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CONTRIBUTIONS TO THE STUDY OF THE EARLY DEVELOPMENT AND IMBEDDING OF THE HUMAN OVUM

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CONTRIBUTIONS TO THE STUDY
OF THE
EARLY DEVELOPMENT AND IMBEDDING OF THE HUMAN OVUM

I. AN EARLY OVUM IMBEDDED IN THE DECIDUA

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II. AN EARLY OVARIAN PREGNANCY

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WITH TEN PLATES AND TWELVE FIGURES IN THE TEXT

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PREFACE

The following memoir combines in one publication two separate papers which deal with the processes involved in the imbedding of the human ovum. They have been associated because of the complementary nature of the evidence they afford regarding the histological characters and the activities of the trophoblast. Each breaks new ground, in respect that while the first paper embodies a description of the earliest phase of the human ovum yet recorded, the second deals with the earliest case of ovarian pregnancy hitherto reported.

The fact that the extremely early ovum described in the first paper is a unique specimen presenting features which have not up to the present been observed, necessitated profuse illustration both by coloured plates and photographic figures. This has rendered the production a costly one, and we desire to express our obligations to the Carnegie Trust of the Scottish Universities for giving us a grant towards the expenses of publication.

University of Glasgow,
July 15th, 1908.

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INTRODUCTION

VERY early stages of the human ovum are necessarily extremely rare. It is only by fortunate and fortuitous circumstances that an occasional specimen comes into the hands of the investigator. Within recent years a number of young ova have been described, which have considerably extended our knowledge, and have served to show that in certain respects the early stages of development in man differ materially from those in lower mammals. The ovum of Hubert Peters, of which an account was published in 1899, still represents the youngest phase known. A specimen described by Leopold in 1906 is certainly earlier than that of Peters, but no embryonic rudiment was present, and in several other respects it must be considered abnormal. On the other hand, the ova described by Graf v. Spee (1905), Beneke, and Jung amply confirm, though they do not extend, the data provided by Peters'. specimen.

Considerable light has been thrown on the problems involved in early human development by recent comparative work, more especially that of Selenka and Keibel on monkeys and apes, and of Hubrecht on Tarsius spectrum. It is now known that the Primates, including Tarsius in that category, form embryologically a group by themselves. All have certain common and peculiar features. There is always present a mesodermic connecting-stalk (*Haftstiel*), through which the vessels of the embryo and chorion are connected without the medium of an allantois; the yolk sac is very minute and is not coextensive with the blastocyst; there is a precocious extra-embryonic coelom lined by middle-layer cells, which are present at a very early period before the appearance of the primitive streak or embryonic axis, and therefore before the formation of the dorsal mesoderm of the embryonic body.

There are other features, however, in which the several orders of the Primates differ *inter se.* In Tarsius the amnion is formed as in the rabbit, dog, etc., by secondary folds, while in monkeys, apes, and man it is already closed in the earliest stages known. The placentation again, in the monkeys (Old and New World), differs from that in the anthropoid apes and man. While the early phases in apes and monkeys, described by Selenka, confirm and explain the corresponding phases in the human subject, none of the stages known reach to the initial stages of the blastocyst, and therefore much is still left for conjecture. The extremely young ovum, which is the subject of the first of the papers in this memoir, represents the earliest stage of any primate form except Tarsius yet recorded, and merits careful and detailed description in respect that it pushes back the limits of the unknown in a sensible degree.

The age of young human ova is, of course, from the nature of the case, quite uncertain. It is usually calculated in terms of the conventional rule formulated by Professor His, but the results of the rule as applied to the youngest known specimens are unsatisfactory and contradictory. In the present case we are fortunate in possessing very accurate data, and an effort will be made by correlating the facts with those known for other specimens to revise the basis on which the age of early ova is calculated.

Not only do the structural features of the early primate blastocyst remain unknown, but the process of imbedding and the initial phases of placentation are also merely matters of surmise. All the ova described before the appearance of Hubert Peters' monograph were found completely imbedded in decidua, and the hypothesis that the ovum becomes surrounded by a process of circumvallation was generally accepted, though in more recent times the results yielded by comparative embryology had caused some doubt on the matter in the minds of a few observers.[1] Several of

[1] In William Hunter's *Anatomy of the Gravid Uterus*, 1774, Plate 35, there is figured a complete decidual cast, in which an ovum about the size of a pea lies imbedded. In his diagrams William Hunter clearly indicated that the ovum is at this stage completely surrounded by the decidua, but he expressed no opinion as to how it becomes implanted therein. The theory that the decidua covers the orifices of the Fallopian tubes, and is pushed out by the ovum as it enters the uterus, has been erroneously attributed to him. (See Historical Introduction to the *Catalogue of the Anatomical and Pathological Preparations of Dr. William Hunter.* John H. Teacher. MacLehose, Glasgow, 1900.)

the ova, such for instance as that described by Reichert, showed a small area of the decidua capsularis (formerly called reflexa) over the blastocyst, which was of a different nature from the rest of the capsule, and apparently composed of cicatricial tissue. They were, notwithstanding, completely enclosed by organised tissue. In Peters' ovum, however, and also in one described by Graf v. Spee (1905) there is a relatively large area from which decidua is absent, and its place is occupied by a mass of fibrin and blood-clot (the "Gewebspilz"). The aperture in the wall of the implantation cavity occupied by this mass was considered by Peters, and also by Graf v. Spee, as the point of entrance of the ovum into the substance of the mucosa, but their preparations do not by themselves conclusively demonstrate the actual process by which the ovum is implanted. To prove how this is effected still earlier stages are required. Our young ovum is a further step in the direction of assured knowledge, and as will be seen later necessitates some modification in the interpretation of the "Gewebspilz" completing the capsule in Peters' specimen, while our ovarian ovum, which is the youngest hitherto described implanted in the ovary, throws considerable light on the nature of the imbedding process.

In the absence of the early stages in the human subject it is necessary to make use, for the purposes of interpretation, of the data provided by Comparative Embryology, but the remarkable variability in the methods of implantation and in the details of placentation in the different mammalian orders, speaks for a certain specific character of the embryological processes involved. Caution, therefore, is required in grafting any data derived from the investigation of the conditions in lower mammals on to the facts known for the human ovum, and the more so as the young ovum we have to describe accentuates the very special features of the human blastocyst in its early phases.

The only competent analogy with the higher primate ovum among the lower mammals is to be found among the forms in which there is likewise a decidua capsularis, for instance the hedgehog among the insectivora, and the mice, rats, and guinea-pig among the rodents. It is to be noted that in these forms, as in the Primates, the amnion is closed from the first, and that the blastoderm shows the phenomenon, to a greater or less degree, of "inversion of the germinal layers." Two methods of imbedding, which will be dealt with in greater detail later, have been described in animals with a decidua capsularis. In the hedgehog, mice, and rats, the ovum is said to be received into a recess or fissure of the mucous lining of the uterus; the epithelium disappears round the blastocyst; the mucous membrane becomes greatly thickened to form the decidua capsularis; and the fissure is cut off from the general cavity of the uterus by the fusion of the lips of the decidual swellings from which the epithelium has likewise vanished. In the guinea-pig the observations of Graf v. Spee seem to prove that the ovum, while still in the early blastocyst stage, destroys the epithelium of the surface at the spot where it becomes implanted, by the activity of its ectodermic cells, and then, by a continuance of the process of destruction and solution, imbeds itself in the connective tissue of the mucosa. One or other of these alternatives must apply to the human ovum, and we submit our two communications as a contribution towards the solution of the problem.

In regard to the initial stages of placentation a very large body of data has been accumulated by comparative embryology, and our views as to the deciduate placenta have undergone considerable modification. Apart from the general character of the placentation in the different orders of mammals, debate has centred on the nature of certain layers of cells which separate the foetal from the maternal blood in the placenta. It is unnecessary here to enter on any detailed account of the various and contradictory opinions which have been held on this histological detail, or of the several theories which have been put forward on the subject of the origin of these layers.[1]

It is now very generally admitted that the evidence afforded by both human and lower mammalian material is in favour of the foetal, *i.e.* chorionic origin of both layers covering the villi in the human placenta. No doubt appears to exist in the mind of anyone as to the cellular layer, generally known as Langhans' layer, but there is still a lack of decisive

[1] The different hypotheses are fully set forth by Hubert Peters, by Webster (*Human Placentation*), and by Strahl (*Hertwig's Handbuch der Entwickelungslehre*); they have also been dealt with by Teacher in his papers on "Chorion-epithelioma," and are briefly summarised by Bryce in *Quain's Anatomy*, vol. i. 11th ed. 1908.

proof regarding the plasmodial investment of the villi, or syncytium. Certain authors have maintained that it owes its origin to the maternal tissues—some deriving it from the epithelium either of the surface or of the glands of the decidua, others holding that it represents maternal endothelium spread over the villi in the interlocking of foetal and maternal tissues, which has long been considered to take place in the development of the placenta.

The idea that uterine epithelium is necessary for the production of the plasmodium was finally excluded by Catherine Van Tussenbrœk when she demonstrated the existence of a syncytial layer on the villi of a chorionic vesicle imbedded in the ovary, and her observation has been confirmed by several investigators. It is just conceivable, however, that if a fertilized ovum developed in the interior of the Graffian follicle, the follicular epithelium might be responsible for the production of the plasmodium; but this cannot be the case if it be proved that the blastocyst may be imbedded in the ovarian stroma outside the corpus luteum. In the second communication embodied in this publication further proof will be provided that such a case may occur.

The theory that the plasmodial layer on the villi is derived from maternal endothelium has become practically untenable in view of the characters of the early ova described in recent years, but it is not quite so certain that it may not owe its origin to the maternal connective tissue in which the ovum is imbedded, altered by the biochemical activities of the ectodermic cells of the blastocyst.

In this connection earlier stages in the development of the plasmodium than have been hitherto available in the human subject, are required for the complete demonstration of its foetal origin in the human placenta. Our young uterine ovum, in virtue of its stage of development, and our case of ovarian pregnancy, being a crucial experiment both on the nature of the imbedding process and on the origin of the plasmodium, bring critical evidence to bear on this question.

I

AN EARLY HUMAN OVUM IMBEDDED IN THE DECIDUA

By THOMAS H. BRYCE and JOHN H. TEACHER

AN EARLY HUMAN OVUM IMBEDDED IN THE DECIDUA

HISTORY OF THE SPECIMEN

The ovum was found by Dr. Teacher in a portion of membrane sent to him for examination by Dr. T. Douglas Brown, in a mixture of urine and blood-clot. The membrane had been expelled by a young woman who had been married for about two years, but who had not before been pregnant. Dr. Brown recognised a portion of fawn-coloured membrane among the blood-clots, which he considered to be probably a portion of the decidua of pregnancy, as the patient had passed the date on which menstruation was expected by about ten days. By the time the specimen reached Dr. Teacher the haemoglobin had diffused out of the clots, and the membrane was no longer distinguishable from them. In order to differentiate the tissue from the clot, about one-third of its volume of 90% alcohol was added to the fluid, and an hour later the mixture was decanted and fresh 30% alcohol substituted. Two hours later, on examining the material in a white porcelain dish, the membrane was readily identified by its somewhat lighter colour. It was roughly quadrilateral in shape, and somewhat broader at one end, measuring 3·8 cm. in length and 2 cm. in breadth. It represented the greater part, if not the whole of the mucous membrane of one wall, probably the posterior wall, of the uterus. It presented the characters of decidua and was mapped out into areas by shallow furrows. Its outer surface had the characteristic appearances of the detached surface of shed decidua.

The margin was in parts rather thick and rounded, in other parts it faded off into very thin shreds. One of the areas near its centre stood up somewhat prominently from the rest of the membrane. The papilla so produced (Figure I) at its right margin slightly overhung a deep furrow, but at the ends and on the left side it sloped gradually down to the general level of the surrounding membrane. This elevated area measured roughly 6 mm. by 3 mm.; it was nearly 3 mm. in thickness, while the rest of the membrane did not exceed 2 mm., and was for the most part thinner. About the centre of the papilla there was a circular mark like a very shallow dimple, and of lighter colour than the rest of the surface. The adjacent tissue was of deep red colour as if congested, and

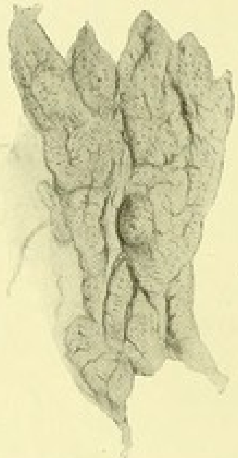

FIGURE I. PORTION OF DECIDUAL MEMBRANE CONTAINING THE OVUM; SLIGHTLY MAGNIFIED.

