules are arranged in a direction more or less parallel, with a foetal extremity and a maternal extremity. The maternal blood circulates from the foetal extremity towards the maternal extremity; the foetal blood flows within its capillaries in the opposite direction.

C. Period of "achèvement" of the ectoplacenta from the 25th to the 30th day.

This work of "achèvement" consists in cellular transformations which bring about the degeneration and absorption of a great number of parts previously formed.

(1) Maternal Tissues. The intermediary region. After the 25th day the multinucleate decidual cells undergo a veritable melting ("fonte") to a state of granular detritus (Fig. 58: Pl. VI.), and this change begins in the cells farthest removed from the lacunæ.

The region of uterine sinuses. In the same way the uninucleate decidual cells undergo a similar degeneration, and the change here also begins away from the sinuses. The result is the formation of a pulpy mass. The 'couche plasmodiale endovasculaire' persists, thickens somewhat, and becomes individualised into distinct cells.

The "couche vésiculeuse protectrice." The uninucleate decidual cells persist; here they do not degenerate. Its vessels remain narrow sinuses, lined by a normal vascular endothelium.

(2) Foetal Tissues. The ectoplacenta. The plasmodial wall of the canaliculi becomes absorbed more or less completely, so that the foetal capillaries, throughout a large part of their extent, are directly in contact with the maternal blood. (Figs. 63, 64, 65: Pl. VI.)

Duval terminates his elaborate work by a short discussion on parturition.

CRITIQUE.—Duval has been the first to correctly describe and interpret the part taken by the foetal ectoderm in the formation of the placenta, indeed a conception at all correct of the rabbit's placentation dates from this masterly work.

Of his elaborate and somewhat artificial classification of the ectoplacenta, and of his rather fanciful representations of "*voies afférentes* and *efférentes*," I propose at this time only to say that the figures are less convincing than the text. The main differences between my own work and that of Duval are to be found in his interpretation of the obscure and controverted points set forth by me in Part I. My own interpretation of these points, together with references to the numerous microphotographs, is there recorded, and this standing appeal to my own work is the short way in which I propose to make any criticism. I now submit Duval's opinions upon these points.

(1) The origin of the giant cells.

These cells appear at the 10th day and are simply hypertrophied connective tissue cells. (Page 605, 1898.) They persist until the 17th day and of their function nothing is known. "*Elles demeurent donc pour nous aussi énigmatiques qu'au début.*" (Page 13, 1890.)

(2) The attachment of the ectoderm to the uterine epithelium.

The ectoderm before its attachment to the uterine epithelium is cellular. (Figs. 10, 12 : Pl. I.) After its attachment at 8 or 9½ days the superficial layers take on a plasmodial change. (Page 332, 1889.)

(3) The origin of the multinucleate decidual cell.

These cells arise from the small, star-shaped connective tissue cells of the corium, and are placed at first some distance from the ectoplacenta. (Fig. 25 : Pl. II.) They appear at 9½ days. (Page 598, 1889.)

(4) The origin and nature of the maternal blood cavities *swallowed* by the ectoderm.

(Page 340, 1889.) "After the 9th day the elements of the plasmodial layer of the ectoplacenta have surrounded the superficial capillaries of the uterine cotyledons, and by the fact of the disappearance of the endothelial wall, which alone limits these vessels, these find themselves reduced to the state of sinuses hollowed out in the substance of the ectoplacenta—such is the origin and nature of the "*lacunes sanguinomaternelles de l'ectoplacenta.*"

(5) The nature of the so-called villi.

The ectoplacenta finds itself at the 12th day divided into a series of columns by the ingrowth of mesodermic partitions. (Fig. 30 : Pl. III.) The axis of these columns is occupied by maternal blood, the superficial end is closed, while through the open deep extremity its axial maternal-blood space communicates directly with a vessel in the maternal placenta. (Page 607 : 1889.)

(6) The fate of the placental glands.

The glandular cul-de-sacs at 9 days are more or less filled with the homogeneous substance which results from the transformation of their cells. These glands will soon disappear, they play no essential role in the formation of the placenta. (Page 336 : 1889.)

(7) The behaviour of the sinus-endothelium.

At the 11th day the capillaries of the intermediary region have their endothelium replaced by a "lame continue de protoplasma." This "lame" has for its origin the ectoplacenta, and constitutes the "couche plasmodiale endovasculaire." (Page 601.) From the 15th day this "couche" glides deeper into the maternal placenta and clothes the uterine sinuses. It reaches in to the "couche vésiculeuse protectrice." (Page 3 : 1890.)

(8) The interjunction of the two tissues, maternal and foetal.

There remains always a limiting ectoplacental layer—the "lame limitante ectoplacentaire" which forms a barrier between the mesodermic foetal tissue and the maternal tissue. In other words the foetal placenta clothes completely the maternal placenta. (Page 608 : 1889.)

(9) The determination of the zone of separation.

At the 10th day there exists in the neighbourhood of the musculature a layer of loose connective tissue. This layer comes later to be composed of uninucleate vesicular cells, and so constituted, is called the "couche vésiculeuse protectrice."

(10) The fate of the decidual cells.

The decidual cells both uni- and multinucleate, after the 25th day undergo a veritable melting ("fonte") to a state of granular detritus. (Fig. 58 : Pl. VI.), and this change begins in the cells farthest removed from the blood-sinuses. (Pages 27, 28 : 1890.)

Duval makes no mention whatever of the formation in the maternal placenta of fibrin-tissue or of fibrin-lamellæ. It will be observed that my own conclusions practically agree with those of Duval in the points :

- (2) The attachment of the ectoderm to the uterine mucosa.
- (5) The nature of the so-called villi.
- (6) The fate of the placental glands.
- (8) The interjunction of the two tissues, maternal and foetal.

Jean Masius in 1889 published a paper (15) upon the development of the rabbit's placenta. Masius was a pupil of Van Beneden, and in the beginning of his paper he refers at some length to Van Beneden's work upon the placenta of the bat. Masius honestly attributes Van Beneden's change of view in respect of the origin of the "organe épiblastique" in the bat, as due in part at least to the study of Duval's preliminary note upon the placenta of the rabbit, which we have previously noted. By this change of view this "organe épiblastique" is now pronounced *wholly* of foetal origin, and consequently is in this respect identical with the ectoplacenta of the rabbit. These maturer results of Van Beneden

in the bat's placenta are now taken by Masius as a starting point for his study in the rabbit. He proposes under the guidance of Van Beneden to answer the two following questions. (Page 90.) What part do the mother and the embryo take respectively in the building-up of the placenta? What are the modifications undergone by the uterine mucosa during gestation? Masius begins his observations at the 8th day "après le coit" and continues it in five stages to the 12th day. The exact ages of his specimens are as follows: 8 days and 5 hours; 8 days and 20 hours; 9 days and 3 hours; 9 days and 5 hours; 12 days. Serial sections have been employed, and the drawings therefrom have been done with a camera lucida. The following is the summary.

Stage I., 8 days and 5 hours. "Après le coit." (Page 91.)

The blastodermic vesicle is free in the uterine cavity, and the primitive line of the embryo is well developed. (Pl. V.: Fig. 1.) The epiblast over the prospective area of placental attachment is differentiated into two layers—a deep layer next the blastodermic cavity, and a layer superficial to this. The deep layer is composed of large cylindrical cells with oval nuclei, which show numerous mitotic figures. The superficial layer facing the uterine mucosa varies in thickness and its free edge is sinuous, due to the presence of large closely-related processes. In this superficial layer, derived from the deeper layer, there is no distinct cell-outline, and the nuclei are scattered in groups irregularly throughout the finely granular ground substance.

Uterine Mucosa.

The uterine epithelium shows the following changes, which result later in its complete disappearance. The nuclei are much larger and more numerous than in the epithelium of a non-gravid uterus, and they are disseminated in the midst of a protoplasmic substance. They are for the most part irregular and angular in shape, the chromatin is retired to their periphery and their centres remain uncoloured and clear. These nuclei multiply by a process of fragmentation. (Fig. 2.) The *derme* of the thickened mucosa is composed of star-shaped or fusiform connective tissue cells, with interlacing processes which lie in the midst of a colourless ground substance. This *derme* is vascularised by many vessels, only the larger of which show the beginnings of a perivascular sheath. Owing to the growth of the *derme*, epithelial cul-de-sacs come to be formed, which cul-de-sacs are continuous on the one hand with the uterine glands, and on the other hand they open into the uterine cavity. These cul-de-sacs (Fig. 3) are greatly convoluted, and their epithelium undergoes the above degenerative changes. The epithelium of the glands, proper, retains its original character.

Stage II., 8 days and 20 hours.

The blastodermic vesicle is fixed by its epiblast to the uterine mucosa, and the line of this fixation is in the form of a horse-shoe, in the concavity of which lies the posterior extremity of the embryo. The fixation begins near this concavity and is always further advanced there. A section through the area of fixation shows (Fig. 5) the two layers of epiblast, with the superficial one enormously thickened. This superficial layer is composed of an abundant fundamental substance, and it

surrounds maternal capillaries which communicate with the vessels of the mucosa. These capillaries have a distinct epithelium. (Fig. 5.)

Uterine Mucosa.

At the place of attachment the uterine epithelium is greatly thinned and in part has disappeared; and the epithelial cul-de-sacs are modified, for their epithelial walls have lost their regularity, in that they show numerous round or oval thickenings, due to an accumulation of nuclei at these points, which project either into the cavity of the cul-de-sac, or into the surrounding connective tissue. These epithelial thickenings become pediculated and finally detached, and the globular masses, rich in nuclei or ground substance, find themselves free either in the cavity of the cul-de-sac or in the surrounding connective tissue. These come to form large globules, and after undergoing special modifications, disappear. The vessels of the mucosa, save the most superficial ones, all show the perivascular sheaths. (Fig. 6: Pl. VI.) The large cells of these sheaths are derived from the star-shaped cells of the surrounding derme, which cells indraw their processes, increase in size, and gather about the vessel. The endothelium of these sheathed vessels is thick.

In the derme are found additional cellular elements, which may be modified leucocytes.

Stage III., 9 days and 3 hours.

The deep layer of the embryonic epiblast begins to form primordial papillæ, short and hollow, which are as yet, entirely lodged in the superficial epiblastic layer. The allantois is not yet joined to the "sereuse" of van Baer, and the axis of these primordial papillæ is occupied by a simple lining of somatopleure. The superficial layer of the epiblast is increased in thickness, and adheres directly to the derme of the mucosa, the epithelium of which has entirely disappeared. This thick layer of epiblast encloses maternal capillaries, and at the side of these typical capillaries, one is able to see in the fundamental substance fine lacunæ, also filled with maternal blood. (Masius does not figure these lacunæ though he says that it is easy to imagine them from Fig. 5.)

Uterine Mucosa.

The two limbs of the horse-shoe-shaped placental attachment are now continued forward in front of the anterior extremity of the embryo. A section through one of these limbs shows the uterine epithelium no longer continuous, only here and there are seen irregular-shaped masses of its degenerate epithelium. Here, too, the deep or cellular layer of the foetal epiblast unites directly with the denuded derme of the mucosa. The superficial plasmodial layer of the epiblast is not to be found here. (Masius pronounces this "un fait curieux," and explains the absence of this plasmodial layer by two rather lame suppositions. (Page 101.) The epithelial cul-de-sacs immediately towards the attached epiblast are widely dilated and their plasmodial walls are ruptured in places, so that in these situations the connective tissue of the derme forms the wall. These cul-de-sacs no longer communicate with the uterine glands proper.

Large masses of the degenerated epithelium of these cul-de-sacs, nucleated or non-nucleated, lie unattached in the midst of the surrounding derme.

The perivascular sheaths are increased, and in all the vessels of the mucosa the endothelium is thickened, though its cells remain distinct. The blood within these vessels contains a large number of "corpuscles énigmatiques."