The prominent lobule is the actual site of implantation. The indistinct dimple-like mark slightly below the centre of the lobule corresponds to the position of the blastocyst. The darker shading represents congestion, and the dark spot above the dimple is a haemorrhage.

a still darker patch above the circular mark was regarded as probably due to haemorrhage into the membrane. The area thus described is very similar in appearance to the lobule of decidua in which the ovum investigated by Leopold in 1906 was enclosed.

Although it seemed improbable that after twenty hours' immersion in a mixture of blood and urine the fixation of the preparation could be satisfactory, the membrane was placed in absolute alcohol, this medium having before been found to be the most satisfactory fixative in similar circumstances. After thirty hours the lobule was excised, imbedded in paraffin, and cut by William Price, the laboratory attendant, into a perfect series of sections 7 microns thick, vertically to the surface of the decidua and in the supposed long axis of the uterus.

The probability of finding a valuable ovum being somewhat remote, thirteen sections, at intervals, were cut out of the ribbon, mounted and stained. In three of these Dr. Teacher recognised what seemed to be an ovum of about 1 mm. in diameter, and the remainder of the ribbon containing about 400 sections was then mounted and stained with haemalum and eosin. At a later stage the first series was restained by Weigert's fibrin stain in order to obtain a more accurate differentiation of the plasmodium from the decidua.

The following details relative to the history of the case have been supplied by the husband of the lady, himself a man of science and therefore alive to the importance of exact data. They can be implicitly relied upon.

The patient and her husband are both healthy. There has never been any uterine disorder. Menstruation has always been regular, the intervening period averaging twenty-six days with an occasional variation up to two days in either direction, the irregularity being however usually compensated; if one interval were short the succeeding interval was usually longer by a corresponding amount, and *vice versa*. The data may be summarised as follows:

September 2nd, 1907. Menstruation began.

September 27th, 1907. Menstruation began.

October 2nd to 3rd or 3rd to 4th. Coitus.

October 19th to 20th. Coitus.

October 25th. Menstruation was expected but did not appear. In the succeeding days the patient felt particularly well; she had no symptoms suggestive of pregnancy except the absence of menstruation.

November 3rd to 4th. Coitus.

On the morning of the 4th of November a discharge appeared like the commencement of menstruation.

On November 5th the bleeding became more profuse than at an ordinary menstrual period, and the clots and membrane were passed towards evening with considerable pain.

The patient made an uneventful recovery, and menstruation re-appeared twenty-six days after the fourth of November.

FIXATION OF THE SPECIMEN.

Notwithstanding the circumstances under which the ovum was obtained the state of preservation of the tissues is wonderfully good. The mixture of blood serum and urine apparently behaved as a neutral fluid, which destroyed the tissues far less than they would have been destroyed by water or even by ordinary normal saline solution. Though we cannot claim that the fixation is perfect, we are satisfied that it is sufficiently reliable for all practical purposes. The nuclei are on the whole well fixed, but the protoplasm is less well preserved and has in parts a slightly macerated appearance. The colouring matter of the blood has been almost entirely dissolved; the red corpuscles are, therefore, shadowy, but they have for the most part retained their normal shape. There is further a certain amount of granular debris in the blood spaces. The effects of precipitation and maceration are not, however, sufficient to invalidate conclusions regarding the essential facts of the histology of the ovum and of the decidua. The embryonic rudiment is somewhat torn, but it has been possible by reconstruction to make good the defect in this respect. It has generally been assumed that the only hope of getting a young normal ovum, is the chance of an operation or of a suicide. The present case shows that even in the case of an early abortion, an ovum may be cast off intact in the mucous membrane, and recovered in quite a satisfactory state of preservation. There is no reason for supposing that the mucous membrane was diseased in this case, and it is probable that the abortion was due to mechanical causes, seeing that it ensued immediately after coitus.

DIMENSIONS OF THE OVUM.

The ovum is completely surrounded by decidua and lies in a blood filled space excavated in it. The dimensions of the cavity at their maximum are 1·95 mm. in its longest diameter (parallel or approximately parallel to the vertical axis of the fragment of decidua figured on page 10), ·95 mm. in depth, and 1·1 mm. in its third dimension. The last measurement is arrived at by summing the number of sections 7μ thick in which the implantation cavity appears. The space enclosing the ovum is thus oval in shape, with its long axis parallel to the surface and about twice the length of its vertical axis, or depth from the surface. The dimensions of the blastocyst itself are rather difficult to determine with exactness owing to its wall being a little folded at several points. In Plate I, Fig. 1 and Plate III, Fig. 3, which represent a section well to one side of the equator of the vesicle, the cavity measures about ·36 mm., and it is approximately circular. In Plate II, Fig. 2 and Plate IV, Fig. 4, which is a section cutting the equator of the blastocyst, the internal measurements are ·77 by ·63 mm. in its two dimensions. The shorter measurement may be taken to represent the maximum size of the cavity, seeing that the blastocyst is obviously compressed and folded at one side; it is probable that the vesicle is spherical at this stage, because the contour of the unfolded wall is approximately the arc of a sphere.

GENERAL DESCRIPTION OF THE SECTIONS.

Plate I, Fig. 1 shows the general relations of parts as revealed by a low power of the microscope. The section cuts the whole length of the decidual lobule described above. It is marked off above by a fissure which indicates the upper limit of the tubercle seen in Figure 1; below it ends in a rounded and slightly overlapping projection which corresponds to the lower edge of the papilla. The free surface of the lobule shows above the mouth of a gland, and over the ovum an irregular depression which is the orifice of the space excavated in the decidua. This does not correspond to the dimple seen on the surface of the lobule; that is represented by a shallow depression which appears on the surface immediately over the centre of the blastocyst, and is seen in Plate II, Fig. 2. The blood-vessels of the decidua are greatly dilated, more especially on the deep aspect of the blastocyst, where they form the same "blood cushion" seen in the ova of Peters, Ercole Cova, and Graf v. Spee (1905). The glands are enlarged and irregular. Beneath the blastocyst there is great extravasation of blood and deposit of fibrin, while the upper part of the tubercle is seen to be occupied by a haemorrhage.

The implantation cavity is clearly marked off all round, but more especially at its outer part, by a darker staining band which, as will be seen presently, represents a layer of necrotic tissue. The cavity is occupied by very irregular strands of tissue, the spaces of which are densely packed with blood corpuscles. Above, the space is encroached on and the zone of necrotic tissue broken up by the haemorrhage already alluded to.

Under a higher power (100 D) the blastocyst wall (Plate III, Fig. 3) is seen to be composed of a lightly staining lamella of protoplasm, in which the cell outlines are indistinctly defined, while the very irregular meshwork occupying the space in the decidua is observed to have plasmodial characters.

In describing the histological details of the several parts, we shall first take the decidua, then the trophoblast, and lastly the embryonic rudiment.

THE DECIDUA.

The surface epithelium has completely disappeared. Whether this be the result of maceration, or is a normal feature, it is not possible to determine. The fact that it is also absent from the outlying parts of the decidua, while it is present in the cases of Peters and Leopold, suggests that it is due to superficial maceration.

There is no coagulum or organised thrombus adhering to the surface over the ovum. The mucous membrane shows all the well known characters of the menstrual decidua. The cells are clear and swollen, the tissue spongy; the vessels are greatly dilated; the glands are enlarged, while their epithelium is desquamating and their lumen is occupied by extravasated blood. The whole membrane is thickly studded with leucocytes, mainly of the polymorphonuclear variety. All round the ovum the marginal lamella of the decidua is in a state of advanced coagulation necrosis, appearing as a hyaline, darkly-staining, and nearly nuclear-free zone dotted with polymorphonuclear leucocytes. Stained by Gram's method this zone stands out as a deeply staining purple band, forming the wall of the implantation cavity. The plasmodium is not everywhere in contact with this layer. Here and there masses of it lie directly against the necrotic tissue, but round the rest of the circumference the two are separated by a space occupied by large mononuclear cells, the nature of which will be discussed below. The necrotic zone is broken up by the haemorrhage in the upper part of the section, and here and there, but in relatively few places, by masses of plasmodium, which are seen spreading outwards along the walls or into the lumina of blood-vessels. The mass of cells seen in Plate II, Fig. 2 and Plate III, Fig. 3, occupying the centre of the space between the cyto-trophoblast and the wall of the implantation cavity, corresponds to the layer of cells seen lying elsewhere immediately within the necrotic zone; the cells have here been displaced inwards by the haemorrhage which has broken into the implantation cavity.

At either extremity of the implantation cavity an interesting condition of the glands is to be observed, from which it would appear that the gland walls resist the disintegration longer than the general tissue of the mucous membrane. The sections across each pole of the chamber show a gland in section with necrotic tissue and plasmodium on either side of it, as if the process of destruction were extending round the gland wall and isolating it. The implantation cavity is, as already stated, completely closed. There is no large aperture filled with blood clot such as is seen in Peters' ovum, or Graf v. Spee's youngest specimen. Over the blastocyst, but distinctly nearer one end of the implantation cavity, is a well marked pocket, ·1 mm. in diameter, partially filled with what appears to be thrombus (Plate III, Fig. 3). Directly continuous with this, and reaching into the implantation cavity, is a spur-like projection of hyaline material only distinguishable histologically from the necrotic zone of the decidua by being devoid of nuclei.

This depression is clearly the mouth of the space in the decidua, but there is no direct evidence to show whether it represents the point of entrance of the ovum, *i.e.* the point where it first began its destructive action on the decidua, or the closed mouth of a fissure into which the ovum had been received. This problem will be discussed in a later section.

THE TROPHOBLAST.

The term trophoblast, *i.e.* trophic epiblast, will be used here in the original sense in which it was employed by Hubrecht, to designate that part of the ectoderm which does not share in the upbuilding of the embryo, or of the amnion in the human subject, but only in the attachment and nourishing of the ovum. The trophoblast includes the whole thickness of the wall of the blastocyst, and is differentiated into two parts—the *Cyto-trophoblast* or *cell layer*, in which the cell outlines are more or less preserved, and the *Plasmodi-trophoblast* or *plasmodium*, in which they are wholly lost.[1]

THE PLASMODI-TROPHOBLAST.

The plasmodi-trophoblast forms an extraordinarily extensive spun-out investment for the ovum. It occurs in masses, bands, or threads. It is difficult to differentiate, in places, the fine threads from fibrin filaments. The plasmodial masses are distinguished by the dark, slightly rusty-red tint with which they stain, forming a sharp contrast with the blue-pink of the immediate wall of the blastocyst, and the red-pink of the necrotic layer of the decidua (Plate III, Fig. 3). The nuclei differ from those of the cyto-trophoblast in respect that they are invariably small and stain darkly. This latter character is due to the finely granular nature of

[1] The terms cytoblast and plasmodiblast were suggested by Van Beneden. The terms used in the text are those now employed by Hubrecht. In so far as there persists a certain remnant of doubt regarding the origin of the plasmodium in the human ovum, the use of these terms at this point of our inquiry involves in some sense a *petitio principii*.

the chromatin network, which in the nuclei of the cyto-trophoblast is more open, loose, and reticular.