Stage IV., 9 days and 5 hours.

The allantois is not yet fused with the "sereuse" of van Baer. The primordial placental papillæ are elongated and are lined interiorly by the somatopleure. The superficial layer of the epiblast is greatly developed, and constitutes the greater part of a new formation, overlying the uterine placental projections. There are now but few capillaries possessing an endothelium in the superficial layer of epiblast—the greater number have lost their endothelium. These capillaries are continuous with those of the derme. They penetrate the epiblast and then lose their endothelial lining, and become large and irregularly-shaped spaces in the midst of the epiblast. (Page 104.) These spaces intercommunicate by numerous fine blood-channels.

Uterine Mucosa.

The formations derived from the uterine epithelium are regularly disposed and form a sort of zone between the foetal and maternal tissues. These formations composed of altered epithelial nuclei and of fundamental substance, either delimit large cavities, or are singly disposed in the midst of the connective tissue of the derme. These large cavities, which represent the former cul-de-sacs, are now filled with maternal blood, for communications have established themselves, through the thin layer of epiblast, between the epiblastic blood-spaces and these cavities.

The perivascular sheaths are decidedly increased, and the endothelium of the sheathed vessels is thickened and in places it is broken through, and the wall of the vessel here formed only of the sheath. The serotinal cells of these sheaths become vesicular (Fig. 20: Pl. VIII.), and between them is established a system of lacunæ which contain blood which has leaked into them through the broken endothelial wall of the vessel.

Stage V., 12 days.

The allantois is now fused with the "sereuse," the primordial papillæ from the cellular layer of the epiblast have lengthened and ramified, and their axis is occupied by a vascular embryonic connective tissue. The superficial layer of epiblast is now enormously hypertrophied and constitutes the principal mass of the placenta. The cellular layer of the epiblast is now represented by several layers which surround the vascular papillæ of the allantois. The perivascular sheaths no longer exist as such, for the whole derme is formed now of their serotinal cells. These have only a single nucleus. (Pl. III.) The maternal blood in the cavities derived from the cul-de-sacs comes to be surrounded by these serotinal cells. The endothelium of the maternal vessels atrophies and disappears.

Conclusions. (Page 114.)

(1) Before the fixation of the blastocyst the uterine mucosa forms a great projection, clothed with epithelium, upon which the placenta is developed.

(2) The uterine epithelium and the uterine glands take no part in the formation of the placenta. The epithelium of the more exposed areas completely disappears, but in the deepest portions of the glands it is conserved throughout pregnancy.

(3) The vessels of the mucosa become surrounded by a sheath of cells which are at first multinucleated; these cells become for the most part uninucleate and vesicular and are called serotinal.

(4) The endothelium of the vessels of the mucosa degenerates and disappears, and the blood filters through in small quantity between the serotinal cells.

(6) Before fixation of the blastocyst, the embryonic epiblast is divided into two layers—a superficial, plasmodial and a deep, cellular.

(7) The epithelial cul-de-sacs become maternal blood-cavities.

“According to my observations the placenta of the rabbit is a new formation of fœtal origin, formed by allantoic villousities ramified in a tissue which arises solely from the epiblast of the embryo. This new formation is soldered to the derme of the mucosa, the vessels of which have formed a system of lacunæ without proper walls, which course through a multinucleated protoplasmic mass, not divided into cells, and arising from a very great increase in the thickness of the superficial layer of the epiblast. In the placenta the maternal blood circulates thus in an epiblastic mass of embryonic origin.” (Page 118.)

CRITIQUE.—Masius' observations are continued only from the 8th to the 12th days, and in consequence his opinion upon three of the controverted points—namely, 8, 9 and 10—is necessarily wanting.

(1) The origin of the giant cells. (Of these cells no mention is made.)

(2) The attachment of the ectoderm to the uterine epithelium.

Before its attachment the ectoderm shows two distinct layers, a plasmodial and a cellular layer. Contact with the uterine epithelium is made by means of the plasmodial layer. (Pages 91-92.) (Masius confesses that he cannot find these two layers over all the area of placental attachment. Page 101.) The attachment is thus plasmodial.

(3) The origin of the multinucleate decidual cells.

These cells only occur here and there in the perivascular sheaths, and at the 12th day the whole derme is composed of serotinal uninucleate cells. (Page 111.)

(4) The origin and nature of the maternal blood-cavities *swallowed* by the ectoderm.

The superficial maternal capillaries are surrounded and their endothelial walls replaced by ectodermal cells. In addition the epithelial cul-de-sacs become maternal blood-cavities. (Page 107.)

- (5) The nature of the so-called villi.

(Neither in the text nor in the drawings is any clear conception obtainable.)

- (6) The fate of the placental glands.

The epithelium of the deepest cul-de-sacs persists throughout gestation. (Page 114.)

- (7) The behaviour of the sinus-endothelium

The endothelium of the maternal vessels thickens and its cells multiply. (Fig. 23: Pl. VIII.) These cells become detached and disappear, and the wall of the vessel is constituted by the surrounding serotinal cells.

Points (8), (9) and (10) are beyond the limit of Masius' age-series. As regards the disputed points my own results agree with those of Masius' only in (7)—The behaviour of the sinus-endothelium.

Charles Sedgwick Minot has written two papers upon the placenta of the rabbit. The first "Uterus and Embryo: I. Rabbit," (16) was published in 1889, and the second "Die Placenta des Kaninchens" (16) in 1890. In a third article "A Theory of the Structure of the Placenta" (16), written in 1891, Minot simply affirms his final position.

"Uterus and Embryo: I. Rabbit" records observations made upon pregnant uteri from the 6th to the 15th day inclusive. The average interval in the series is 24 hours, though the gestation of 10 days is altogether wanting. Since in the following year, 1890, Minot completely changes many of his present interpretations, I shall only very shortly summarise this first paper.

SUMMARY.

"In the resting uterus of the rabbit there are six longitudinal folds. The ovum attaches itself in or between the two folds nearest the mesentery and the placenta is there developed." (Page 376.)

Uterus at 6 days and 3 hours. Uterine cavity is dilated, and the shape of the uterine glands is much altered. The epithelium is everywhere thickened. "I have failed to preserve the ovum." (Page 343.)

Uterus of 7 days and 3 hours.

The placental swellings are well marked, and are due to an hyperplasia of the connective tissue cells. The capillaries herein are dilated and are surrounded by beginning perivascular sheaths. The cells of these sheaths are derived from connective tissue cells.

Uterus of 8 days and 3 hours.

The perivascular sheaths have grown, the vessels have increased in size and their endothelium is thickened. The uterine epithelium is degenerated, "a hyaline degeneration with hyperplasia of the degenerating elements." The epithelium of the glandular cul-de-sacs is not degenerated. "The embryo is attached to the maternal placental surface only by the ectoderm" and this attachment is a plane surface.

(Fig. 1: Pl. XXVI.) This figure of Minot's represents the ectoderm as altogether cellular.

Uterus at 9 days and 3 hours.

The superficial glandular layer of the placental cotyledons is now distinct. The endothelial lining of the blood-vessels is considerably thickened. While the deep portions of the glands show little change, the upper portions are greatly degenerated. Over the area of placental attachment the uterine epithelium is thinned "corroded." (Page 357.)

Uterus of 9 days and 17 hours.

The thickened ectoderm has now become less distinctly cellular, cell-outline is partly obliterated—"degeneration is here going on." (Page 359.)

Uterus at 11 days and 3 hours.

Placenta is distinctly pedunculate. The multinucleate cells have appeared in the sub-glandular region and the perivascular sheaths have greatly increased. (Pl. XXIX.)

The three zones of placenta are well marked.

- (a) The outer zone, where the blood-vessels are very wide with degenerated endothelium.
- (b) The sub-glandular zone is now occupied by the multinucleate cells. These cells are derived from clusters of connective tissue cells. "The development of these cells would repay more accurate observation." (Page 361).
- (c) The glandular layer. The glands are altered, they are cylindrical in shape, contorted, and constitute an actual network. The uterine epithelium has disappeared and the foetal surface is covered by the mesothelium. Between the glands are blood-vessels with embryonic blood. The ectoderm has entirely vanished.

Monster cells now appear.

"I regard them as detached epithelial cells, but I have failed to ascertain positively their origin." (Page 365.)

Uterus of 13 days and 3 hours.

The placental surface is covered by mesothelium and between this and the glandular layer is the vascular mesoderm. The dentations of the glandular layer suggest "a series of foetal villi covered in part by a thin epithelium and covered at their tips by a relatively thick epithelium." (Page 370.) The multinucleate cells have increased in number and in size. The outer zone is solidly packed with perivascular cells.

Uterus at 15 days and 4 hours.

The glandular zone is slightly thicker and the columns of mesoderm run down more distinctly, and the foetal vessels come close against the glands. The sub-glandular zone shows its endothelium advanced in degeneration and with projecting cells, and some of the vessels contain

coagulum. In the outer zone the expansion of the vessels is far less active near the muscularis than further in, and here too the vascular endothelium is degenerated. The monster cells still exist.

"Die Placenta des Kaninchens" appeared in 1890 (16). In this short paper the gap in the former age-series is filled in, and Minot takes occasion to reconsider several of his previous observations, notably his glandular zone. He notes that in his former paper "Uterus and Embryo" he had not studied gestation-stages from the 10th to the 12th day, and he also confesses that he had not known the work of Duval. (Page 115.)

SUMMARY.

At the 6th day. "The placental area of the ovum is remarkable for the thickness of the ectoderm; this thickening corresponds to the ectodermal swelling of recent authors, but only in part, because, without recognising it as such, the superficial layer of the uterine epithelium has been attached to this swelling. This is an error that Strahl has noted, and into which are fallen Duval and Masius." The ectoplacenta is a combined tissue, composed of ectoderm and of uterine mucosa.

At the 7th day. The uterine glands of the placental region dilate and present a great thickening of their epithelium.

At the 8th and 9th days this thickening comes to obliterate the lumen of the gland.

At the 10th day. The bottom of the glands present still a cylindrical epithelium.

At the 11th day. The foetal villousities, already evident on the preceding day, take on rapid growth. "I believe that at first the villousities penetrate into the part of the glands left free by the resorption of the epithelium." (Page 119.) Each villosity is covered by the thick epithelium of the placental area and contains a prolongation of vascular mesoderm. Between these villousities are maternal capillaries, which, widely dilating, compress and cause to disappear the connective tissue of the mucosa, and consequently they come to occupy the whole space between neighbouring villousities, that is, between the double epithelial covering of these villousities.

At the 12th day. "The foetal villousities form altogether a layer very distinct, in the deeper parts of which are still some remains of glandular epithelium." (Page 120.)

At the 14th day. The foetal villousities are more distinctly seen and recognised as the structures which, in his earlier paper, he had considered glands. The epithelial walls of these villousities are of the nature of partitions, and they probably enclose between the two epithelial layers a middle layer of vascular maternal tissue, containing the circulating channels of maternal blood. (Page 121.)

"A Theory of the Structure of the Placenta" (16) appeared in 1891. Minot has now studied Duval's completed work, and he here at the beginning of his paper simply states the two errors into which he thinks Duval to have fallen. These are: (1) "interpreting the hypertrophied endothelium of the maternal vessels as foetal ectoderm;" (2) "regard-

ing the sections of the tissue separating the mesoderms of adjacent villi as tubes, instead of as sections of partitions." (Page 125.)

CRITIQUE.—I shall consider Minot's three papers together, culling his reconsidered results from one or the other. His opinions upon the points of controversy are as follows :—

(1) The origin of the giant cells.

These cells appear at the 11th day and are especially numerous in the ob-placenta. "I regard them as detached epithelial cells, but I have failed to ascertain positively their origin." (Page 365.)

(2) The attachment of the ectoderm to the uterine epithelium.