The central strands of plasmodium are arranged round the cyto-trophoblast in many places as an apparently laminated formation, with numerous spaces or clefts, which give an appearance of sharp separation of the layers, but between the spaces the cellular layer passes directly into the plasmodial. In some of the isolated masses of plasmodium vacuoles occur, which are either empty or partially filled with granular material. The vacuoles occur in some instances as single spaces, but more frequently they are multiple, and all intermediate stages are seen between masses in which vacuolation is commencing, and the spun-out plasmodial reticulum, the meshes of which are filled with maternal blood corpuscles. Plate v, Fig. 5, shows the characters of the plasmodium as revealed by a higher power of the microscope. To the left and below, a mass of plasmodium is seen lying free in the blood space, and in the early stage of vacuolation, while further to the right, interposed between two portions of decidua, is a larger and more vacuolated portion which is in direct contact with the necrotic zone of the decidua. It lies in the lumen of a greatly dilated capillary which has become directly continuous with the blood space round the ovum by the destruction of its wall. The endothelium of the vessel still persists on the surface of the detached mass of decidua to the left. At first sight it might be inferred that this mass of plasmodium was a portion of the closely adjoining network of the same tissue, but this is not so. When traced through the series of sections it was found to occupy the lumen of the vessel for a considerable distance, and to spring ultimately from the general plasmodial mass much nearer the pole of the blastocyst, where it could be seen entering a gap in the vessel wall.

In Plate viii, Fig. 10, an irregular mass of vacuolated plasmodium is seen lying in a bay in the necrotic zone; it is extending into the decidua in close relation to a vessel which appears in the adjoining sections. In other situations large masses of plasmodium are spread out against the inner face of the necrotic zone—as if anchoring the ovum in the cavity.

The great inequality between the plasmodial mass in the upper part and that in the lower part of the section figured in Plate iii, Fig. 3, is clearly due to the haemorrhage into the upper part of the implantation chamber. The effect of the blood extravasation comes out rather more clearly in Plate II, Fig. 2, in which the plasmodial meshwork can be observed to be pressed down to some extent on the wall of the blastocyst, while the layer of large cells elsewhere lying immediately within the necrotic zone is displaced inwards. The larger masses and bands have, as might be expected, resisted the pressure, and one process remains applied to the decidua as what appears to be an anchoring strand (Plate III, Fig. 3). The inner part of the plasmodi-trophoblast has the appearance of irregular branching lamellae laid down round the wall of the blastocyst. In no section, or part of a section, is any portion of the wall of the vesicle left uncovered by a plasmodial layer. Here and there in the formation there are masses of what appears to be coagulum, but it is not impossible that some of these, at any rate, represent portions of necrosed plasmodium.

The distinctive dusky-red colour of the plasmodium is brought out in Plate V, Fig. 5. At this magnification a granular structure is revealed in the protoplasm which is absent from the cyto-trophoblast, and under a still higher power this appearance is discovered to be due to an alveolar structure in the protoplasm.

The whole appearances presented by the plasmodium lead one to infer that the extraordinary irregularity in the disposition of the layer is due to a process of vacuolation which has broken up the larger solid masses into a sponge-work, and that the trabeculae of this sponge-work have broken down so as to allow the blood shed into the implantation space by the opening of the vessels, to pass into its meshes.

We thus reach a conception of the origin of the primitive blood lacunae in the trophoblast not unlike that of Peters, but it will be observed that the spaces are produced, in the first instance, entirely in the plasmodi-trophoblast. In this respect our ovum reveals a condition of the human blastocyst hitherto unsuspected; its walls are at this early stage almost wholly plasmodial, with the exception of a thin germinal layer or mother-zone of cyto-trophoblast forming the immediate wall of the vesicle.

While our specimen speaks for the production of the blood lacunae by the formation of spaces in the trophoblast into which the extravasated blood is shed, it cannot be concluded that they are formed in the first instance in a uniformly thick lamella of plasmodium constituting a tolerably regular wall to the blastocyst. The plasmodi-trophoblast from its very nature is probably highly irregular from a very early stage, and therefore the blood lacunae may in part represent spaces intervening between outgrowing plasmodial masses—between what may, in fact, be termed primitive plasmodial villi.

THE CYTO-TROPHOBLAST.

The cyto-trophoblast constitutes a relatively thin lamella which forms the immediate wall of the vesicle. The lamella is sharply differentiated from the plasmodi-trophoblast by its staining reactions. It is tinted, in haemalum and eosin preparations, a delicate blue-pink colour. The cell outlines are nowhere sharply defined, but they can be readily made out in sections in which the blastocyst wall has been tangentially cut. Elsewhere the appearance is rather that of a zone of protoplasm with embedded nuclei. As has been already mentioned spaces occur between the cyto-trophoblast and the inner laminated layer of the plasmodium, but between the spaces the two formations are directly continuous. While at these points the cell-layer and plasmodial layer are distinguished in histological characters, the transition from the one to the other is not sharp and defined; the cell-layer changes its tone to pink, and passes uninterruptedly into the dusky-red plasmodial layer. The nuclei are extraordinarily irregular in size, though all show the same loose character of the chromatin reticulum, with one or two chromatin nucleoli (Plate VII, Fig. 7). They differ markedly, as already stated, from the nuclei of the plasmodium, which stain deeply and have a granular appearance. Here and there the innermost nuclei tend to be arranged in a row for a short distance, as if the cells next the cavity were assuming the epithelial disposition which characterises this zone in Peters' ovum. This arrangement of the nuclei is also seen in Leopold's youngest ovum, but in our specimen it is much less definite even than in that extremely early stage.

The nuclei of the cyto-trophoblast are clearly in very active division. Mitotic figures are not numerous, nor are they very well preserved, but their presence indicates that the ovum was in all probability in active growth shortly before being cast off. The cell characters are best made out in the tangential sections which cut the poles of the blastocyst. Plate VIII, Fig. 11, is a photograph of one pole and Plate VII, Fig. 7, is a drawing of the other. A great many of the cells have either double, triple or even multiple nuclei. This may be observed both in the drawing and photograph. In the photograph (Plate VIII, Fig. 11) the cell outlines are clearly distinguishable; there is evidence of cell division; and it may be pointed out that the large dividing cells belong to the innermost layer of the cyto-trophoblast. The absolute continuity of the cyto-trophoblast and plasmodi-trophoblast is brought out clearly in Plate VII, Fig. 7. The appearances here, and all round the blastocyst wall, altogether preclude any other conclusion than that the cyto-trophoblast, by active and continuous proliferation of its cells, is gradually differentiated at its outer margin into plasmodi-trophoblast. The cyto-trophoblast is, in short, the germinal zone of the trophoblast.

At one or two places the cyto-trophoblast shows minute buds extending from its outer aspect. In one situation the bud has taken the form of a narrow cell column, on each side of which, but separated from it by a space, is a strand of plasmodium. The space does not contain blood, but corresponds to the clefts seen elsewhere between the cell-layer and plasmodium. These buds, though very rare, we take to indicate a commencing proliferation of the cellular layer, which will ultimately lead to the formation of the cellular villi of Peters' stage. The grounds on which this opinion is based will be discussed later; meantime it may be stated that these buds are clearly outgrowths of the cell-layer, and not plasmodial strands which have reverted to a cellular condition.

At no point does the cyto-trophoblast show any such columnar disposition of its cells as would indicate the presence of a layer of embryonic ectoderm in any part of the wall of the blastocyst, nor any thickening which could represent the formative cell mass continuous with the trophoblast.

It will be convenient at this point to consider the origin of the large cells which are seen lying free in the blood space within the necrotic layer of the decidua. These cells closely resemble bodies which are certainly cross sections of plasmodial strands, but when traced through the sections it becomes quite certain that they are not continuous with the plasmodium, but are really isolated cells. Plate VI, Fig. 6, shows them at a point where they form almost a continuous layer for a considerable extent. The necrotic zone of the decidua is depicted. The inner edge of the dead or dying tissue is extremely irregular and is excavated into bays, many of which include one or more of the cells under consideration. Within the layer itself are seen spaces inclosing cells in different phases of degeneration. The nuclei are identical with those of the completely free cells, and the protoplasm stains the same dusky-red in both cases. There are two ways of interpreting these appearances.

(1) The cells within the spaces in the necrotic tissue may be foetal, *i.e.* trophoblastic, derivatives which, having wandered outwards, are here caught in the act of attacking the necrotic wall of the implantation space and so causing its gradual enlargement.

(2) The cells may belong to the decidua itself, and are being set free from the necrotic zone as it is absorbed and the implantation cavity is enlarged.

The following considerations are in favour of the latter alternative:

(1) The cells cannot be cross sections of plasmodial strands because they cannot be traced back into the general plasmodial meshwork.

(2) The outer shell of trophoblast is entirely plasmodial. No cells which can be definitely identified as embryonic, occur anywhere except in that part of the wall of the blastocyst which we have called the cyto-trophoblast.

(3) The cells, both in the character of the nuclei and reactions of the protoplasm, agree with cells further out in the decidua, which are clearly degenerating maternal cells, and are distinguishable from the trophoblast in both these respects. They are quite different from the wandering trophoblast cells of later phases.

(4) The plasmodium and necrotic zone of the decidua are not everywhere directly in contact with one another; a union between the two occurs only here and there; elsewhere a space is left between the two containing red blood corpuscles and leucocytes. There is no indication that the wall of necrotic tissue is being absorbed by phagocytosis in the strict sense of the term; the appearances suggest rather solution by enzymes produced by the trophoblast.

On the whole we are inclined to conclude that these elements are derived from the necrotic zone of the decidua; that they are in short decidual cells set free in the process of absorption of the necrotic tissue. It must be admitted however that there is no histological criterion by which it can be absolutely determined whether they are maternal or foetal derivatives.[1]

THE CONTENTS OF THE BLASTOCYST.

THE MESOBLAST.

The cavity of the vesicle is occupied by a very delicate cellular reticulum, or loose syncytial tissue which has the characters of mesenchyme. It represents the earliest stage yet observed of the mesoblast. This mesenchymatous tissue shows no signs of cleavage into a parietal and a visceral layer; it is not yet arranged in a definite and denser layer round the wall of the vesicle, nor are there any processes of it indenting the wall.

The constituent cells of the mesoblast are minute, rounded or stellate elements united together by very delicate protoplasmic threads. They are brought out in the drawing reproduced in Plate III, Fig. 3, but the network which they form is somewhat obscured by the delineation, in the

[1] Since the above was written we have had the opportunity of seeing a demonstration by Graf v. Spee of the early phases of placentation in the guinea-pig, at the meeting of the Anatomische Gesellschaft in Berlin (April 23rd, 1908). Graf v. Spee showed that in the guinea-pig there is a layer of cells of foetal origin outside a plasmodial formation, which, though less extensive, has the same character as the plasmodium in our human ovum,—in short, that there are three layers of the trophoblast. Until his account of his preparations is published we can do no more than point out that Graf v. Spee's researches may possibly necessitate some modification of our interpretation of these elements.

interests of exact reproduction of what the section shows, of an extremely delicate reticulum, which is clearly an artefact due to precipitation of the fluid basis of the tissue. The coagulation of the tissue has clearly caused some contraction of the mesoblast, which has resulted in its withdrawal from the centre of the vesicle so as to leave a clear space in which the embryonic rudiment is situated. This retraction of the mesoblast has caused some degree of tearing of the embryonic rudiment.

THE EMBRYONIC RUDIMENT.

In the absence of any spot in the wall of the vesicle which could by any possibility be regarded as embryonic ectoderm, and of any thickening which could represent the inward projecting embryonic knob, we must recognise the embryonic rudiment in two closed vesicles which occupy the central retraction space in the mesoblast. There is a larger vesicle and a smaller. It is unfortunate that the larger is collapsed and considerably torn, while the smaller, though complete, is probably slightly displaced, as it is not directly in contact with the larger sac.

The larger vesicle extends through 24 sections (Figure II, 1-24), and therefore measures in this axis ·168 mm. The cells forming its walls are small compared with those of the trophoblast, and are cubical rather than columnar, but the protoplasm is frayed, and it is evident that the cell bodies have suffered considerably from defective fixation. The nuclei are rounded and fairly regular, though an occasional flattened nucleus occurs in what appears to represent the roof of the cavity. The vesicle hangs free in the central space, being definitely attached at one point only, where presumably the mesenchymatous tissue was more resistant.

A reconstruction in wax (Figure III) makes it quite certain that we have to do with a closed but torn and collapsed vesicle with uniform walls; there is no distinction between the cells of the roof and those of the floor. There is no indication of a passage from the cavity towards the surface of the blastocyst.