The ectoderm is cellular throughout, large distinct cells. "How this ectoderm is soldered to the uterine epithelium I do not know." A part of the uterine epithelium probably persists and forms the outermost covering of the villi.

(3) The origin of the multinucleate decidual cells.

These cells are derived from clusters of ordinary connective tissue cells. "The development of these cells would repay more accurate observation."

(4) The origin and nature of the maternal blood-cavities, swallowed by the ectoderm.

These cavities are not swallowed. The foetal villi plunge into the vascular maternal tissue. Adjacent villi enclose between their epithelial walls a middle layer of vascular maternal tissue containing channels for maternal blood.

(5) The nature of the so-called villi.

These villi are finger-like processes and contain a central core of vascular mesoderm covered by one or two layers of epithelium. This covering epithelium is derived in part from the ectoderm and in part from the uterine epithelium.

(6) The fate of the placental glands.

The glands disappear, their epithelium is absorbed, save that of their deepest cul-de-sacs. (Minot's oldest gestation sac is one of 15 days.)

(7) The behaviour of the sinus-endothelium.

This endothelium degenerates, its cells increase in size and become globular and multiply; the superficial of these fall into the blood stream. "the expansion of the vessels is far less active near the muscularis," and the result is the determination of a more compact area next the muscularis.

(8) The inter-junction of the two tissues, maternal and foetal.

There is an inter-growth of these two tissues. The foetal villi plunge into, and come to include between them, maternal vascular tissue.

(9) The determination of the zone of separation.

"In the outer zone the expansion of the vessels is far less active near the muscularis," and the result is the determination there of a more compact area.

My own results agree with those of Minot in the three points:—

- (1) The origin of the giant cells. (Minot has only inferred it.)
- (2) The attachment of the ectoderm.
- (7) The behaviour of the sinus-endothelium.

Innocenti Clivio's "Contribution" (17) appeared in 1890. It deals with the development of the placenta from the 5th to the 15th day. As Clivio practically agrees with Duval I shall summarise, but very shortly, his paper.

SUMMARY.

At the 5th day. The perivascular cells—the "*cellules vésiculeuses vaso-adventices*" of Duval—make their first appearance, and the first stages of degeneration are observed in the uterine epithelium.

At the 7th day. The degeneration of this uterine epithelium is more marked, the cells losing their individuality.

At the 8th day. The foetal ectoderm begins to adhere to this degenerated epithelium, and the ectoderm at this stage is altogether cellular.

At 9th and 10th days. The adherence of the ectoderm is accompanied by the disappearance of the uterine epithelium. When this adherence has acquired a certain extent, this ectodermal lamina becomes divided into two layers—a superficial layer where the cells are not distinct, and a deep layer composed of sharply-defined cells—so that from this time the "*ectoplacenta*" is differentiated into a plasmodial and cellular layer.

At the same time ingrowths from the ectoderm penetrate the uterine mucosa, and gradually surround the superficial capillaries. These capillaries, after being surrounded by the foetal plasmodium, lose their endothelial wall and become so transformed into *lacunæ*, hollowed out in the plasmodial layer. This plasmodial layer is undoubtedly of foetal origin.

At 12th and 15th days. The *lacunæ* hollowed out in the plasmodial layer of the *ectoplacenta* become divided by parallel columns of ectodermic tissue into a series of small canals, these canals containing always maternal blood. Between each of these columns, which are called "*canals ectodermics*," mesodermic elements are found.

The "*couche endovasculaire plasmodiale*" glides in from the foetal placenta and clothes the walls of the uterine sinuses.

CRITIQUE. Clivio's results are so nearly in accord with those of Duval that I shall not separately tabulate them, but to his one point of disagreement with the French observer I draw special attention. For Clivio observes that the attachment of the ectoderm to the uterine epithelium is altogether cellular, and that the plasmodial layer of the

ectoderm makes its appearance only after this attachment is established. This statement agrees entirely with my own observations as recorded in point (2).

J. D. Doormann's very short paper (19) appeared in 1893. He deals very briefly with the "fastening" of the blastodermic vesicle within the uterus in the case of the rabbit. Of the connection between the foetal ectoderm and "uterus wall" only two stages are described. This attachment is instituted by means of an intermediate layer, intermediate between the ectoderm and the maternal corium, derived exclusively from the maternal epithelium. The ectoderm itself is described as cellular, but the author is not very clear as to the ultimate behaviour of this intermediate layer. In this layer at the 7th day he describes large vacuoles formed by localised mucoid degeneration. The subsequent fate of these vacuoles is not indicated.

Doormann's paper thus throws light upon only one of our disputed points, namely:—

(2) The attachment of the ectoderm to the uterine epithelium. This attachment, he says, is cellular on the part of the ectoderm.

Ulesko-Stroganowa's "Beiträge" (23) appeared in 1896.

The authoress professes to concentrate her interest upon two questions:—

- (1) The manner of adhesion of the ovum to the mucous membrane.
- (2) The origin of the intermediate layer.

This profession, as will appear, the article scarcely fulfils. After a short description of the mucous membrane of the non-gravid uterus in the rabbit, Ulesko-Stroganowa begins her study of the placenta only at the 10th day. In the naming of the different areas into which at this date the uterine mucosa naturally falls, she follows Minot, though she has strangely misunderstood his "sub-placenta."

"At the 10th day the stroma of the placental folds is hypertrophied and changed into decidual cells; these are large, polygonal and transparent, with large, round or oval nuclei, and show with Fleming's solution rose-colored, radial, cytomitoma threads. There is no intercellular substance, the glands have disappeared, but in the midst of these cells are dilated vessels with endothelial walls." This quotation describes accurately our intermediary region of multinucleate decidual cells. But when a little further on are described, "in the placenta where the villi are packed closely together, large, transparent, polygonal cells with round or oval nuclei, foetal in origin, though they resemble the cells of the uterine decidua," it is at once evident that the authoress has interpreted neither the origin nor the nature of this region.

This tissue of large cells of foetal origin is called the "decidua foetalis." "The relation of this foetal decidua to the placenta is plain, for the closer the foetal decidua comes to the uterine decidua the more luxuriantly the former grows, until at length, pressing and penetrating deeply into the uterine decidua, it reaches the maternal capillaries."

Large spaces now become apparent through the breaking-down of the cells: these are filled at first with large homogeneous masses. It is natural that spaces so made should fill with maternal blood, as they certainly communicate with maternal capillaries. The uterine decidua continues to exist in the superficial layer in the form of the so-called "perivascular sheaths."

Such is Ulesko-Stroganowa's description of the maternal and foetal placenta at the 10th day. Her two appended photographs present, as Marchand says, "nothing to see," and the reader is left in hopeless confusion. As regards the origin of the different tissues which she describes, the authoress can only speak hypothetically for she has not examined the earlier stages.

The note on the presence of glycogen will be found in Section (B).

The description now passes to a gestation of 20-23 days. "Over the uterine decidua which lightly covers the muscular wall there is a structureless necrotic mass. The space between the placenta and the thin layer of decidua is divided into thin-walled cavities containing maternal blood. As pregnancy approaches conclusion the blood-spaces in the decidual layer become larger and more numerous. Its wall of decidual tissue gradually loses its swollen endothelium, and the pressure of the foetal decidua into uterine decidua is accompanied by the decay of both tissues."

Ulesko-Stroganowa argues from her conclusions that:—

- (1) The giant cells found in the spaces between the villi represent very rapid growths torn from the syncytium.
- (2) The giant cells which are found in the serotina in different periods of pregnancy originate from the elements of the cell layer of the villi.
- (3) The syncytium is a structure of foetal origin, arising from the cell-layer of the covering of the villi.
- (4) This syncytium can be considered a colossal multinucleate cell which covers the villi and forms the side of the intervillous space.

The "giant cells" here described are evidently none other than our multinucleate decidual cells, and the "syncytium" is the portion of the foetal ectoderm become plasmodial.

The paper scarcely repays its study, for at no point does it contribute to the knowledge of the structure or the development of the placenta.

Alexander Maximow's investigation (18), which was published in 1897, deals chiefly with finer histological details. As a considerable portion of this paper is devoted to a description of the structure and origin of the "glycogen-containing cell," a complete summary will be found under Section (B), while I shall consider here only his histological observations.

Maximow begins his study at the 8th day, when he describes the perivascular sheaths formed by "uninuclear glycogen cells" with large processes which interlace, forming a reticular tissue.

The uterine epithelium takes no part in the formation of the placenta.

The thickened ectoderm is altogether cellular, only after the attachment of the ectoderm and its subsequent contact with maternal blood does it become in part plasmodial.

By the 10th day the placenta is largely composed of blood vessels with thick sheaths. ("As soon as the ectoderm has reached the uninuclear glycogen cells it irritates them and they change into large multinuclear cells; this change is due to hypertrophy, a breaking-up of the nuclei, and a running-together and blending of several cells.")

The endothelium of the superficial capillaries disappears, the glycogen cells of the sheaths open out, and allow the maternal blood to come out between them and into contact with the ectoderm.

New spaces form within the plasmodial ectoderm which fill with maternal blood.

At the 11th day the inward growth of the embryonic tissue into the placental swelling ceases. At this time the ectoplacenta appears as a system of parallel villi.

At the 15th day "the placenta has reached the height of its development."

The maternal blood-spaces which appeared in the foetal plasmodium now come to occupy the space between the villi, parallel to their axis. Multinucleate glycogen cells are present in the ectoplacenta, "carried far from their point of origin," and included within the plasmodium.

In the "intermediary layer" the junction of the foetal plasmodium and the sinus-endothelium can be seen. The thickened lining of the uterine sinuses is endothelial in origin.

The placenta at the end of pregnancy shows only retrogressive changes. By diminution of the perivascular sheaths the blood-spaces become wider, the endovascular layer becomes flattened and atrophied, and may disappear.

The periplacenta and obplacenta are at this date dealt with and in connection with the latter the giant cells are described. Maximow affirms that these cells arise from connective tissue or endothelial cells. "These giant cells reach their full development on the 22nd or 23rd days, they afterwards completely disappear without our being able to give explanation of their meaning or formation."

My own results agree with those of Maximow in the following points:—

- (2) The attachment of the ectoderm to the uterine epithelium.
- (3) The origin of the multinucleate decidua cells. (I may say that Maximow and myself stand alone here and that my own observations were made before I had learned the opinions of Maximow.)
- (7) The behaviour of the sinus-endothelium.

Kossmann's paper (20), which also appeared in 1897, is concerned in part with the origin of "syncytiums" in the placenta of the rabbit.

In describing the development of the rabbit, Kossman says that by the 7th day the membrana pellucida has disappeared, the membranes

lying direct on the uterine epithelium. The latter has proliferated into processes and recesses, and by the loss of the cell membrane becomes the syncytium. The nuclei of this last multiply by direct division, fatty degeneration occurs in the protoplasm, with the formation of vacuoli. These changes are most marked on the surface, a distinct single layer of cylindrical epithelium persisting in the bottom of the glands up to the 7th and 9th day.

The mucosa is arranged in six folds, arranged in pairs symmetrical to the mesometrium; the pair next the latter hypertrophy, those opposite are flattened by the growing embryo; the two others are still visible at 7-9 days, but disappear later. The primitive ridge the embryo—develops opposite the hollow between the mesometral folds. The blastoderm is closely applied to the mesometral folds, and the ectoblast becomes many-layered. Through crumplings of the surface of the ectoblast, small papillæ arise, which push themselves into the the syncytium. At 8-9 days the allantois reaches this point with the foetal vessels, pushing the blastodermic wall before it. The ectoblast not growing so quickly, is stretched, and at the 10th day is again one-layered. By this time the villous processes of the allantois have extended deeply into the uterine mucosa, and with their covering of somatopleure and ectoblast form the chorionic villi. The ectoblast is thus so stretched that it is difficult to recognize its nuclei and cell-boundary, but Kossmann thinks these are present to the end of pregnancy. The villi push the syncytium before them. The chorion and uterine mucosa become intimately blended, but within the syncytium remain undoubted spaces—in part old gland spaces, in part vacuoli. The origin of the decidua from the reticulated connective tissue round the capillaries is disputed. The capillaries between the villi lose their endothelium, and thus a communication arises between the maternal blood-vessels and the lacunæ of the syncytium.

Upon the following points Kossmann's observations, in part at least, agree with my own:—

(2) The attachment of the ectoderm to the uterine epithelium. (Kossmann evidently wishes to convey the idea that this attachment is cellular.)

(6) The fate of the placental glands.

Frænkel in 1898 published a paper (21) in which a short mention is made of the placenta of the rabbit.

In describing pregnant uteri from the pig, cow, sheep, dog, cat, rabbit, squirrel, guinea-pig, rat, mouse and mole, Frænkel devotes two pages to the rabbit, giving a general report of his investigation of 12 uteri. After describing the non-pregnant mucosa he says that the uterine epithelium changes gradually into a typical broad syncytium, which is present wherever the foetal ectoderm is apposed to it. Wide capillaries are seen showing a distinct broad syncytium, in no other way connected with other tissues, for example, the uterine epithelium. Near to the point where the foetal ectoderm is in apposition to the uterus, the syncytial epithelium of the latter stops sharply, and the foetal ectoderm becomes closely united with the maternal tissue replacing completely the uterine epithelium, but forming such a distinct continuation of the same

that the greatest mistakes might easily occur. His conclusions are:— that the uterine epithelium is destroyed by the ectoderm, that the ectoderm is applied as a single layer of epithelium at a point where the uterine epithelium has already disappeared, that the ectoderm grows into the maternal connective tissue, and that a syncytium develops from the three sources above mentioned. Two drawings are given of the placenta—"early and advanced stages."

F. Marchand's "Beiträge" (24) appeared in 1898.

This author affirms that in the rabbit's placenta three questions remain to be decided, viz:—

(1) The relation of the uterine epithelium to the attachment spot of the ovum.

(2) The behaviour of the foetal ectoderm in relation to the uterine epithelium.

(3) What tissues form the wall of the maternal blood-cavities in the foetal placenta.

The specimens from which his observations are derived are seven in number, and range from the 8th to the 15th days inclusive, with an average age-interval of 24 hours. In two instances, that of 9 and 15 days, the age of the gestation sac is expressed as problematical. The accompanying plates are not particularly conclusive.

SUMMARY.

Uterus of 8 x 24 hours. The connective tissue of the placental folds is swollen, and the deeper capillaries show beginning perivascular sheaths, the individual cells of which have a clear content and contain glycogen.

The epithelium of the glandular cul-de-sacs is a low cylindrical, while in the gland-mouths and on the surface the cells are much larger and longer, the nuclei have directly multiplied and cell-outline is becoming indistinct.

The foetal ectoderm lies for the most part quite free opposite the surface of the uterine epithelium, only at one spot is there commencing adherence. This ectoderm shows already two definite layers, a plasmodial and a cellular. The plasmodial layer is formed from the underlying cellular layer—the cells of the latter gradually become more prominent, increase in size, lose their outlines, and fuse into homogeneous protoplasmic masses which gradually overspread the whole cellular layer. This soft plasmodial layer fuses, despite a zona pellucida, with the uterine epithelium.

Uterus of 9-10 days. (1) Uterine epithelium. The formation of the syncytium from the uterine epithelium can now be followed further:—the individual cylindrical cells swell enormously, become homogeneous and multinucleated, and cell outline disappears. Cilia are in places still recognizable. The gland luminæ are sealed with this syncytium as with a plug, and so an unbroken syncytial face is presented to the foetal plasmodium. Where ectoderm is already attached this syncytium is now broken through, its rupture being brought about

by two factors :—(a) The constantly stronger-growing mucosal vessels and their sheaths. (b) The ectoderm growing inward from the surface. The maternal vessels with their sheaths thrust themselves into the syncytial masses separating the deeper parts from the superficial.

(2) The vessels of the placental site. The vessels in the vicinity of the fixation-site increase in size, their endothelium thickens, and the uninucleated cells of their perivascular sheaths become more numerous, and mitotic figures are common. These glycogen vesicular cells have a definite membrane, scanty cell-protoplasm arranged in radial projections round the nucleus. "The multinucleated glycogen cells in the deeper layers and in the placenta foetalis show the same appearances apart from multiplication of nuclei and their great size." (Page 20.)

(3) The attachment of the ectoderm and the first formation of the foetal placenta :—The foetal placenta is formed in different degree at different parts, in some places it being much more deeply attached. Over some areas there is no plasmodial layer, and the cellular ectoderm is directly applied to the uterine syncytium.

The ectoderm grows into the syncytium in three different ways :—

- (a) By formation from the ectoderm of vesicular cells, which penetrate into the syncytium.
- (b) By formation of multinucleated vesicular cell-bodies with membranous envelope and fluid contents, which also penetrate the syncytium.
- (c) By formation of large compact masses of separate polyhedral cells, which penetrate the syncytium.

The mesoderm increases in amount and the primordial villi of ectoderm appear, though the term "villus" is not suited to designate this growth. (Page 25.)

The superficial layer of the uterine mucosa becomes changed into a cellular and soft mass—the intermediate zone. The deeper mucosa is better preserved; it shows wide vessels and isolated glandular cul-de-sacs plugged with syncytium.

(4) The formation of the blood-spaces of the foetal placenta.

A large number of the blood-spaces are formed actually in the cellular layer of the ectoderm. Also irregular blood-spaces are formed by extravasation immediately underneath the ectoderm, and in the midst of the loose cellular tissue of the intermediate zone. "Beginnings of such spaces give one the impression of vacuoles created by transudation of fluid from the succulent tissue." (Page 31.) Some of these spaces may arise out of ectodermic cells which have become vesicular. Where the deeper tubular, ectodermic processes ("villi") are formed, the blood lacunæ occupy a large part of the space between them. The glandular epithelium takes no part in the formation of the blood-spaces. (Page 32.) The vessels from the deeper mucosa become widened in their entrance into the intermediate zone, and become directly connected with the extravasation spaces therein. "These spaces receive now in part a cellular covering on the inner side of the ectodermal layers which can be followed to the complete lining of the

maternal vessels." (Page 33.) (Figs. 14, 15.) "The early disappearance of the endothelium in the superficial vessels of the mucosa I cannot confirm." These endothelial cells become the lining of the blood-spaces, and the trabeculae in these spaces.

Uterus of 11 days. The ectodermal processes reach deeper; they consist of round and polyhedral vesicular cells, and they form besides, tubes of cylindrical cells which surround the mesodermal villi, which are, in part, vascular. "The chief interest here is in the blood-spaces of the foetal placenta. The larger spaces underneath the surface of the ectoderm are clothed with elements, rich in protoplasm, and separated usually by fine cell boundaries. Sometimes there are no cell boundaries, and so long trabecular masses project into the lumen of the blood-spaces, or they fill up the spaces between the ectodermal processes, and are connected by protoplasmic bridges, between which, spaces are present with maternal blood." These elements lining these blood-spaces are derived from the endothelium of the pre-existing vessels, for "if one examines the vessels which come out of the deeper mucosa one can see that their endothelium, in their transition into blood-spaces does not disappear, but is directly continued into the lining of the spaces." The endothelial cells swell up, their protoplasm becomes soft and finely fibrillated, and their nuclei multiply and give rise to large multinucleate protoplasmic bodies which line the blood-spaces and project irregularly into them. "There is no doubt in places, as for instance (Fig. 19) where an ectodermal process which is deep in the mucosa, comes into contact with the altered blood-space, that the lining of the blood-space has nothing to do with the ectodermal plasmodium." (Page 36.)

Uterus of 12 days. The formation of blood-spaces is completed, the foetal placenta projects like a pillow, and the boundary is sharp between it and the maternal part. A continual ectodermal covering is no longer present on the surface of the foetal placenta, since the allantoic tissue with its vessels occupies an increasing area. The deeper layers of the ectoderm reach to the base of the foetal placenta, where they form the blindly-ending ectodermal processes which sheathe the allantoic villi. "The large vessels of the maternal placenta with their sheaths composed of multinucleated glycogen cells show the known proliferation of their endothelial cells, which near the foetal placenta are changed into a multinucleated protoplasmic mass, in which the glycogen cells seem to disappear. It is difficult to determine the share which the glycogen cells take in the formation of the protoplasmic substance. (Page 38.) More toward the musculature the protoplasmic lining of these vessels decreases more and more until only a flat layer, similar to the thick endothelium, is found.

Placenta of 14 days. "The foetal placenta sits on the maternal part like a thick pillow. The "ectodermal pillars" are now distinct and are separated by mesodermic villi. These pillars consist of a highly-nucleated protoplasmic mass, which is filled with irregular hollow spaces containing maternal blood, and which communicate with the vessels of the maternal placenta. These pillars are plasmodial and are derived in part from the foetal ectoderm, and in part from other elements, vessel-sheaths, etc., found on the surface of the mucosa. The mesodermic "villi" now multiply and branch, especially near the

surface, and they penetrate and divide the "pillars," splitting them into smaller and smaller lamellæ, in which the now tubular and much-twisted maternal blood-capillaries run. The passage of the maternal vessels into the blood-spaces of the pillars can be followed. Delicate mesodermal tissue with allantoic capillaries fill the spaces between the protoplasmic lamellæ. The maternal blood-spaces in the lamellæ are sharply bounded and a special lining is wanting, though the inner boundary of the protoplasmic wall is marked off as if by a definite edge. (Figs. 26, 27, 28.)

Placenta of 15-16 days. Practically the same appearances are found. "A horizontal section of the coarser arrangement of the placental lamellæ is figured. (Page 43.) One recognizes that the lamellæ occupy the space between the much-folded mesodermic villi, and these latter are in transverse section somewhat radially branched. The middle of the branched system is occupied by a somewhat larger foetal vessel."

Resumé of chief results. (Pages 44, 45.)

I. The connection of the ectoderm and uterine mucous membrane takes place by means of a previously formed ectodermal plasmodium, which fuses with the epithelial plasmodium (syncytium) of the uterus. (In places where the ectodermal plasmodium is not fully formed, the cellular layer enters into immediate connection with the syncytium).

II. The ectodermal plasmodium as such, disappears for the most part during the attachment.

III. The blood-spaces of the foetal placenta arise at first as vacuoles or lacunæ within the ectoderm, and within the cellular layer formed from it, and from other elements, blood-sheaths, etc., found on the surface of the mucosa. These vacuoles or lacunæ become filled with maternal blood extravasated from the superficial mucosal vessels, owing to a loosening of the vessel wall, and they soon receive a special cellular lining derived from the proliferating endothelial cells of the maternal vessels whose perivascular cells disappear.

IV. The uterine syncytium is mostly absorbed by the proliferating ectoderm, save small remains pressed away to the margin of the placenta. We can exclude any origin of the lining of the vessels from the ectoderm or the epithelium of the uterus.

A short comparison with the placenta of the cat concludes the paper.