The smaller sac extends through six sections (Figure II, 26-31), and measures therefore ·042 mm. The cells forming its walls are more flattened than those of the larger vesicle. It is quite certain that though

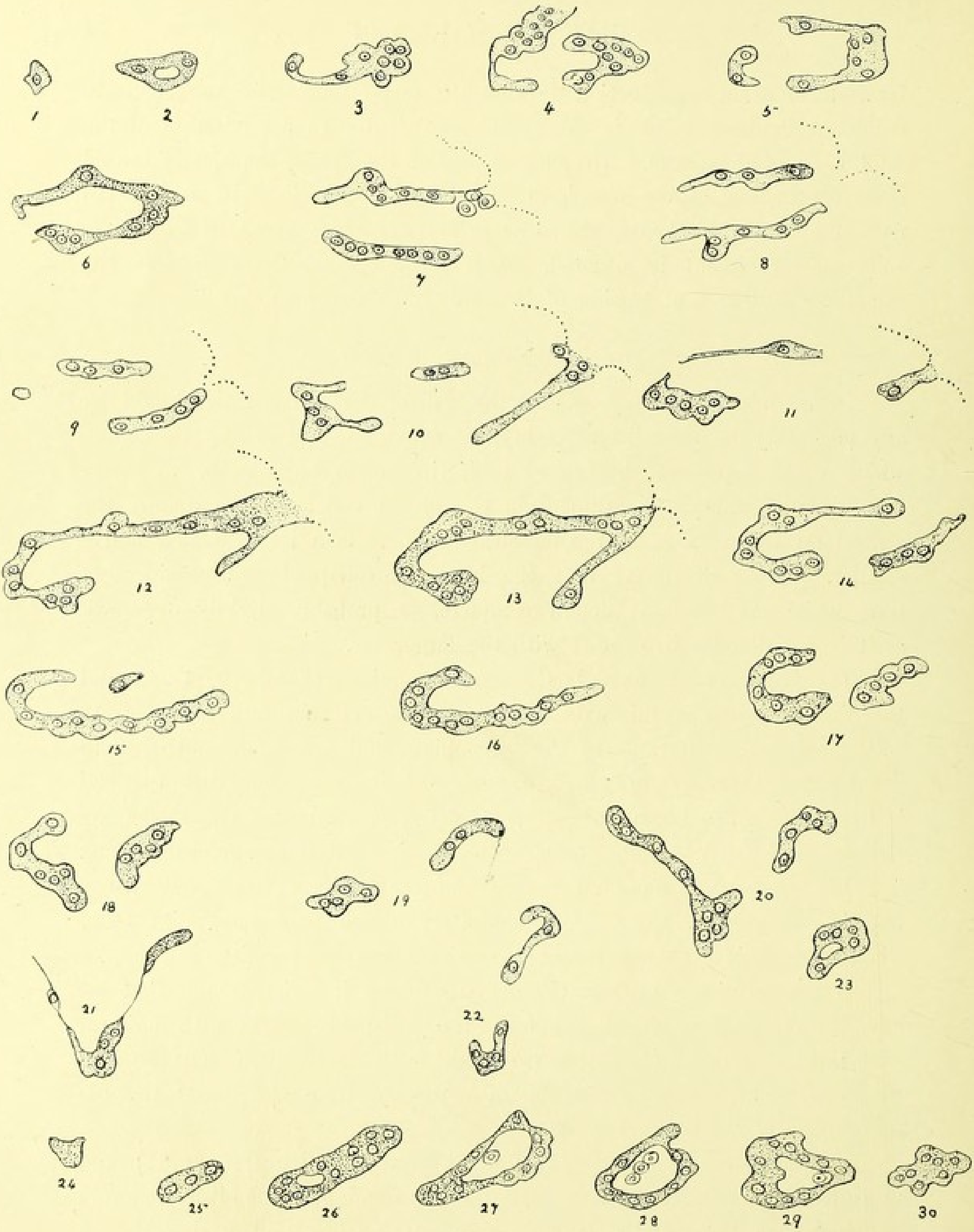

FIGURE II. OUTLINE DRAWINGS OF PORTIONS OF THE EMBRYONIC RUDIMENT AS IT APPEARS IN THIRTY SUCCESSIVE SECTIONS. ×320 D. The exact histological characters are shown in Plate VII, Figs. 9 and 10.

it is of very minute size the formation is a closed sac, and not an accidental grouping of the mesoblast cells. It is important to note that while the larger vesicle is attached definitely only at one point, the smaller is closely surrounded by mesoblast strands. These are absent only in one section, and on the side looking towards the position in the central space which is occupied in other sections by the larger vesicle.

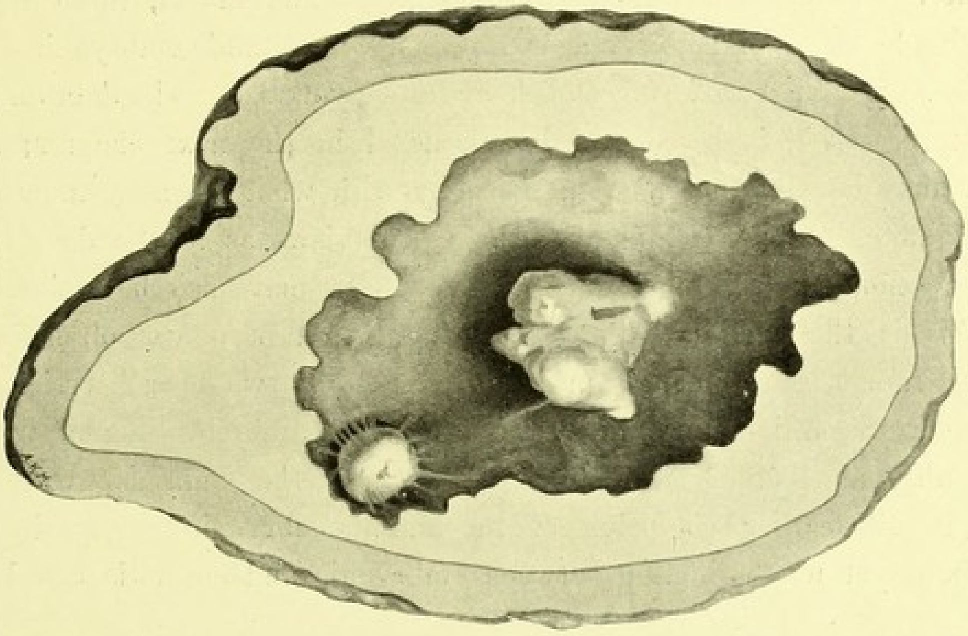

FIGURE III. DRAWING OF A RECONSTRUCTION WAX MODEL OF THE BLASTOCYST. $\frac{143}{1}$.

The outer darker layer is the cyto-trophoblast; the inner lighter, the mesoblast represented as if solid. The irregular cavity is the retraction cavity in the mesoblast. It contains two vesicles: the larger is the torn and collapsed amnio-embryonic vesicle, the smaller is the entodermic vesicle.

The model was constructed by building up wax plates to represent what was really a cast of the cavity of the blastocyst, with a space in its centre containing the vesicles. The model was then cut across so as to present to view the portion of the retraction cavity containing both vesicles. This portion of the model was then cast in plaster of Paris, and an outer case constructed which represents in a diagrammatic fashion the cellular layer of the blastocyst wall.

The model (Figure III) shows the relative sizes of the two sacs, and their position in regard to one another. The space between the two is obviously considerable, but as it contained no mesoblast it is probable that there has been a certain amount of accidental displacement. The appearances strongly suggest that the larger vesicle has suffered most in the shrinking of the tissue surrounding it. It seems to have collapsed and drawn away from the smaller vesicle. Two forces must have operated upon it—the centrifugal traction of the shrinking mesoblast, and a centripetal traction due to the precipitation of its fluid contents and contraction of its walls. The result of these opposing forces is the extensive tearing of the walls of the vesicle that has taken place. The other vesicle being very much smaller, and not so directly in the centre of the retractive force, has suffered much less.

After careful consideration of the sections and model, the conclusion is inevitable that the larger vesicle represents the amnio-embryonic cavity, and the smaller the entodermic vesicle or future yolk sac. The data on which this interpretation is based will be discussed in the next chapter; meantime it may be said that it is in harmony with what we now know of the early primate blastocyst, and with the recent views as to the development of the amnion in several lower mammals. It may also be pointed out that this is the earliest phase of the human embryo yet observed. In Peters' ovum the rudiment consisted likewise of two closed vesicles, but the larger or amnio-embryonic vesicle showed a differentiation of the floor into embryonic ectoderm, and the roof into the amnion. Our ovum shows a still earlier condition of the amnio-embryonic cavity, in which there is as yet no distinction between embryonic and amniotic ectoderm.

DISCUSSION OF DATA

From the foregoing description it will be apparent that the present ovum differs in certain important respects from any human ovum hitherto described. It is also in some of its features unlike any ovum with which we are acquainted among the lower mammals.

The special characters of our specimen may be summarised as follows:

(1) The blastocyst is completely enclosed in decidua except at one point, where there is a small gap closed by a mass of fibrin and leucocytes. The wide gap closed by the mushroom-like mass of fibrin and blood clot seen in Peters' ovum is entirely absent.

(2) The ovum lies, bathed in blood, in a relatively large implantation chamber with the walls of which it is not united. There is no interlocking or mixing of maternal and foetal tissues. The innermost layer of the decidua lining the cavity is in a state of advanced coagulation necrosis, and this, together with a certain amount of fibrinous deposit, forms a layer of dead material which is practically complete except at one or two points where blood-vessels have been opened up, and at one end where a haemorrhage has broken into the implantation chamber.

(3) The wall of the blastocyst consists of an inner lamella (cyto-trophoblast or cell layer) composed of cells rather ill-defined from one another, and continuous externally with an extremely irregular formation which has definitely plasmodial characters (plasmodi-trophoblast). This forms a straggling reticulum, the meshes of which are filled with maternal blood (primitive blood lacunae). There is no protrusion of the cyto-trophoblast into the plasmodi-trophoblast strands.

(4) The cavity of the blastocyst is filled by a delicate tissue having the characters of mesenchyme. There is no cleavage of this early mesoblast

into a parietal and a visceral layer; it does not form a distinct lamella round the wall of the cavity; and there are no protrusions from it representing future mesoblastic villi.

(5) The embryonic rudiment is represented by two eccentrically placed vesicles slung in the mesenchyme by fine protoplasmic threads. They are quite separated from the wall of the blastocyst by mesenchyme, and the cells forming the two sacs have definite and different characters, but *inter se* show no differentiation. The cells of the larger (amnio-embryonic) vesicle are cubical; those of the smaller (entodermic) vesicle are flattened.

Remarkable as some of the features of this new ovum are, there is no reason to suppose that it is in any way abnormal or pathological. Every one of its characters, as we shall now proceed to show, harmonises admirably with known later stages. It is in no sense contradictory or bizarre. It is not only consistent in itself, but is also consistent both with admitted facts and with inferences founded on these facts.

In the following discussion we shall first establish the position of our ovum relative to the earliest ova hitherto recorded, more especially those of Leopold (1906) and of Peters, and consolidate the basis of our interpretation both of the trophoblast and of the embryonic rudiment.

COMPARISON OF THE PRESENT OVUM WITH THOSE OF LEOPOLD AND OF PETERS.

In Leopold's ovum nothing like an embryonic rudiment was found. Towards the centre of the implantation cavity is a sac which Leopold regarded as the blastocyst. It is a thin walled and irregular vesicle containing tissue similar to the mesenchyme in the present ovum and in that of Peters, but infiltrated with red-blood corpuscles, obviously maternal, and separated more or less from the wall of the vesicle by a space containing blood corpuscles (cf. Leopold, 1906, Plate x, Fig. 18). The wall of the blastocyst is described as a thin mantle of ectoderm showing two layers of cells, the inner consisting of rounded or oval elements closely applied to one another and almost filled by large darkly staining nuclei, the outer of larger granular cell-masses with one or several nuclei, having thus the characters of plasmodium. The cells of the inner layer he distinguishes as Langhans' cells. Here and there the layer thickens into buds of Langhans' cells covered by plasmodium. These buds stretch out into long processes containing cells of both types, but there is never any outgrowth of mesoblast into them. Both cell layers are certainly of ectodermic origin, indeed Leopold regards any separation of them as inconceivable in light of the appearances in his specimen. The processes are attached here and there to the decidua, the terminal cells insinuating themselves among the tissues of the latter. The implantation cavity is a globular space filled with maternal blood in which the ovum floats freely, being anchored only by the tips of the trophoblastic processes.