CRITIQUE.—These "Beiträge" of Marchand, the most complete of the German contributions to the study of the rabbit's placenta, do not compare favourably either in clearness of description, in faithfulness of depiction, or in accuracy of results with the *Mémoire* of Duval. Marchand's conception even of the fundamental plan of the placenta is most ambiguous, and its divisions into maternal and foetal portions are altogether confused. The influence of Hubrecht's work on the hedgehog (25) is everywhere evident, indeed Marchand claims to have discovered a "trophospongia" in the rabbit's placenta which "corresponds completely" to that in the hedgehog. But in this Hubrecht

himself is against him, for in his study of the placentation of the hedgehog (Journ. of Micr. Sci. 1890, p. 327) Hubrecht says that "*perivascular* proliferation by which we can account for the origin of the trophospongia seems to occur in the rabbit." Moreover Hubrecht's trophospongia is exclusively of maternal origin, while Marchand derives his from both maternal and foetal elements. Several of Marchand's observations are on the face of them inconsistent. What of the foetal plasmodium which is formed before attachment of the blastocyst, which disappears at the time of attachment, and which re-appears on the 14th day — a conglomerate of maternal and foetal elements? What of maternal blood-cavities in the foetal placenta which are first mere vacuoles in the midst of the ectoderm, which become filled with blood from a neighbouring vessel, whose wall (including its endothelium) becomes loosened, and which become immediately lined by endothelial cells which have arisen from the loosened endothelium of the vessel? Following are Marchand's observations upon the "disputed points."

(1) The origin of giant cells.

Marchand does not mention these.

(2) The attachment of the ectoderm to the uterine epithelium.

The connection of the ectoderm and uterine mucous membrane takes place by means of a previously formed ectodermal plasmodium. (Marchand qualifies this statement by saying that in places where the ectodermal plasmodium is not fully formed the cellular layer enters into immediate connection with the uterine syncytium).

(3) The origin of the multinucleate decidual cells.

Multinucleate glycogen cells arise from the foetal ectoderm, and also from the endothelium of the maternal vessels. (The multinucleate cell of distinct individuality does not exist for Marchand.)

(4) The origin and nature of the maternal blood-cavities *swallowed* by the ectoderm.

The blood-spaces of the foetal placenta arise at first as vacuoles or lacunæ within the ectoderm, and within the cellular layer formed from it and from other elements, vessel-sheaths, etc., found on the surface of the mucosa.

(5) The nature of the so-called "villi."

The "villi" are the vascular, blindly-ending mesodermic processes which lie between the "ectodermal pillars."

(6) The fate of the placental glands.

At the 9th and 10th days the glandular cul-de-sacs are plugged with syncytium. "This glandular epithelium takes no part in the formation of the blood-spaces."

(7) The behaviour of the sinus-endothelium.

"The large vessels of the maternal placenta show the known proliferation of their endothelial cells, which near the foetal placenta are changed into a multinucleated protoplasmic mass."

- (8) The inter-junction of the two tissues, maternal and foetal.

There is no line of demarcation between the two tissues. There is a trophospongia, a tissue common to both maternal and foetal portions, and in the midst of this all definite inter-junction is lost.

- (9) The determination of the zone of separation.

Marchand does not mention it.

- (10) The fate of the decidual cells.

This question goes beyond the age-limit of Marchand's specimens.

My own observations do not agree with those of Marchand upon any one of these points. The most that can be said is that in (7) there is some slight agreement.

Opitz in 1899, at the February meeting of the Obstetrical and Gynaecological Society of Berlin, presented the Vortrag:—Vergleich der Placentarbildung bei Meerschweinchen, Kaninchen und Katze mit derjenigen beim Menschen (37).

Beginning with a preliminary comparison of the work of Ruge and Kossman in respect of the origin of the syncytial covering of the villus, Opitz goes on to consider his own work, first in the guinea-pig and afterward in the rabbit.

In the rabbit the work is critical rather than original, and in the opening sentence Opitz thus defines his position: "I now come to the corresponding condition of the rabbit, and unhappily I am not in the fortunate position of possessing a great deal of material, as with the guinea-pig. However, the exact study of an ovum, 18 days old, for which I thank Professor Ruge, has given me important revelations (as even after this time there are still new appearances), the correctness of which seem to be confirmed by illustrations of earlier stages, as given by Kossman and Marchand." As during these earlier stages the observations of Kossman and Marchand are often contradictory, it is difficult to imagine how the study by Opitz of an 18 day placenta could establish a position between them.

Opitz passes in short review the various stages of gestation after the attachment of the ovum, and his paper partakes, both in manner and in substance, of the nature of an exegesis. For the greater part he follows Kossman, using his illustrations and in the main agreeing with him. In the matter of the attachment of the blastophere, however, he falls under the influence of Marchand and affirms the existence of an ectodermal syncytium, traversing thus the correct, in our view, observation of Kossman that this syncytial layer is solely uterine.

The illustrations are all conspicuously diagrammatic, especially "Schema iv." There is little original or first-hand work in the paper and its value is rather that of a critical contribution to the literature of the subject.

Alexander Maximow, after an interval of three years from the date of his former paper (18) on the rabbit's placenta, in 1900 published a second contribution—Die ersten Entwicklungsstadien der Kaninchen Placenta (38).

During this interval, in his own country Kossman, Opitz, and especially Marchand, have published studies of the rabbit's placenta.

Maximow acknowledges this work and its effect is most apparent in that he retracts his earlier contention as to the cellular attachment of the ectoderm to the uterine mucosa. Maximow states that his object in this second paper is "to ascertain the most exact description of the morphology of the earliest and most important stages of the formation of placental tissue in rabbits and especially the finding of the origin and the importance of all parts of it." (See page 706.)

The period of gestation studied ranges from the 8th to the 11th days inclusive, with an age interval in the series of one day—24 hours. He confesses that his former mode of procedure of cutting open the gestation-sacs and excising the placenta with its attached uterine wall, to have been crude, and now advocates the fixation of the uterine cornu *in toto* before section of the gestation-sacs is made—the method pursued by myself.

As in his earlier paper Maximow begins his study at the 8th day of gestation, and while his description of the corium of the cotyledons is here more elaborate, in all essential details, e.g., the origin and formation of the perivascular sheaths, the growth of the sinus-capillaries and the behaviour of their endothelium, the nature of the inter-cellular ground substance—it remains the same. The great departure from his former paper comes with the description of an ectodermal syncytium by means of which the ovum is attached to the placental cotyledons. This syncytium is described as a protoplasmic layer, in some places thick, granular and dark-stained with numerous large chromatin-rich nuclei—a genuine ectodermal syncytium and a product of the cellular ectoderm.

This ectodermal syncytium is not figured before its attachment to the maternal cotyledons but is only shewn (see pb. Fig. 1) after it has become soldered to the "altered uterine mucosa" (mp. Fig. 1). This altered uterine mucosa is called the "uterine syncytium" and from the first its description tallies dangerously with that of the ectodermal syncytium.

Maximow argues that the attachment of the ectoderm to the uterine mucosa is effected by means of the fusion of these two syncytia:—an ectodermal syncytium, foetal, and a uterine syncytium, the maternal. He affirms that though these syncytia are soldered closely together they are at this stage easily distinguished, for between the two is to be found in many places a layer of closely-crowded vacuoles, and the protoplasm of the ectodermal syncytium is closer and darker and its nuclei are larger and contain more chromatin than those of the uterine syncytium. These differences are only of degree, are merely relative, and the argument fails completely to convince, while a critical study of Fig. 1, Plate XXX., wherein these observations are represented, gives the direct negative to the thesis of the text. For from this figure alone it seems to me conclusive that the ectoderm (ed) is altogether cellular, that (pb) and (mp) indicate, not two syncytia but simply the "altered uterine mucosa," and that (x) indicates the space, not between the ectoderm and the ectodermal plasmodium, but between the ectoderm and the "altered uterine mucosa"—the uterine syncytium.

Maximow states that the "incorrect interpretations" of his former paper in this respect were due to the fact that he had, in his work, largely employed as a fixing agent osmic acid, which does not permit a sharp differentiation to be drawn between ectodermal and uterine plas-

modium, and that he had detached the placental swelling in fresh condition from the gestation sac. "This wrong impression found further support from observations of those parts of the placental site where in subsequent stages the ectoderm, with no plainly developed syncytium, attaches itself directly to the uterine mucosa." (Page 711.)

At the 9th day the perivascular sheaths of the corium have increased in thickness coincident with the further growth of the vessels. Their endothelium is intact save in the most superficial capillaries where the endothelial cells form no longer an uninterrupted layer and where the wall is partly formed by the perivascular uninucleate-decidual cells. (Fig. 2, Gz.) These superficial capillaries lengthen, enlarge and become convoluted; they reach to the under surface of the epithelial syncytium, effect in this under surface corresponding concavities, while at the same time the inter-glandular connective tissue septa are thinned.

In the above description Maximow has elaborated his former study at this stage and in so doing attributes to the endothelium lining the superficial capillaries a behaviour different from that lining the deeper vessels. For in the superficial vessels he says that the endothelial cells become in places dislocated and "removed from one another," and the wall of the vessel is in these places maintained by the uninucleate-decidual cells of the perivascular sheath. He illustrates this fact in Fig. 2 Gz., but it seems to me that he has confounded the flattened uninucleate-decidual cell with the modified endothelial cell, for, according to my own observations and also from my interpretation of Maximow's plates, the endothelium of the vessels, whether superficial or deep, behaves, at this stage, in the same way, and it is only later and when the vessel is within the grasp of the foetal plasmodium that the hypertrophied and multiplied endothelial cells fail to afford a complete lining to the vessel, become dislocated and disappear.

Maximow returns at this stage to a discussion of the ectodermal and uterine syncytia. On page 714 he confesses that these two syncytia are "mixed up completely and are no longer distinguishable," though on page 717 he claims that in the masses of the mixed syncytia the embryonal nuclei are to be distinguished by their "size, their richness in chromatin, granular appearance and large nucleoli." As shown in Fig. 2, these distinctions are scarcely evident.

Maximow asserts that the ectodermal plasmodium or syncytium removes the uterine syncytium, acts upon it by a process of chaemotaxis, the loose masses of the uterine plasmodium retiring before the other's advance, more and more deeply into the gland channels of the placental cotyledons where it fragments and undergoes degeneration. On the other hand, "the ectodermal syncytium never degenerates, on the contrary it shows great activity; *in many places it is now as formerly independent of the ectodermal cell-layer and appears to be separated from the latter by an interval*, though in other places new cells can be seen going over from the cellular layer into the plasmodium and enlarging the same. An independent growth the plasmodium cannot have because its nuclei do not multiply, but it is, as I have said, a viable tissue, though in places its nuclei degenerate."

I confess to some wonder as to the "viability" of the ectodermal syncytium as above described. The italics are my own, for my conten-

tion is that the interval described by Maximow as existing between the syncytial and cellular ectoderm, is, on the contrary, the interval between the ectoderm, which at this stage is altogether cellular, and the uterine syncytium; or in other words the plasmodial layer which Maximow claims as ectodermal syncytium, we identify as the hypertrophied and degenerate maternal epithelium, both surface and glandular, of the placental cotyledons.

I now epitomise Maximow's study of the 10th and 11th days.

On the 10th day, the most important stage for the study of the origin of the placenta, according to Maximow, the following: The large protoplasm masses in the deeper layer,—the remains of the uterine syncytium, show beginning degeneration in that the nuclei lose their oval or round form, seggregate and become attached to the surrounding tissues, especially the capillaries, while the cell protoplasm becomes looser and vacuolated. *A direct communication between the ectodermal syncytium and these degenerating protoplasm masses is no more to be seen.* (The italics are mine). The gland-mouths which existed formerly in the superficial layer, having been taken up by the ectodermal syncytium have disappeared. The whole superficial layer consists solely of capillaries and syncytial masses, which later resolve, at the boundary between the superficial and deep layers, into irregular protoplasm masses with ectodermal nuclei lying in the ground substance and between the capillaries.