There are distinct points of resemblance between our ovum and that of Leopold, but the differences are also strongly marked. The first striking point of contrast, apart from the absence of an embryonic rudiment, is that in our case the trophoblastic processes are entirely plasmodial; any cells which could bear comparison to Langhans' cells are confined to the thick wall of the vesicle, and the anchoring strands of plasmodium are fewer in number. The undifferentiated condition of the blastocyst wall in our ovum, and the absence of a cellular layer in the trophoblastic processes, lead one to infer that it is probably younger than Leopold's.

While the characters of the blastocyst, the haemorrhage into its interior, and the absence of an embryonic rudiment are abnormal features in Leopold's ovum, on the other hand, in respect of the trophoblast it very possibly represents a normal intermediate stage between the present specimen and Peters' ovum. It is known that in later stages the villi develop practically normally in the absence of an embryo, and doubtless the trophoblast may also do so at this early stage.

The blastocyst wall in Leopold's ovum, while it has a general likeness to that in the present ovum, is a less definite and a thinner structure, and has a greater resemblance to the layer of cells, with commencing cubical arrangement, covered by endothelium-like syncytium, which constitutes the greater part of the blastocyst wall in Peters' specimen (cf. Leopold,

Figure 18, with Peters' Figures 1 and 22). Leopold's ovum further resembles Peters' more closely, (1) in having two kinds of cells in the trophoblastic processes, and (2) in the characters of the mesoblast. The principal difference between the two is that the trophoblastic processes are more numerous and much thicker in Peters' ovum, so that, as compared with Leopold's specimen, the blood lacunae are much reduced in size, and the trophoblast takes the form of a thick layer containing blood spaces. The attachment of the primitive villi to the decidua appears to be very similar in both cases, but the degree of intermingling is much greater in Peters' ovum, and the condition of the decidua is also different. Whereas in Leopold's ovum (see his Figures 23 and 24) the zone of decidua next the trophoblast is largely in the state of coagulation necrosis, characteristic of the present specimen, in Peters' case the decidua has a much more living appearance; there is more mingling of living cellular elements, and the amount of necrotic material visible is relatively small. There is evidence of active reaction on the part of the decidua in Peters' case, as shown by the presence of large numbers of polymorphonuclear leucocytes and formation of new vessels; this is less marked in Leopold's case, but the invasion of leucocytes is very striking in the present specimen. All three ova however show a very distinct reaction as far as dilatation of blood-vessels is concerned, and this is greatly exaggerated in Leopold's case by congestion which is probably due to the mode of death.

In respect therefore of the trophoblast the ovum of Leopold may with some confidence be considered as a stage intermediate between the present ovum and that of Peters'; but as there was no embryonic rudiment the comparison cannot be carried further.

When the embryonic rudiment in the present case is compared with that in Peters' blastocyst, it is at once apparent, that if our interpretations be correct, this ovum is at a considerably earlier stage of development.

THE EMBRYONIC RUDIMENT.

It will be necessary to explain at this point the data on which our interpretation of the embryonic rudiment is based.

The mammalian blastocyst is a hollow vesicle with a knob of cells projecting into its cavity from one point on the wall (Figure IV). The ectoderm of the wall or *trophoblast* is concerned in the processes of imbedding and placentation, the inward projection constitutes the embryonic blastema. Whereas in the rabbit the cells forming the embryonic knob become spread out flat at the upper pole of the blastocyst (Figure V, *a*), and are soon exposed on the surface, by the disappearance of the thinned out trophoblastic covering (Rauber's layer), in another series of mammals the knob remains inturned and a cavity appears among the cells of

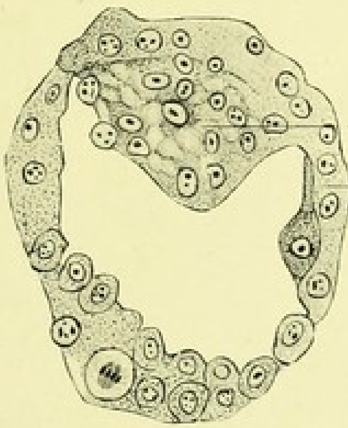

FIGURE IV. BLASTOCYST OF TARSIUS SPECTRUM (AFTER HUBRECHT), FROM "QUAIN'S ANATOMY," 11TH ED. VOL. I. EMBRYOLOGY.

the knob. In some cases the roof of this cavity early breaks away (Figure V, *b*), and the embryonic ectoderm, becoming flattened out, is exposed on the surface just as in the rabbit. In other instances the roof of the cavity persists and forms the definitive amnion (Figure V, *e*, *f*). There is very good reason for believing that this is the case in the human subject. Owing in all probability to the nature of the processes of imbedding, the embryonic knob or formative-cell mass remains in its original position, and the trophoblast becomes uniformly thickened all over the sphere. The embryonic rudiment lags behind in development, and there is a relatively enormous expansion of the trophoblast shell, which is concerned at first in the excavation of the implantation cavity and then in the nourishment of the embryo.

The entoderm is probably split off, to judge from the stages in

Tarsius, before the embryonic ectoderm is differentiated from the amniotic. Owing probably to the relatively great expansion of the trophoblast

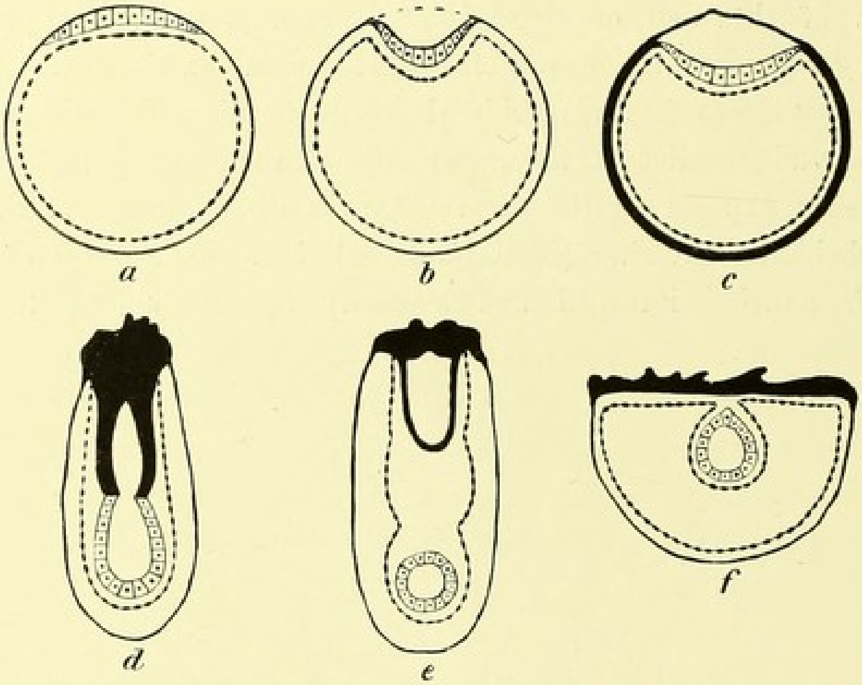

Figure V. Diagrams to illustrate the condition of Entypy of the Germinal Area (T. H. Bryce, from "Quain's Anatomy," 11th Ed. Vol. I.).

The trophoblast is represented by continuous black lines or masses, the entoderm by interrupted lines, the embryonic ectoderm, and in certain figures the amniotic ectoderm by epithelial cells.

Each figure represents the blastodermic vesicle. *a*, of the rabbit; *b*, of the mole; *c*, of the bat; *d*, of the mouse or rat; *e*, of the guinea-pig; *f*, of the kalong (Pteropus edulis).

In the rabbit (*a*) the cells of the embryonic knob early become arranged as an epithelial plate at the upper pole of the blastocyst; the covering layer of trophoblast (Rauber's layer) disappears and it is exposed on the surface—there is no amnio-embryonic cavity.

In the mole (*b*) the embryonic plate is for a short time inturned. The hollow is filled with trophoblast cells which disappear, and the plate straightening out is exposed on the surface as in the rabbit.

In the bat (*c*) a more distinct cavity appears in the heart of the embryonic knob. The floor of this forms the embryonic ectoderm which is necessarily at first concave (*i.e.* inturned); the roof persists as the *primitive* amnion.

In the mouse or rat (*d*) the covering layer of trophoblast roofing in the primitive amniotic cavity becomes greatly thickened, and the slightly inturned embryonic plate is pushed inwards as the blastocyst elongates into a tubular shape, until the layers (ectoderm and entoderm) are apparently reversed in position.

In the guinea-pig (*e*) the same inpushing occurs, but the amnio-embryonic rudiment and the trophoblastic thickening are separated; the amnio-embryonic vesicle remains a closed vesicle and forms the *definitive* amniotic cavity.

In Pteropus (*f*) the conditions are much the same as in Cavia, but the blastocyst remains rounded and there is no greater inturning of the layers than occurs in the early phases of the mole.

shell, and tardy differentiation of the embryonic rudiment, the entoderm does not grow round the blastocyst wall, but takes the form of a small closed vesicle, the cavity of which very possibly appears within a solid mass of cells. The amnio-embryonic cavity is excavated in the heart of the embryonic knob (Figure VI), and its floor, necessarily at first concave, and therefore apparently inverted or inturned, becomes the embryonic plate, while the roof becomes the amnion. The mesoblast appears very early and fills the space between the rudiment and the trophoblast. It is uncertain whether the amniotic lamella is from the first separated from the

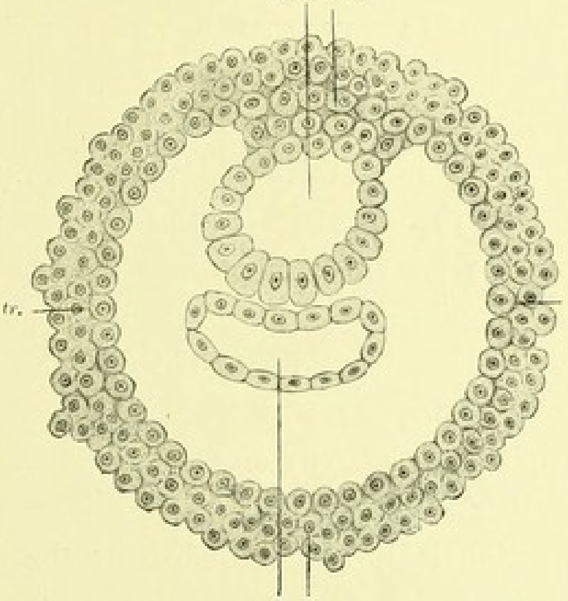

FIGURE VI. HYPOTHETICAL STAGE OF THE HUMAN BLASTOCYST (T. H. BRYCE, FROM "QUAIN'S ANATOMY," 11TH ED. VOL. I.).

tr., trophoblast; *am.*, amnio-embryonic cavity; *am.s.*, amnion stalk; *ent.*, entoderm.

This diagram was designed to show, in one figure, the probable early condition of the trophoblast, and an early phase of the embryonic rudiment, but the size of the cavity of the blastocyst relatively to the size of the amnio-embryonic and entodermic vesicles, is probably rendered too small. We do not know how soon the trophoblast shell begins to assume dimensions so much out of proportion, as they appear in our ovum and in Peters'. The trophoblast is shown with a cellular and a plasmodial layer, but it is probable that when the plasmodium is at the stage represented, the embryonic rudiment is not so far differentiated as it appears in the diagram. With these qualifications the figure, which was printed before the present ovum was obtained, is probably not essentially incorrect.

trophoblast. In Figure VIII, p. 45, they are represented as remaining connected, because it seemed impossible, without the existence of such a connection, to explain the presence of the amnion duct seen in Beneke's ovum, or the appearance of an open amnion as seen in Mall's pathological cases. While in man there is no true reversal of the germinal layers such as seen in mice and rats and the guinea-pig, there is no doubt that the plate of embryonic ectoderm is inturned, and strong probability that the condition is a primary one and not due to a precocious formation of amnion folds.