A new tissue has now developed in the central part of the placental folds, namely, the blood spaces of the placenta foetalis filled with maternal blood. These form rapidly and subsequently to the conditions already described. The hollow continuations of the cell layer of the ectoderm, the "primordial villi," have entered deeper into the mucosa and have grown out in many places into hollowed side-branches. Into the interior of these "villi" the allantoic vessels commence already to grow from the external coelome. Outside of the "primordial villi" the superficial layer of the placenta consists of capillaries with ectodermal syncytium between them. Now appears under the enlarged glycogen cells a loosening of the capillary wall. It yields, becoming more and more expanded by pressure until it bursts at a certain place. Maternal blood so escapes and meets the ectodermal syncytium and effects in it by the process of extravasation a hollow space which grows gradually in size and lies under the surface of the placental formation (see Fig. 6) which finally can become very large and which elevates the cell layer of the ectoderm with the syncytial layers always attached to it, bulges it and thins it so that the ectodermal cells lose their cylindrical shape and become cubical and flat.

The vessel, whose wall consists of large glycogen-cells and which shows on its inner surface single endothelial cells, appears funnel-shaped and goes into a space outlined by ectodermal plasmodium (Fig. 6, 1.). Where they exist one can follow single endothelial cells so far as the transition place of the capillary into the large blood lacunæ of the syncytium. (e.x. Fig. 6.) If the wall of the vessel, before extravasation, consists only of endothelial cells, some few of these may be found on the inner surface of the ectodermal syncytium of the lacunæ; these soon degenerate by shrinking of their nuclei and protoplasm, separate and

disappear. (Fig. 5, e¹.) Therefore the maternal blood comes from the superficial capillaries of the placental folds into hollow spaces outlined by ectodermal syncytium, in which the circulation is at first incomplete so that fibrin-formation occurs in these. From these lacunæ the blood forces its way between the syncytium masses, owing partly to blood pressure and partly to the fact that there are found in the ectodermal syncytium in many places vacuoli which latter connect with the lacunæ containing circulating blood. (Figs. 4 & 6, l.) Between the villi are found ectodermal syncytial masses which form a network of protoplasmic trabeculæ of different thickness and in the meshes of which maternal blood circulates.

The growth of the ectodermal cells forms the villi and gives the material for the new masses of ectodermal plasmodium. Of the growing in of the ectoderm into the mucosa we must speak with great care. An active entrance of the foetal tissue into the maternal one in the early stages must be supposed, but this does not last long; actually up till the moment when the first blood spaces are formed in the syncytium by extravasation. Though later the foetal syncytium enters deeper in many places and comes especially within reach of the so-called intermediary layer, the ectodermal villi never reach the level of the syncytium lumps in the glands. The ectoplacenta does not develop at the expense of the mucosa, but chiefly by independent growth of the embryonal tissue.

At this stage the intermediary layer appears, which consists of multinucleate glycogen-cells developed from the uninucleate perivascular decidual cells. The walls of the vessels loosen and the maternal blood bathes directly the cells and they take up the blood corpuscles into their bodies.

This practically concludes Maximow's study of the 10th day. Fig. 7 shows admirably a capillary-sinus lined in part (to the right) by endothelium and in part (to the left) by syncytium; the junction of the two tissues is seen at x. Maximow, by means of this figure alone disproves Marchand's assertion that the syncytium lining the blood vessels of the placenta foetalis originates from maternal endothelium.

At the 11th day, the last period studied, Maximow states that he finds only a further differentiation of former tissues and that in order to shorten the work he will describe only the capillaries in the intermediary region of the placenta and the following is a short summary:

The foetal placenta is composed of rather long villi formed by the growing cell layer of the ectoderm, which contain already embryonal vessels and which branch more and more. Between the villi is found the variously formed network of the syncytium with the blood lacunæ. The intermediary zone consists of two layers:—

- (a) Superficial layer, formed altogether of great masses of multinucleate glycogen-cells.
- (b) Deeper layer, formed in addition, of already-degenerated remains of uterine epithelium.

The capillaries which connect the blood spaces of the placenta foetalis with the deeper maternal vessels, have no capillary sheaths; they possess a lumen, often narrow and often widened, and are convoluted

and therefore are rarely seen in their whole length. (Fig. 12.) Superficially the walls are formed of ectodermal plasmodium in which lie degenerated cells (glycogen-cells), while deeper they are formed chiefly of glycogen cells, multinucleate and uninucleate, and some few endothelial cells which in the deeper part of this region hypertrophy (Fig. 12, e) and contain often a number of degenerated red and white blood corpuscles.

Between the superficial and deep lengths of the capillary is to be found the most interesting place of the whole placenta (x). Here the foetal and maternal tissues meet. The large endothelial cells cease suddenly while above the plasmodial masses have not yet approached towards the last endothelial cell, and in the space between, the glycogen cells bound directly the lumen. (Fig. 12, x.) These glycogen cells lie here mixed up with deeply-entered, isolated, ectodermal protoplasm masses and they undergo remarkable changes; they hypertrophy like the endothelial cells, do not store up a large amount of glycogen, but contain instead a great number of red blood corpuscles which gradually disorganize and leave behind within the large cells, formations like cell debris. These glycogen cells which line the vessel in part here are characteristic of the intermediary region while, where the foetal and maternal tissues meet, the endothelial cells in their hypertrophy become quite similar to these glycogen cells.

This completes Maximow's present research and I quote now his "Conclusion."

"In the ectodermal swellings at the 8th day are found two layers—an inner one, cellular, and an outer one, syncytial which attaches itself to the placental folds. The epithelium of the placental folds changes also into a syncytial mass which is quickly pushed into the depths of the glands by the ectodermal plasmodium and there degenerates completely. The ectodermal plasmodium enters into the tissue of the mucosa, sending into it hollow "primordial villi." In the depth of the mucosa thick sheaths of glycogen cells form around the vessels, while the superficial capillaries have thin walls which consist of uninucleate glycogen cells and an incomplete endothelial lining.

The ectodermal plasmodium after displacement of the uterine epithelium, grows around these superficial vessels everywhere, the walls of which in consequence of the hypertrophy of the glycogen cells, become loosened, are stretched and finally torn by the blood pressure, so that an extravasation directly into the syncytium masses takes place. By this means originate immediately in these masses lacunæ filled with maternal blood which change, in the further growth of the embryonic tissue of the ectodermal cell-layer as well as of the plasmodium (continually formed anew out of the same), into the complicated lacunæ-system of the placenta foetalis found between the villi. In the intermediary layer the endothelial cells of the maternal capillaries lie directly upon embryonal syncytium of the blood lacunæ of the placenta foetalis without it being possible to ascertain the entering of the same into the lacunæ. At the 10th day these endothelial cells begin to hypertrophy and form finally the large-celled lining of the blood spaces of the maternal placenta, which can be followed to the blood-spaces in the intermediary region lined by embryonal syncytium."

This paper of Maximow's shows abundant care and pains-taking research and is a valuable contribution to our knowledge of the rabbit's

placenta. While the observations cover only a comparatively short period—namely, four days—yet, as Maximow states, these are the important days of construction. The technique has been good and the illustrations are well and faithfully worked out. Leaving for the time the “disputed points” out of the question, the main differences between Maximow’s results and my own are two—(i) the structure of the ectodermal swellings and their attachment to the uterine epithelium; (ii) the origin and nature of the maternal blood cavities in the foetal placenta.

After a close study of the text and especially of the plates, these differences seem to me to be due rather to interpretation than to fact, for the incidents in the life-history of the placenta as portrayed in these plates, correspond exactly to their representation in my own photomicrographs. To my mind in Maximow’s Fig. 1, the ectoderm is altogether cellular and the plasmodial layer to which it is attached is single, and solely maternal, this plasmodial layer being simply the uterine mucosa, both surface and granular, become enormously hypertrophied and plasmodial. Maximow claims that only part of this syncytium is uterine, the deeper part, while the superficial part is ectodermal; I maintain that it all is uterine. A study of the earlier stages of gestation helps in this matter and I think that my own photomicrographs show conclusively that the ectoderm is altogether cellular both before its attachment and afterward, until at the 10th day it meets maternal blood.

The second point of difference leads naturally from the first, for having two syncytia, a maternal and a foetal, Maximow finds difficulty in disposing of them. His disposal of the uterine syncytium by making it “retreat” into the placental glands, appears artificial, and moreover there is thus needlessly created a zone of difficulty, —a region where foetal and maternal structures commingle and become confused. In this zone of confusion it is that the foetal plasmodium meets first the maternal vessels and where appear in the foetal ectoderm the first maternal blood-spaces. Unfortunately a process sufficiently intricate is so rendered rather more obscure. Maximow considers the maternal blood-spaces in the placenta foetalis as due to hap-hazard extravasations into the foetal ectoderm, that the superficial maternal capillaries lined either by endothelium or glycogen-cells, rupture upon the approach of the foetal plasmodium, and maternal blood is so extravasated into the foetal plasmodium; blood-spaces in the foetal ectoderm are thereby created, which in the further growth of the embryonic tissue are changed into the complicated lacunæ-system of the placenta foetalis.

Against this supposition there appear to me two reasons:—

(1) The capillaries rupture at the junction of foetal and maternal tissues; the one tissue is plasmodial and dense, the other cellular and lax. Blood extravasated follows always the line of least resistance and in consequence it would not enter the plasmodium at all—this an active viable plasmodium—but would be confined solely to the intermediary region.

(2) The blood-spaces of the foetal placenta at this stage always definitely occupy the axes of the ectodermal columns. If these spaces are due to extravasation only, extravasation always more or less hap-hazard, how account for their definite and ordered distribution?

I quite admit that the maternal vessels often rupture when and where Maximow maintains, but my contention is that these extravasations are passive, that the foetal plasmodium is the active agent, and that it surrounds, swallows, the blood-space, in its inward deeper growth. From the time of the first contact of the ectoderm with the corium of the placental cotyledons, the inward growth of the ectoderm is always more advanced along the lines of the maternal vessels. The ectoderm follows these vessels swallowing them, replacing their former cellular walls by its own plasmodium. If the vessel have ruptured (if the stream expand into a lake) the adventitious walls of the extravasation are still followed, and the "lake" included. In this way we can, I think, account, in part, both for the columnar disposition of the foetal placenta and also for the axial arrangement in the columns of the maternal blood-spaces.

I regret that the number of the "disputed points" upon which Maximow and I agree are now reduced to two :

- (3) The origin of the multinucleate decidual cells.
- (7) The behaviour of the sinus-endothelium.

SECTION B.

GLYCOGEN IN PLACENTA AND FŒTUS.

The presence of glycogen in the placenta was discovered by Claude Bernard in 1859. In that year his paper "*Sur une nouvelle fonction du placenta*" (1) appeared, the object of which was to establish "that amongst its uses, without doubt diverse and multiple, the placenta is destined during the earlier period of fœtal development to accomplish the glycogenic function of the fœtal liver, before the function of the liver is established."

Bernard's first researches throughout several years were made upon ruminants, and were unsuccessful. He then had recourse to rabbits and guinea-pigs.

"In the placenta of these animals I now found a white substance formed by the epithelial cells or glandular masses, and I perceived further that these cells were full of this glycogen matter. This mass of glycogenic cells seemed to me to be situated principally between the maternal and fœtal portion of the placenta, and after becoming fully developed it seemed to atrophy in proportion as the fœtus approached the moment of its birth. I have thus recognized that the placenta of rabbits and guinea-pigs is formed of two portions having distinct functions—the one vascular and permanent up to birth; the other glandular, preparing the glycogen matter and having a duration more restricted."

Bernard thus summarises his paper :—

"There exists in the placenta of mammals a function which up to the present remained unknown, and which appears to supply the glycogenic function of the liver during the first period of embryonic life. This function is localized in an anatomical glandular element, or epithelial, of the placenta, which in certain animals (e.g. rodents) finds itself mingled with the vascular portion of this organ."

While Bernard has correctly described the general distribution of the glycogen in a placenta of from 14 to 20 days, in that "it seemed to be situated between the maternal and fœtal portion of the placenta," he made no attempt to localize the glycogen further than to say that it is found in the "epithelial cells or glandular masses" by which it is secreted.