The views enunciated above find their full justification in this the earliest phase yet known of the human blastocyst, and lead at once to the identification of the larger vesicle as the amnio-embryonic and the smaller as the entodermic sac.[1]

It is right however to say that a rather different interpretation might possibly be put upon the facts, were the hypothetical stage imagined by Minot[2] taken as the initial phase. He represents the amnio-embryonic cavity as a transverse slit in a thickened portion of the blastocyst wall, consisting apparently of the formative-cell-mass merged with the trophoblast. Our ovum might represent a phase in which the entoderm had been separated off, but the amnio-embryonic slit had not yet appeared, and the embryonic ectoderm had not been differentiated. The larger sac would in this event be the entodermic sac, and the smaller might be considered a mere accidental grouping of the cells of the mesoblast. There is no doubt however that the smaller sac is closed, and that it is a definite formation. The second interpretation is further excluded by the absence in any part of the blastocyst wall of any such thickening as represented in Minot's

[1] The views adopted in the text are given at greater length in my article in *Quain's Anatomy*, 11th ed. 1908, vol. I. Embryology. They are founded mainly on the works of Graf v. Spee, Van Beneden, Hubrecht and Selenka. The chief difficulty which lies in the way of such an interpretation is the presence of an amnion duct in some lower Primates and in Beneke's ovum and the existence of a passage connecting the amnion with the intervillous space in pathological cases such as described by Mall. Such a condition may well be secondary, and it is so interpreted by Selenka and Keibel, but the appearances might indicate a very precocious formation and closure of amnion folds. In my article in *Quain*, having never seen any distinct recent statement on Professor Keibel's part regarding the amnion, I was led into the error of implying that he still held the latter view. In a personal conversation with him however, I learn that he has long accepted the primary closure of the amnion in man, and in a proof of his forthcoming *Normentafel* for man, which he has been good enough to send to me, I am glad to find that his views are essentially similar to those I have myself been led to adopt. Our case confirms his early position (1890) regarding the inversion (reversal) of the layers in the human embryo; there is no such reversal in the strict sense of the term, but in so far as the plate of embryonic ectoderm is inturned, there is a parallel between the early stages in mice, rats, etc., and those in man, as first pointed out, I believe, by Graf v. Spee in 1889. It is now known however that this early inturning is a feature of pretty general occurrence in mammals; true inversion (*Keimblätterumkehr*) is brought about by secondary conditions which are not present in the case of the human ovum. T. H. Bryce.

[2] *A Laboratory Text-Book of Embryology*, 1903.

figures. The diagrams here given supply an explanation of the facts at once simpler and more direct.

One of the most puzzling features of early primate ova is the precocious formation of the middle layer cells in the cavity of the blastocyst. The present ovum is not yet early enough to warrant a final judgment on the subject, but two new points emerge. The mesoblast arises at a still earlier stage than it does in Tarsius, and it completely fills the blastocyst. The extra-embryonic coelom seen in Peters' stage has not yet been formed. The probability that the extra-embryonic coelom is produced by splitting in the mesoblast therefore becomes a certainty.

In regard to the origin of this early mesoblast two remarks suggest themselves. The attachment of the mesenchyme to the amnio-embryonic vesicle more definitely and firmly at one point, may possibly indicate that it is arising from the ectoderm and from the same region as it does in Tarsius, *i.e.* from the future hind end of the embryonic plate, where the primitive streak will afterwards appear. On the other hand it is not impossible that the mesoblast arises contemporaneously with the entoderm from the embryonic knob; that in short the entoderm, even while coming into existence, is differentiated into an epithelial lamella which constitutes the lining of the yolk sac, and a vascular mesenchyme which is concerned in forming the vessels of the connecting stalks and chorion, and the blood and blood-vessels of the yolk sac. The study of the sections and of the characters of the cells rather inclines one to accept the second alternative, which could without much difficulty be reconciled with what is known concerning the origin of the vascular mesenchyme in later stages.

THE PROCESS OF IMBEDDING.

Having now discussed the characters presented by the present ovum, and its position in point of development relative to the earliest stages hitherto known, we proceed to consider its relations to the decidua, and the mode of implantation. In the absence of earlier stages, it will however be necessary to consider at greater length than we have yet done the comparative data available on these points. As already explained only those cases among the lower mammals in which there is a decidua capsularis provide a competent analogy.

The hedgehog presents certain resemblances in respect of the gross characters of its placentation to the human subject; there is not only a decidua capsularis, but also a general primary, and a definitive discoidal placenta. For these reasons, among others, Hubrecht undertook the investigation of the development of the placenta, which has led the way towards a clearer understanding of the human placenta.

The ovum of the hedgehog while still a small hollow blastocyst settles down at the bottom of a groove in the uterine mucosa. The epithelium around it disappears and at the same time a decidual swelling occurs in both lips of the groove, which thus enlarge and meet over the ovum. A certain amount of destruction of the connective tissue of the mucosa takes place, bleeding results, and a plug of blood clot is formed between the lips of the decidual swellings. The epithelium next disappears from the contracting lips, and they coalesce to complete the inclosure of the ovum.

The ectoderm of the blastocyst proliferates into a relatively thick lamella, which Hubrecht named the "trophoblast." It surrounds the whole blastocyst, and the formative cell mass projects into the interior as a knob of cells. The trophoblast on the one hand rapidly establishes a union with the proliferating decidua, and on the other becomes hollowed out into cavities, into which maternal blood is shed from the capillaries which have been opened up by its destructive activity. At first the trophoblastic shell is complete and the greater part of it becomes penetrated by mesoblastic villi which are vascularised from the yolk sac forming a primitive vitelline placenta, but the definitive placenta is formed by villi which receive their blood-vessels from the allantois.

At a certain stage therefore there is a diffuse placenta, while the definitive placenta is implanted upon the area of decidua adjacent to the uterine wall, *i.e.* decidua serotina or basalis. As this develops the vitelline placenta applied to the decidua reflexa gradually undergoes atrophy. The main difference between these arrangements and those that prevail in man is that the primitive placenta is supplied in the latter by vessels which develop in the *Haftstiel*, or connecting stalk of mesoderm, and correspond to the allantoic vessels. The *Haftstiel* is, as now well known, a feature peculiar to the Primates, there being further no free allantois.

Accurate data regarding the chronology of imbedding and development in the hedgehog are wanting.

In the mouse the process of imbedding is in some respects very similar to the type seen in the hedgehog. The ovum becomes lodged in a furrow on the side of the slit-like lumen of the uterus farthest from the mesometrium. The epithelium disappears in its neighbourhood; decidual development occurs in the adjacent endometrium, which swells up into a thick cushion all round the ovum. The swelling gradually obliterates the middle region of the lumen, leaving however at first an open passage along the opposite wall of the uterus. The space between the lips of the decidual swellings is at first blocked by the ectoplacenta, but later the epithelium disappears—apparently as a result of atrophy due to pressure, the exposed decidual surfaces coalesce, and the capsule is completed. Besides great hyperplasia of the decidua cells, new vessels are formed which are directed towards the ectoplacenta, and when the union of trophoblast and decidua is accomplished, the placenta is developed in the region where the decidua capsularis is finally closed. The part of the decidua, therefore, which is developmentally reflexa plays the part of serotina. Prior to this there is generally some haemorrhage into the implantation cavity, and the shed blood is supposed to be used as pabulum for the growing ovum.

The further development of the placenta does not concern us except in one particular, viz.—the uterine epithelium, as is clear from the work of Burckhard, plays no part in the formation of the placenta; this is achieved in this case, as in the case of the hedgehog, by the union of foetal ectoderm and decidual connective tissue, and by the opening of maternal blood-vessels into spaces formed in a thickened portion of the trophoblast.

The time relations in the case of the mouse and rat are very accurately known. They will be discussed in the chapter dealing with the age of the present ovum, but it may here be noted that imbedding commences on the fifth day after fertilization, and that the ovum at that period is a small hollow blastocyst, not materially larger than the fertilized ovum before the commencement of segmentation.

In the guinea-pig imbedding seems to occur in a different fashion. According to the researches of Graf v. Spee the ovum, while still in a very early blastocyst phase, loses its zona pellucida, and actively attacks the endometrium. It destroys a small area of the epithelium, and passing through the gap so produced, continues its destructive action on the connective tissue of the mucous membrane until a cavity is formed sufficient for its complete inclosure. The opening in the epithelium is blocked for a time by the cells of the future ectoplacental pole of the ovum, the epithelial and foetal cells remaining in contact at this point. Necrosis, followed by solution of the dead cells, now overtakes a considerable area of the endometrium, with the result that a considerable space (*Implantationshof*) is formed round the ovum. This is filled with fluid and is lined by more or less necrotic and dissolving tissue. Outside this zone, active proliferation takes place leading to the formation of a decidua which completely surrounds the blastocyst. The placenta is formed from the ectoplacenta, which becomes drawn down, owing to changes in the uterus, towards the middle of the lumen; maternal blood-vessels are developed in this position, and the final result is that, in spite of the initial difference in the manner of implantation, the relations of placenta to uterus are very similar to those in the mouse. It is sufficiently clear that in this case also the uterine epithelium takes no part in the formation of the placental tissues.

The imbedding of the guinea-pig ovum is effected on the seventh day after coitus; segmentation is complete, but the size of the ovum is not appreciably increased. When implantation has taken place the ovum grows and develops with great rapidity.

In all these cases fertilization apparently occurs in the upper part of the Fallopian tube; segmentation is completed during the transit of the ovum to the uterus, which it reaches but little increased in size and still enclosed in the zona pellucida. This envelope now rapidly disappears, and implantation of the ovum takes place forthwith. In the mouse and guinea-pig the endometrium does not show the slightest trace of alteration from the non-pregnant state until the epithelium has disappeared, and the ovum commences to attack the deeper tissues; decidual development then rapidly follows. Whether this is the same in the hedgehog is not quite clear. In all these cases the ovum becomes completely enclosed, and after a period in which it lies free in the implantation cavity, it obtains attachment to the maternal connective tissue by means of the development of a special part of its ectoderm.

While the present ovum is the youngest yet described it is not yet sufficiently early to demonstrate the actual mode of implantation in man, but it brings us nearer to a comprehension of the process in several respects.

In regard to the antecedent phenomena there is no reason for believing that they are different from those in other forms, and we may consider that the ovum reaches the uterus as a small blastocyst still enclosed in the zona pellucida. The cavity of the human uterus is of course vastly larger, relatively to the ovum, than that of the hedgehog, mouse or guinea-pig, but it is narrow and slit-like. It differs from that of the mouse in having, as far as the corpus uteri is concerned, a perfectly smooth surface, free from crypts or furrows, with the exception of the mouths of the glands, which are too minute in an undilated state, to admit an ovum. The idea that the ovum becomes imbedded in a gland is apparently not now held by any one. Our ovum is imbedded near the centre of a smooth, rounded elevation, similar to, but higher than, many other small areas lying between the furrows, and it appears highly probable that the elevations and furrows alike have arisen as the result of decidual proliferation. We have no evidence that this development takes place prior to the imbedding of the ovum. Indeed, from what occurs in the mouse and guinea-pig, we might from analogy infer that the human ovum may imbed itself in practically unaltered endometrium. This question will be considered again in the chapter on the age of the ovum, and the relations of imbedding to menstruation.

When we consider the appearances of this elevation, the shape of the uterine lumen and the characters of the mouth of the implantation cavity in our specimen, we must conclude that in the initial stages the process of imbedding in the case of the human ovum is in all probability similar to that which Graf v. Spee describes as occurring in the guinea-pig rather than to that which occurs in the mouse or hedgehog, though it is not impossible that the ovum settles into one of the slight hollows which are present on the surface of the normal endometrium. This opinion is of course no new one; it has been advocated by Peters, Graf v. Spee, Leopold and many others, but our case enables us to amplify the conception in some particulars.

We would describe the imbedding of the human ovum as follows: The ovum having attained the stage of an early blastocyst, and measuring about ·2 mm. in diameter (*i.e.* approximately the size of the mature oocyte), comes to rest in a slight depression, but neither a crypt nor a fissure, in the endometrium, destroys the surface epithelium, and continuing its destructive activity passes into a space in the decidua which has thus been produced. Necrosis followed by solution (digestion) of a considerable mass of the endometrium follows, resulting in the formation of an implantation cavity. So far we agree with the views expressed by Graf v. Spee regarding the human ovum in 1905. Changes leading to the production of decidua begin immediately after the solution of the epithelium, and the elevation is formed which is the characteristic resting-place of all the four earliest ova at present known. The mouth of the implantation chamber is probably blocked by a mass of blood clot, the cavity having meantime been filled by blood shed from the opened-up maternal capillaries. The present specimen shows a narrow orifice only ·1 mm. in diameter, and the sealing substance is rather thrombus-like material than blood clot. The relatively-wide gap (·8 mm.) in the surface of the mucosa closed by blood clot and fibrin, which characterises the ova of Peters, Jung, Stolper and Graf v. Spee, is here entirely absent. If we have proved our thesis that the present ovum is the earliest yet recorded, we must conclude that this gap is not the portal of entrance properly so called—it is much too large—but is a secondary formation, being produced by the subsequent destructive activity of the trophoblast threatening to destroy the roof of the implantation chamber. The smaller extent of the fibrine cap in Leopold's ovum, and the fact that it is in two portions, would, if our view be correct, find a ready explanation.

The ovum now rapidly differentiating develops a thick trophoblast all round the blastocyst as in the hedgehog, and not at one point as in the other species (see Figure VI, p. 33). The ovum is at first free in the implantation cavity. The trophoblast from a very early stage,

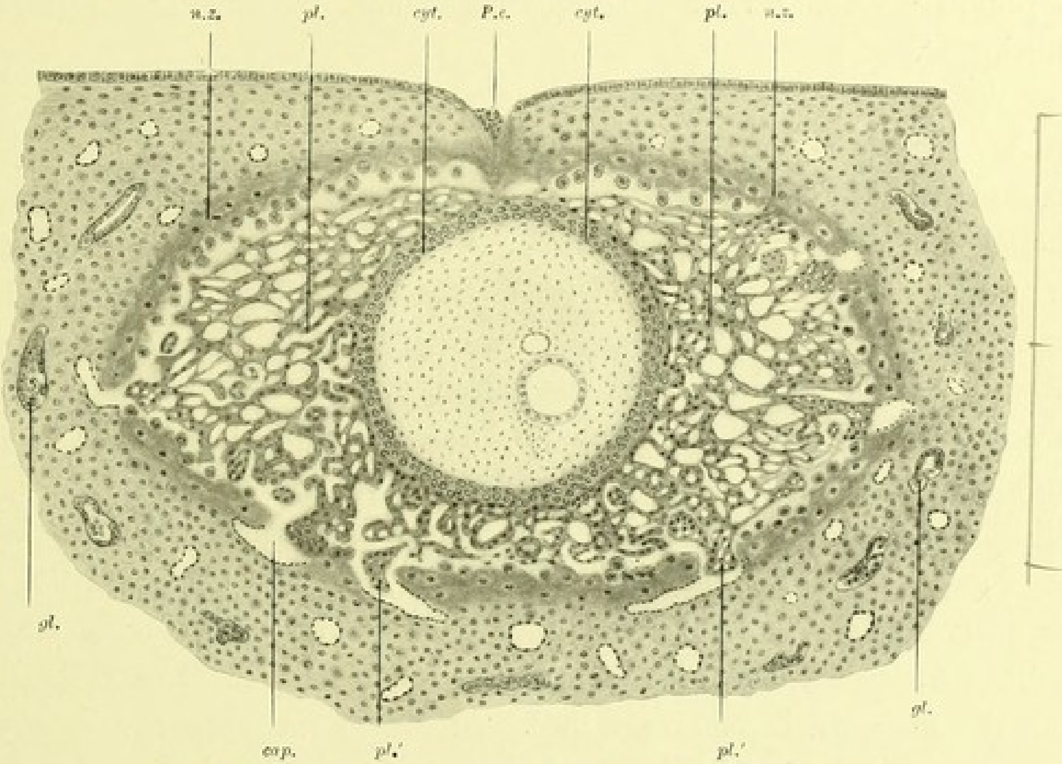

FIGURE VII. DIAGRAM OF TEACHER-BRYCE OVUM. MAGNIFIED 50 D.
(T. H. BRYCE, DEL.)

P.e., point of entrance; *cyt.*, cyto-trophoblast; *pl.*, plasmodi-trophoblast; *n.z.*, necrotic zone of decidua; *gl.*, gland; *cap.*, capillary; *pl.'*, masses of vacuolating plasmodium invading capillaries. The cavity of the blastocyst is completely filled by mesoblast, and imbedded therein are the amnio-embryonic and entodermic vesicles. The natural proportions of the several parts have been strictly observed.

as in the bat (Van Beneden), shows a cellular layer (cyto-trophoblast) and a plasmodial layer (plasmodi-trophoblast). The plasmodium throws out buds which stretch towards the walls of the decidual chamber, and it is continually being added to by active proliferation in the cellular layer. In the first place the plasmodial masses exert mainly a destructive action; this results in the production of a relatively large implantation cavity such as seen in our specimen (Figure VII). The destruction of the decidua is necessarily associated with the destruction of vessel walls and the opening up of glands. Haemorrhage occurs into the cavity, but the blood does not coagulate. It serves to nourish the ovum, and after a time it begins to circulate among the trophoblastic processes. Up to this stage the ovum has not become attached to the decidua. It now becomes fixed, first by anchoring strands of plasmodium and later by the development of primitive cellular villi. Our specimen shows the very initial stages of attachment.

We may here digress for a moment to point out a very suggestive analogy with the normal ovum in respect of its influence on adjacent maternal tissues, presented by an embolus of *chorion-epithelioma* in its development into a secondary tumour.[1] The embolus, usually somewhat larger than the imbedding ovum, lodges in the fork of a blood-vessel, the wall of which soon shows degenerative changes identical in character with those seen in the decidua around the present ovum. These occur prior to the invasion of the tissues by the tumour cells. The injured blood-vessel dilates into a more or less globular aneurismal cavity, and there may be considerable growth of the embolus in its interior before invasion begins. The blood in the neighbourhood of the embolus does not coagulate, until secondary changes, which need not be discussed here, bring about that result. After a time the tumour elements invade the maternal tissues and the embolus becomes attached. At this stage appearances may be found very similar to those around the margin of Peters' ovum.

The formation of the aneurism with its necrotic wall, round the embolus finds a parallel in the behaviour of the decidua round the human ovum. We may assume that, as in the case of the guinea-pig ovum, there is primarily destruction of a fairly wide zone of tissue, which draws away from the ovum partly, at least, on account of the swelling which accompanies coagulation necrosis. The shed blood must further stretch the soft decidua just as the wall of the vessel is stretched into the wall of an aneurism, and the necrotic zone of the decidua is removed, like the necrotic wall of the aneurismal sac, before attachment can take place. Also, as in the

[1] "On the Development and Natural Healing of Secondary Tumours of Chorion-epithelioma," by John H. Teacher, *Jour. Path. and Bact.* vol. xii. part iv. 1908.

case of the embolus, the necrosis is at first progressive, but soon, reaction taking place in the surrounding tissue, it becomes more capable of resistance, and consequently of effecting a union with the trophoblastic processes, as will be described later.

The appearances of the necrotic zone of the decidua and of the plasmodium in our ovum all suggest that the process of destruction is not one of erosion by direct cellular activity or phagocytosis, but a sort of digestion or solution due to the action of extra-cellular substances probably of the nature of enzymes. Further, it appears probable that the vacuolated and spun-out condition of the plasmodium is due to the formation in the vacuoles of a digestive fluid, and that when this is shed by the rupture of the vacuoles its place is taken by maternal blood. In this way all the appearances of the plasmodium are readily explained. Possibly the secretion also contains an enzyme which prevents coagulation of the blood; but it is also not impossible that the surface of the plasmodium may behave towards the blood like an endothelium, thus preventing coagulation. The fact that coagulation readily occurs in the neighbourhood of the placenta, or tumour, when a considerable extravasation has taken place, is rather against the idea that there is an active coagulation-hindering enzyme.

The plasmodial formation characteristic of the present ovum has hitherto been described only in connection with a young ovum recorded by Stolper. The ovum which measured 2·5 × 2·2 mm. in diameter, was obtained by curetting undertaken on account of menorrhagia simulating abortion, although no menstrual period had been omitted. It presented a close resemblance to Peters' ovum, and was fairly well fixed. On one side of the ovum the villi were long and rather more advanced in appearance than in Peters' case, but on the other side there was an extraordinary development of spun-out plasmodium, which was not attached to the adjacent decidua, and was not accompanied by a corresponding development of the Langhans' layer. Much of this plasmodium was degenerated or even necrotic, and Stolper states that "es kann nicht physiologisch sein." In the light of our ovum, the occurrence of such a condition of the plasmodium in Stolper's case, probably represents the abnormal persistence of what is normal in an earlier stage.

It will be recollected that in Leopold's ovum both layers of the trophoblast are represented in the irregular villi, and that in Peters' specimen the epithelial villi are broader bands composed of Langhans' cells and covered by an endothelium-like layer of syncytium bounding the blood lacunae. Our specimen seems to represent a phase hitherto unknown, in which the ovum is largely unattached and the villi are wholly plasmodial. Leopold's ovum is a stage in which attachment is proceeding and the plasmodial villi are becoming replaced by cyto-trophoblastic processes or villi, while Peters' ovum represents a stage in which attachment is taking place, and the necrotic zone having largely disappeared, there is a mingling of foetal and maternal tissues; in short, formation of a placenta has begun. In the later stages destruction of decidua no doubt continues, but far less actively.

With regard to the manner in which the purely plasmodial masses become replaced by processes containing both cyto-trophoblast and plasmodi-trophoblast, three possible explanations present themselves:

(1) The trophoblast may from the beginning be plasmodial and the cell-layer may arise by differentiation within the plasmodium. Such a possibility has been suggested, among others, by one of us (Dr. Teacher in his studies on Chorion-epithelioma), but it is very difficult to reconcile with the characters of the spun-out and vacuolated plasmodium in the present ovum.

(2) In terms of the view expressed by Leopold and already referred to, the broad processes seen in Peters' ovum may arise by the formation of buds of the cyto-trophoblast which grow outwards into the plasmodial strands, much in the same way as the mesodermic processes grow into the primitive epithelial villi. Much of the plasmodium would thus be reduced to the endothelium-like lining of the blood lacunae.

This explanation also presents difficulties in view of the characters of the early plasmodium. It is difficult to picture the process imagined, and therefore we are inclined to fall back on a third possibility, viz.:

(3) That the cyto-trophoblast grows out as cellular masses and columns, not so much into the plasmodial strands, but into the spaces between the strands.