Godet in 1877 (1) describes in the rabbit's placenta a glycogen-layer. This layer is formed of large multinucleated cells rich in glycogen, and is found immediately underlying the fœtal villi. Indeed, "the epithelioid tissue covering these villi is formed from a part of the large cells of the glycogen-layer." This glycogen-layer answers exactly (it is also figured), to our intermediary region of multinucleate cells. Godet also speaks of smaller vesicular glycogen-containing cells in the deeper regions of the placenta. Godet's "*Recherches*" deal only with the placenta at mid-term or thereby—in his earliest gestation sac the embryo was 2 cms. in length.

In order to maintain a chronological discussion I shall now give, very shortly summarized, the studies of Langhans and Merttens upon the presence of glycogen in the human placenta and membranes.

A first contribution to the literature of glycogen in the human placenta and foetal membranes was made in 1890 by Langhans in his paper on "Glycogen in pathological new formations and the human membranes." For mounted sections he recommends staining with tincture of iodine, diluted with three or four parts absolute alcohol; for clearing he uses *oleum origani*, which preserves the stain longer than other methods. After describing glycogen in cartilaginous and bony tumours, tumours of the testicle and ovary, the epithelium of uterus, cervix and vagina, as well as tumours of other organs, he takes up very briefly glycogen in the membranes. "I do not know that any investigator who has taken up the anatomy of the membranes has given results as to glycogen in them; the following observations are only fragmentary." He then says that he has not found it in the fully developed placenta, only in young ova with a diameter of $1\frac{1}{2}$ to 2 cms. Its presence is most constant in the amnion in its epithelium and connective tissue. The chorion is rich in glycogen, which is present, not in the epithelium, but in the connective-tissue cells below, appearing as small half-moons on the foetal side of the cells; in the decidua it occurs as free granules, and also as half-moons in the large polyhedral cells—the half-moon being directed towards the uterus in the vera, and the ovum in the serotina. Also in the smaller cells at the ends of the processes. It is not present in the canalized fibrin in the serotina, but occurs in the knots of large-celled tissue at the points of the villi which Langhans formerly considered as maternal, but now regards as derived from the cellular layer of the chorion.

J. Merttens (4) whose work was done in the Pathological Institute of Langhans at Bern, in describing an ovum, found in the *débris* of the curetting 16 days after the termination of the menstrual period, refers to the presence of glycogen in the decidual cells as follows: "Between the ampullary decidual layer and the villi there lies that layer which I have above regarded as the analogue of the later compact layer. (See Figs. 3 and 4.) It encloses the whole ovum right round the villi, to the thickness of .35 mm. Even with a low power it stands out in contrast to the deeper layer just described, by its very large cells and the many spaces lying between them. The cells have usually the form of a thick spindle, the length being up to .057 mm., and the thickness .045 mm. They lie as a rule parallel to the surface. Peculiar to them all is a deep red stained border, which forms the convex side turned towards the placental space. It is like a half-moon, i.e., broadest in the middle, and its shimmer diminishes gradually towards the interior of the cell. It stains deep red with eosin. The iodine reaction shows that we have here to do with glycogen. This exactly agrees with the observations of Langhans, who found in the decidual cells these half-moons, with their convexity turned towards the placental sinuses. This border frequently sends to its middle and between the two cells lying beside it a plug-like process."

Sections are given showing this portion of the decidua under low and high power.

In describing portions of the uterine mucosa near the ovum he says "a much greater difference of the two layers, the superficial and the deep, appears in the structure of the mucosa; in the upper there are decidual cells, such as have been described above in the ampullary zone. They have a polyhedral shape, a very clear protoplasm which frequently is only slightly stained with eosin, usually a distinct border, which may however be absent so that they seem to run together. With the glycogen test, the glycogen half-moon appears in individual cells, only at very few points and quite near the surface, and only at the side turned towards the uterus."

The observations of Langhans and Merttens are at the best fragmentary.

The most important contribution to the study of glycogen in the placenta has been made by Maximow in the placenta of the rabbit. This paper (5) which was published in 1897 I have previously referred to under section (A) so far as it dealt with points of histology or histogeny, but I now give a complete summary of the paper itself.

After referring to Duval's results Maximow mentions his own material and methods; his observations are based on five rabbits, in which the date of impregnation was noted, and representing the 8th, 9th, 10th and 11th days of gestation, and some 35 others from the later periods of gestation, of which the duration was determined by the development of the placenta.

Under the first stages of the development of the placenta he describes the vascular sheaths, composed of cells with the single nucleus and a membrane, and within the latter, a transparent homogeneous substance, which is "nothing else than glycogen." The structure of these "uninuclear glycogen cells" is given, his results differing from Duval in this that, instead of each cell being shut off by a membrane their processes interlace forming a reticular tissue. On Duval's assumption of a cell-membrane the glycogen must be stored in the body of the cell, while Maximow believes that it is originally in the meshes of the reticulum. By the 10th day the placental tumour consists almost entirely of broad vessels with thick sheaths, the rest of the mucosa being reduced to small spaces between. Towards the free surface of the mucosa the vessels have a narrower calibre, their sheaths are thinner, and the endothelium present only here and there. This may be due to the fact that the endothelium does not follow the rapid growth of the walls of the sheath, or its cells may have become converted into uninuclear glycogen—containing sheath-cells. The ectoderm in embracing the vessels, finds the endothelium absent, and does not bring about its atrophy as Duval says. The surface epithelium becomes changed into a continuous mass of protoplasm with degenerative nuclei, as does also the epithelium of the glands. When the ectoderm is still simply applied to the surface of the mucosa there is no ectodermal plasmodium—it appears later, but it plays an important role in burrowing into the mucosa. As soon as the ectoderm has reached the uninuclear glycogen cells it irritates them, and they change into large multinuclear cells, rich in glycogen. This change is due to a hypertrophy, a breaking-up of the nuclei, a running together and blending of several cells.

Having described how a kind of membrane develops round the uninuclear cells from their processes becoming united, he says that a marked glycogen formation takes place in them, pushes the nuclei of adjacent cells together, thins the membranes separating them, while that at their periphery remains thick; thus arise the large multinuclear cells with a distinct membrane. Division of nuclei does not take place by mitosis, but by direct breaking-up—amitosis. In addition to glycogen fat-granules are found in the multinucleate cells on the surface of their processes, never as globules but as irregular granular masses. In these cells also, especially when surrounded by maternal blood, appearances arise, resembling erythrocytes of the maternal blood, and with the same colour reaction—as noted by Masquelin and Swaen, and Masius. Also at full-time large bodies are seen, recalling the Russell bodies of malignant tumours. The glycogen cells now open out, and allow the maternal blood to come out between them, and into contact with the ectoderm; wherever the blood touches the latter the ectodermal plasmodium appears, and now we recognise two layers, a deeper one of well-developed unblended cells—Van Beneden's cytoblast—and a superficial protoplasmic layer—Van Beneden's plasmodiblast. As the latter never shows metosis, and Duval's description of its growth by ametosis is incorrect, it is dependent for its continuance on the cells of the layer below. Duval is wrong in giving to the cytoblast a secondary importance—it persists to the end of pregnancy, and provides for a growth of plasmodium. As the ectoblast burrows into the mucosa, it thus behaves in two ways. Between the vessels it forms processes of cytoblast alone, in contact with the vessels a plasmodium appears, the glycogen cell playing an important part in the nourishment of the embryonic tissue. At the 10th day new spaces form within the plasmodium itself, which fill with maternal blood. By the 11th day these changes have affected not only the surface vessels but also the deeper ones, and about this time the inward growth of the embryonic tissue into the placental swelling ceases. At the 10th day the foetal vessels are brought by the allantois into relation with the ectoderm of the placental area. From this period the ectoplacenta appears as a system of parallel villi, which afterwards branch.

Under the placenta at the height of its development he describes its development at the 15th day as, though it continues to grow, there is nothing new after this date. He divides it into the maternal placenta, the intermediate layer and the foetal placenta. Under the foetal, special attention is drawn to the cellular deeper layer of the ectodermal epithelium, which never comes in contact with maternal blood. These ectodermal cells are small with clear transparent protoplasm, few fuchsin-staining granules and one or more nuclei. The plasmodium covering stains more deeply, shows no cell-boundaries, but abundant fuchsin-staining granules aggregated round the nuclei, sometimes fat granules and small clear vacuoles. The blood-spaces which appeared in the latter now come to occupy the space between the villi parallel to their axes. In the portion of foetal placenta next the intermediate layer the villi branch less, the plasmodium is more developed, appearing as numerous thick strands and trabeculae of striated protoplasm, cell divisions appear forming multinucleate cells—the nuclei being not round

but angular, and arranged in groups parallel to the striation of the protoplasm. The intermediate layer containing the ends of the villi is very complicated. The complicated appearance is due to the behaviour of the ectoderm between the vessels and in relation to these. The plasmodium may embrace groups of the multinucleate cells and cut them off. These isolated groups give the characteristic appearance to this layer. Their glycogen is absorbed, the protoplasm gathers round the nucleus, fat-granules appear, the membrane disappears, and the protoplasm is finally lost in the plasmodium. Also masses of exudations seen between these atrophying cells and staining intense green with safranin, are probably a degenerative product of glycogen. The ends of the villi reach these degenerating groups of glycogen cells, and as the cellular layer towards the end of the villus is always better developed, may it not be that the embryonal tissue is nourished by the glycogen cell-masses? Multinucleate glycogen cells are present also in the ectoplacenta—in its plasmodium by which they have been isolated from the maternal tissue, and carried far from their point of origin. Ulesko-Strogonowa alone has described the foregoing appearances in the intermediate layer, but she erroneously considers the glycogen cells to be modified ectoderm cells. We find that on the 9th day the branching blood-spaces which represent the capillaries of the mucosa are enclosed by the uninuclear glycogen cells; the atrophying tissue between these has by the 15th day disappeared. The nuclei with protoplasm round them are now larger and the reticulum of processes thicker. In places the spaces between the vessels is sometimes increased by the production of degenerative tissue, representing broken-down glycogen cells. The vessels, modified capillaries, have the vascular sheath already described lined by an endovascular plasmodium. (Duval.) The term is incorrect because the cells have boundaries; they possess 2-3 nuclei, and lie in 2-3 layers, the superficial flatter, the deeper rounder; sometimes in heaps projecting into the lumen. Fuchsin granules are abundant, the nuclei rich in chromatin, and show fragmentation and also metosis. Noteworthy is their relation to the maternal blood, which is throughout rich in leucocytes. These are sometimes heaped on the plasmodium, and often have penetrated the cell where they undergo retrogressive changes. Vacuoles are seen full of breaking-down leucocytes. Their nuclei during this process come to colour deeply, by the Altmann method. Erythrocytes (degenerating red corpuscles) are also present in the plasmodium. Duval has not noticed these changes, and Masius and Minot only touch on them. In addition to its relation to the maternal blood the plasmodium has interesting relation to the glycogen cells; it embraces them and they even come to bulge into the lumen of the vessel. The cells thus absorbed, atrophy. What is the origin of this endovascular plasmodium? Masius, Minot and others make the foetal placenta stop at the intermediate layer, and regard this plasmodium as modified capillary epithelium, while Duval makes it an extension of a foetal ectodermal plasmodium. His view would explain its destructive action on the maternal leucocytes, but "I regard it as a modified endothelium, were it not we should find the true endothelium atrophying." Duval says he could not find the demarcation line, but "it appears to me that it may be seen in the intermediary layer." We note "how the thin darker-stained, striated layer of the ectoplacental plasmodium lying on

the multinucleate glycogen cells is suddenly replaced by polygonal cells with distinct border, much clearer, almost homogeneous protoplasm, and larger nuclei." (Figs. 5, 6.) Numerous leucocytes and erythrocytes are seen in the latter, and the nuclei are often breaking up. Blood-spaces are also present, lined by glycogen cells only—no endovascular plasmodium. The enclosing cells are loaded with granules or drops, sometimes so abundant as almost to obscure the nucleus. (Fig. 10m.) The relation of these spaces to the endothelium-lined ones could not be traced.

Under the placenta at the end of pregnancy the disappearance of the ectodermal plasmodium from the villi in the ectoplacenta has been so fully described by Duval that it need only be referred to. In the intermediary layer and also in the maternal placenta retrogressive changes occur in the glycogen tissue, which is converted into polygonal, compressed multinuclear cells, rich in fat. (Fig. 11 Gz.) By the diminution of the perivascular sheath the blood-spaces become wider, and the endovascular layer flattened, atrophied, and it even disappears. The vessels of the "*couche vésiculeuse protectrice*" are unchanged.

The changes in the mucosa and connective tissue of the periplacenta are described—mostly retrogressive. A progressive change has not received sufficient attention or been understood. The ectoderm which at first is a single layer of small cells, becomes in the second half of pregnancy a stratified, cylindrical epithelium, showing mitosis. These cells "give the material for the formation of multinucleate giant cells of colossal size, and finely-grained protoplasm; smaller giant cells and fine fat granules also occur in them. These giant cells grow into the degenerating maternal tissue, and broken down flakes of tissue, and atrophied atoms of nuclei are seen. (Fig. 12.) These phagocytic giant cells are seen also in the ob-placenta of Minot. When they burrow deeply they also degenerate, their nuclei showing pyknosis.

As to the ob-placenta; while the surface epithelium degenerates, that deep in the glands grows, so that at labour the whole mucosa of the ob-placenta is covered with a new epithelium. The degeneration of the foetal epithelium is described. The origin and structure of the "monster cells" of Minot are described. Minot makes them epithelial, but Maximow agrees with Duval that they are connective tissue. Stroganowa makes them degenerated glands. The ob-placenta is difficult to study, through the contraction of the muscle, disturbing relations; the preparation must be fixed *in toto* before it is cut up for hardening. The cells arise both in the mucosa and in the muscular layer. In the mucosa they arise from the perithelium of the capillary (Fig. 15), the connective tissue cells whose processes are united with the endothelium. It is possible that they also arise from the endothelium. They are most abundant near the surface of the mucosa. In the muscularis they arise also in the capillary wall (Fig. 17), but the contraction of the muscle and the blood squeezed out of the vessel masks their origin. Their large size and multiple form is described. The protoplasm is arranged in parallel threads, and two layers may be distinguished—peripheral and central. (Fig. 15.) Fat drops are seen even in the youngest. The nuclei have a distinct membrane, in which the threads of the protoplasm and of the nucleus end. The dimension of the nucleus is wide

and it contains large nucleoli. More than one nucleus arises by amitosis. The division of the nucleus may be followed by that of the whole cell (Fig. 16), which is rather a degenerative change. A degeneration and destruction of the nucleus is also noted—small blebs appear on the surface, which break off into the protoplasm, containing no nuclei, only chromatin. Sometimes they are nucleated. The extrusion of the nucleus itself into the protoplasm also occurs. Appearances are also noted resembling central bodies with attraction spheres. The giant cells reach their full development on the 22-23 days, and undergo retrogressive changes in the last 2-3 days, ending in their complete destruction and absorption, "without our being able to give explanation of their meaning or function."

Maximow's observations are based upon an age-series not by any means complete, and his results are in consequence fragmentary. As regards the general distribution of glycogen in the placenta his results agree with my own, though he maintains that in the perivascular sheaths the glycogen granules lie between the branching processes of the uninucleate cells, and not in the cells themselves. In addition, Maximow, though he has correctly interpreted the origin of the multinucleate decidual cells and their great store of glycogen which persists till near the end of gestation, accounts in no reasonable way for the presence in the foetal placenta of detached areas of these cells, for he says "multinucleate glycogen cells are present also in the ectoplacenta, in its plasmodium, by which they have been isolated from the maternal tissue, and carried far from their point of origin."

Maximow does not mention a "separation zone."

SECTION C.

FAT AS FOUND IN PLACENTA AND FETUS.

So far as I know the only observations hitherto made upon the presence of fat in the placenta of the rabbit have been a short paragraph in the paper, "The Occurrence of Nutritive Fat in the Human Placenta," written by Thomas Watts Eden in 1896, a few short sentences by Marchand in his "Beitrag"—"Die Placenta des Kaninchens"—in 1898, which we have already summarised, and a few isolated observations by Maximow. In this assertion I am reinforced by Eden, who in 1896 considered himself first in the field, even in regard to the human placenta, though at the close of his paper he candidly yields precedence in this respect to the two German observers, Apfelstedt and Aschoff. Since these two papers, published within three months of one another, are the only systematic studies of the presence of fat in the placenta, and since the human placenta shows a distribution of its fat strictly analogous to that of the rabbit's placenta, I shall at first very shortly summarise these two contributions, and afterwards shall discuss more particularly the few sentences which treat of the rabbit.

Apfelstedt and Aschoff in a paper (1) on malignant tumours of the chorionic villi, describe a pregnant uterus of two months, removed by total extirpation. I quote here only the passages bearing on the presence of fat. The specimens were fixed in Fleming's solution and stained with safranin.

In describing the placenta Aschoff says: "The villi appear surrounded by a reddish-black border, as the inner layer, if not entirely, is almost free from fat granules. Where the red cell-knot joins itself to the inner red band the syncytium surrounds it as a fine black line. One point, however, is worthy of note in the accompanying preparations. Where the two villi abut, and consequently the syncytium on both sides does not lie free in the inter-villous space, there fat is absent. Conversely we find where the rapidly-growing cells of the inner layer break through the syncytial sheath, and become connected with the inter-villous spaces, numerous fat granules make their appearance in these cells. Therefore I believe that the fat granules do not belong absolutely to the syncytium, but occur everywhere where the chorionic epithelial cells, under which I include both cell-layers, come into the most direct interchange with the inter-villous spaces. As to the question whether such appearances are normal, or whether here a pathologically changed ovum was present, it can only be decided by the observation of fresh ova of this month, preserved in the same way."

As to the presence of fat in the "boundary layer between placenta and decidua serotina," he says, "I have already mentioned that the syncytial masses grow into the mucous membrane as well as the individual cells. They can be very readily recognised by the regular spots of fat in the Fleming preparations. The masses projecting from the cell-layer show much less, often absolutely no fat. The difference between

the rapidly-grown epithelial villi and the decidual cells becomes in the Fleming preparations more difficult to distinguish on this account, that the upper layer of the mucous membrane, at least in patches, shows a considerable accumulation of fat granules, which hide more or less the cell and nuclei. Is it a question here of a fatty degeneration of the rapidly-grown cells, or of the decidua? Is it possible that the mucous membrane, degenerated into fat, disappearing by absorption, is absorbed by the syncytium in the form of fine fat granules? I cannot decide these questions. So far as I can see the decidual cells are, except in this layer, free from fat. On the other hand there are present in these patches many leucocytes with breaking-down nuclei, all through the mucous membrane."

Speaking of the "*decidua serotina*" he says further: "In the Fleming preparations there appears in all the superficial glands a decided fatty degeneration of the epithelial cells: the difference in the granular appearances is very clear, where the glands and the syncytial masses lie close together; in places large and small granules lie entangled irregularly in one cell, in places they are of uniform size, and thickly sown throughout the protoplasm."

T. Watts Eden in what he calls "*A Preliminary Communication*" (2) agrees in the main with the previous observers, though he states that Aschoff "*scarcely appreciates the physiological importance of the observations.*" Eden used in the preparation of his specimens both Müller's and Marchi's fluid, and counterstained with safranin, or logwood and eosin.

In a six weeks ovum he found minute droplets of fat in the two layers of epithelium covering the villi, the plasmodial and cellular layers. These droplets were of uniform size, discrete, and were confined to the perinuclear protoplasm. "The stroma of these villi contain here and there a trace of fat."

Eden maintains that the plasmodial layer of the villi shows great proliferative activity, and regards this as of great importance since it shows that the deposit of fat occurs in actively growing tissues.

Many of the decidual cells contained minute, discrete droplets of fat in the perinuclear protoplasm, and at the 6th month this deposit was greatly increased.

In a ripe placenta, though the plasmodial layer has ceased to grow and degenerative changes are present, the great majority of villi retain their vitality and in these a free deposit of fat is present with the same distribution as in the younger specimen. The serotina now shows many degenerative changes, and though it contains fat it is doubtful whether now it is a physiological deposit.

"The placenta indeed appears to be a storehouse of nutritive fat just as is the liver," and while "it would seem to be that fat is deposited from the maternal blood in the epithelium of the villi and stored up there by the foetal tissues for their use . . . it is not clear how a deposit of fat in the decidual cells can be made available for the purposes of foetal nutrition."

Turning now to the placenta of the rabbit Eden claims to have examined two specimens, one from an early and the other from a late period of gestation. I quote now his exact words. "In both there

was a marked deposit of fat, chiefly in the superficial glandular layer of the maternal placenta, but also, though to a less extent in the processes of the chorionic mesoblast, which form the homologues of the villi of the human placenta." This is the extent of his observations in the rabbit. It is not quite clear what he means, by "superficial glandular layer" unless he has adopted the older and mistaken nomenclature of Minot. Again in the "chorionic mesoblast" I have never been able to discover the least trace of fat. It is singular to note that while Eden in the human placenta has described the presence of fat in the epithelial covering of the villi, he has altogether failed to discover it in a similar situation in the rabbit, where my own work shows it to exist and in considerable abundance.

Maximow's paper (5), Section (B), is completely summarized in Section (B), for it deals chiefly with glycogen. His observations upon the presence of fat in the rabbit's placenta are as follows:

During first stages of development of placenta.

Fat granules are found in the multinucleate cells on the surface of their processes, never as globules, but as irregular granular masses.

At the 15th day.

The cellular layer shows fat granules and small vacuoles, and also the multinucleate cells.

At the end of pregnancy.

In the intermediary layer and also in the maternal placenta retrogressive changes occur in glycogen tissue, which is converted into polygonal, compressed, multinucleate cells, rich in fat.

So far as these observations of Maximow's go, they agree with my own, though from his mistaken classification of the regions of the placenta it is often difficult to localise his fat-bearing areas.

Marchand's contribution to our knowledge of fat as found in the rabbit's placenta is as follows: "The outer edge of the lamellæ (our tubules) is much corroded, and on the surface there lie scattered or in groups large, bright, polyhedral cells which often fill the pits in the lamellæ. Besides these are often found flat cells with flat nuclei, in the vicinity of which you can see, in preparations fixed in Fleming's solution, small fat droplets. Since these flat cells behave in their position in the same way as the large cells, and here and there pass into them, as also the fat drops, I assume that the flat cells represent the remains of foetal epithelium."

Marchand here describes the fat droplets as we have found them in the ectodermal walls of the tubules;—"the large bright polyhedral cells" are most probably multinucleate decidual cells with the "flat cells" of foetal ectoderm or maternal endothelium next the blood channels.

A complete summary of Marchand's paper may be found in Section A.

SECTION D.

IRON AS FOUND IN PLACENTA AND FÆTUS.

The literature of iron will be found in its place in the bibliography that follows. As it deals only with its presence in animal and vegetable cells, and in the liver and spleen, it does not call for discussion here. So far as I know, no work has been done upon the localisation of iron in the placenta, though its presence therein must necessarily be inferred from such work as that of L. Hugouneng, who subjecting the fœtus to a chemical analysis at different periods of intra-uterine life finds a fœtal hypersiderosis during the third trimester of gestation. The chemical analyses of the placenta itself as performed by Grandis, Sfameni, Nattan-Larrier, Letulie and others are in this respect incomplete.



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