The further changes could be conceived as follows: the greater part of the early plasmodium disappears after being spun out into the fine threads seen in many parts of our sections, while the marginal cells of the cyto-trophoblastic columns continue to form new plasmodium. On the other hand, the plasmodium may in part persist, the strands arranging themselves over the cytoblast columns as an endothelium-like layer, while

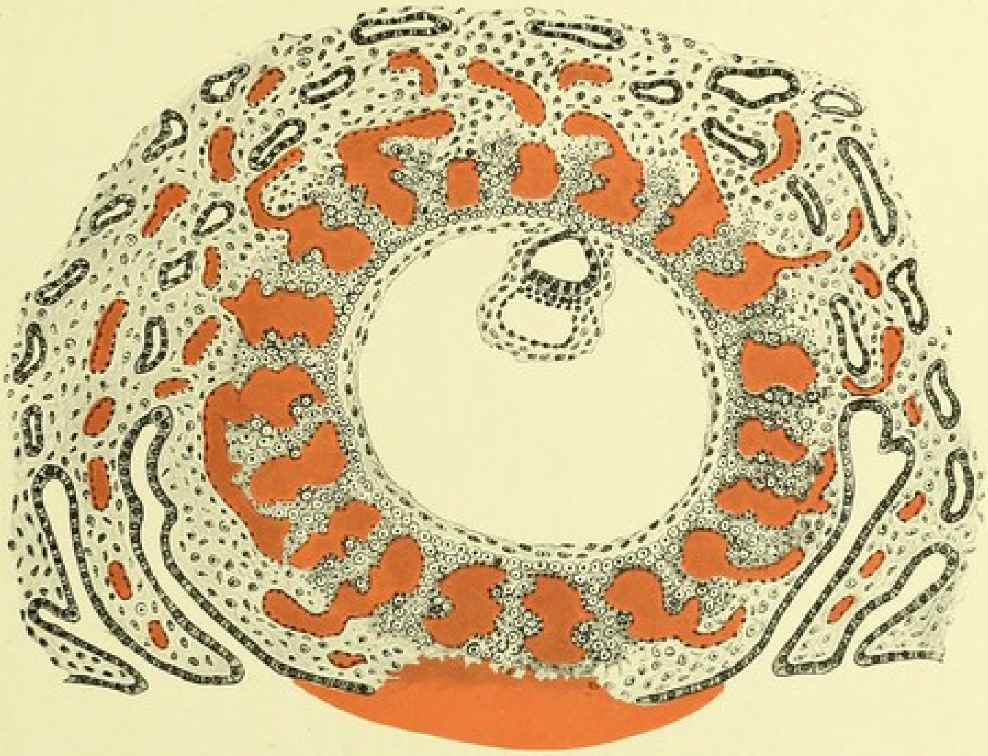

FIGURE VIII. DIAGRAM OF A HYPOTHETICAL STAGE OF THE HUMAN OVUM IMBEDDED IN THE DECIDUA SOMEWHAT YOUNGER THAN PETERS' OVUM. THE EMBRYONIC RUDIMENT IS PROPORTIONALLY ON TOO LARGE A SCALE. (T. H. BRYCE, FROM "QUAIN'S ANATOMY," 11TH ED. VOL. I.)

the outlying parts remain as the irregular masses invading the decidua. It appears probable that the extensive plasmodium is in great part a temporary formation provided for the early enlargement of the implantation cavity. The attachment of the ovum is effected when the columns of cyto-trophoblast reach the decidua at points from which the necrotic layer has been removed, and become fixed by the terminal cells insinuating themselves among the elements of the decidua. The accompanying figure (Figure VIII) presents in a diagrammatic form an ovum at a stage intermediate between our ovum and that of Peters.

The later stages of attachment and of the formation of the placenta do not here concern us, but it must be pointed out that our specimen establishes a difference, though perhaps it may be one of degree not of kind, between the processes involved in the imbedding of the ovum, and those which characterise the commencement of placentation. A distinction must therefore henceforth be drawn between the initial stages and phases of implantation or imbedding and those of attachment or placentation.

THE AGE OF THE OVUM AND RELATION OF IMBEDDING TO MENSTRUATION

The following chapter is of the nature of an appendix to the descriptive part of our memoir. It deals with the age of our ovum and certain theoretical considerations regarding the decidua which arise in connection with that problem. In attempting to place our specimen, in point of age, among other recorded cases we were met with so many difficulties and contradictions that it seemed worth while to ascertain whether, by applying the precise data of our own case to the other records, we could arrive at a more consistent chronological sequence than afforded by His' rule. We have therefore reviewed the literature from this point of view, and shall now give the result of our enquiries.

In estimating the age of the human ovum or embryo, it is customary to make use of the convention of His, and to reckon, as the approximate age of the ovum, the interval between the date on which the first omitted period should have commenced and the termination of the pregnancy. This is fairly satisfactory from the embryological point of view when dealing with embryos of the sizes commonly found, but it conflicts not only with some facts of clinical experience, but also with the data of comparative embryology, and it fails altogether when applied to many of the very young ova which are on record.

For the calculation of the age of the present ovum we have quite precise data regarding coition. The coitus of 2nd October may be definitely rejected as a possible factor in the case. The data provided by several of the cases which are summarised in this section make it certain that fertilization must have taken place after, and was presumably effected by, the coitus of 19th October. Any other conclusion would be so inconsistent with the character of the ovum itself and would involve so many gratuitous and unnecessary assumptions, that the case has the practical value of ascertained pregnancy after a single coitus. As the abortion began on November 4th and was completed on November 5th the total interval between coitus and expulsion is 16½ days.

While the time occupied by the spermatozoa in traversing the genital passages is not known in the human subject, the observation of Birch-Hirschfeld[1] proves that they reach the Fallopian tubes in large numbers within 24 hours, and in the rabbit the distance from the vagina to the upper parts of the tube is known to be traversed in from a ¼ hour to 2 hours (Milnes-Marshall). It is therefore unnecessary to allow for an interval of more than 24 hours between coitus and fertilization. In those animals in which the phenomena have been actually observed, such as the mouse and the rabbit, fertilization occurs forthwith, and although the possibility of its being delayed is not denied in view of other facts of comparative embryology, there is no valid reason for supposing that it may not occur in the human subject immediately after the spermatozoa reach the upper third of the Fallopian tube, where it may be assumed that they normally encounter the ovum.

There are no very reliable data regarding the length of time that spermatozoa may survive in the genital passages. They have been observed in a living state after nine days, but it by no means follows that they retain fertilizing power so long. The comparative infrequency of fertile insemination during continuous cohabitation, seems to point to there being some special circumstances connected with a successful impregnation. Were spermatozoa to retain for long their power of fertilization, no ovum should escape fertilization. It seems reasonable to assume, on the analogy of the lower mammals, that the favourable conditions are the occurrence of insemination and ovulation simultaneously or at no great distance of time. The shortness of the oestrus period in lower mammals may perhaps be looked upon as a means of attaining this end. If allowance must be made for the possible survival of spermatozoa for long periods, any attempt to establish a sequence of stages is futile. We proceed

[1] Cited from Leopold, *Uterus und Kind*, Leipzig, 1897.

therefore on the assumption that in the majority of instances insemination and ovulation nearly coincide, and for the sake of argument allow 24 hours for fertilization to occur.

If we now deduct from the total interval of 16½ days 24 hours for the period between insemination and fertilization, there remain 15½ days.

The favourable state of preservation of the ovum, as already shown, precludes the possibility of its having been retained in the uterus for any length of time, and this is consistent with the fact that not more than 36 hours elapsed between the first symptoms of abortion and its completion. If it be assumed that development ceased soon after the commencement of abortion, at least 24 hours must be deducted at this end of the scale, and we have left a period of 14½ days as the probable maximum age of the ovum.

If the age be calculated from the data regarding menstruation it works out thus:—Menstruation should have occurred on October 25th, or 28 days after the date of the former period. Between this and the first symptoms of abortion 10 days intervened, making the minimum possible age of the ovum 10 days. If on the other hand the intermenstrual interval had equalised itself to the usual average of 26 days, the allowance on this occasion, seeing that the previous interval had been 25, should have been 27 days. On this basis the minimum possible age would come out as 11 days, or, according to the convention of His, 12 days. Now we know that degenerative changes commence some days before the appearance of the menstrual discharge. It therefore seems necessary to allow some time, probably as much as 3 days, during which the fertilized ovum exercises some influence over the uterus which results in the arrest of the destructive changes. This would bring the probable minimum age of the ovum up to 13 days. Taking all the factors into account, the absolute limits of age may be stated as from 12 to 15 days, but, as will be seen later when the data regarding other recorded ova are considered, a computation of from 13 to 14 days is probably correct. Moreover, it will be found to agree very well with such facts of comparative embryology as are applicable.

The chronology of the early stages of development are most accurately known in the case of the white mouse, but they have also been ascertained with considerable exactness in the cases of the guinea-pig, rabbit, pig and dog. The nature of the attachment of the ovum to the uterus and its course of development are so different in the pig and dog from what they are in man, that comparison is impossible, except with regard to one point which will be taken later. The relatively short gestation period of the three rodents, and the individuality in the behaviour of the ova of different species, compel us to exercise caution in applying the facts of their development to the elucidation of human embryology.

In the mouse the rate of development is known very accurately up to the 10th day, and the results of Sobotta, Burckhard, Jenkinson, and Melissinos show no great difference in respect of chronology. Fertilization occurs very soon after coitus; by the end of the first 12 hours the ova are for the most part in the two-celled stage of segmentation; and by the end of 48 hours they consist of from 16 to 24 blastomeres. Development then proceeds more rapidly, and the differentiation into an outer layer and an inner group of cells becomes apparent. The zona pellucida is still complete. By the end of the 3rd day the ova have reached the uterus, the zona pellucida is beginning to disappear, and the morula has become a hollow blastocyst. The ovum now elongates, and up to the beginning of the 5th day is engaged in the process of inversion of the germinal layers. On the 4th day implantation commences by the removal of the uterine epithelium in the neighbourhood of the ovum, and fixation occurs on the 6th day at the earliest, though not until the 8th day does the ecto-placenta take form. At this point, however, the lagging behind of the embryo relatively to the trophoblast in the human ovum produces a state of affairs so different that further comparison becomes impossible.

Duval indicates the 7th day as the period of attachment in the rabbit, but the ovum in this case is not completely imbedded, and the development of the blastocyst is quite different from that in the human subject. On the other hand, the similarity of the process of imbedding in the guinea-pig to what is theoretically probable in the human subject makes it a more favourable subject for comparison.

Von Spee figures numerous ova of the guinea-pig either free in the uterus or in process of imbedding. None of these are earlier than the beginning of the 7th day after coitus, and nearly all are in the early blastocyst stage. There is no marked change up to the end of the 7th day. At 7 days 13½ hours the ovum is a hollow vesicle of considerable size, completely imbedded, and shows an enormous advance compared with ova 24 hours younger. This may be explained by supposing that whereas the growth of the ovum is relatively slight before implantation, development proceeds very quickly after imbedding is complete.

It seems improbable that the human ovum could be imbedded earlier than that of the guinea-pig, and we therefore agree with the opinion expressed by Graf von Spee that imbedding in the human subject cannot take place sooner than 7 days after fertilization. By this time in all probability segmentation is complete, but the ovum has hardly increased in size, still retaining the dimensions of the unfertilized oocyte, *i.e.* about ·2 of a millimetre in diameter.

The rate of development after imbedding is more rapid in the rabbit than in the mouse, and much more rapid than in the guinea-pig. These variations are probably, in part at any rate, to be explained by the different methods of implantation. Development seems to be retarded in the early stages in forms with a decidua capsularis, and in the human ovum the retardation of the evolution of the embryonic rudiment compared to the trophoblast is a very striking feature. If, therefore, seven days be arbitrarily allowed for segmentation and the early phases of implantation, another seven days does not seem too much to allow for the growth and development of the ovum up to the stage presented by our case, when we consider the rate of growth in the mouse and guinea-pig, and allow for the much longer gestation period in the human subject.

In comparing the present ovum with other human ova, it seems advisable, in order to restrict the range of error as far as possible, to consider only those which may be estimated as at most a week older than it is; therefore no ovum larger than Graf v Spee's "Gle" is included in our series. Further, only those are considered which have a reasonably complete and precise history, and have been obtained under favourable circumstances, or in such condition as precludes retention in utero for more than a day or two after the cessation of development. A number of otherwise valuable young ova have therefore been omitted, namely those of Ahlfeld, Beigel and Löwe, Breuss, van Heukelom, Hitschmann and Lindenthal, Hoffmeier, Keibel (1890), Kollmann, Leopold (1906), Marchand, Rauscher, v. Spee (1905), Stolper, and Wharton Jones. The ovum No. 11 of Mall is also omitted as being pathological. There remain eleven recorded ova which meet our requirements, namely those of Peters', Jung, Merttens, Beneke, v. Spee (v. H.), Leopold (No. 1), Reichert, Rossi Doria, Eternod, Frassi, and v. Spee (Gle). The data regarding these eleven cases will now be briefly summarised and tabulated.

For purposes of comparison in the histories and table, the age of the present ovum is taken as 13-14 days. In assessing the relative age of other young ova, the total size of the ovum, the size of the blastocyst, and where it is known the size and state of development of the embryo are all taken into account. It is probable that ova vary slightly in the rate of development of the embryo, and still more in the rate of growth of the trophoblast. Considerable variation in the rate of development is known to occur in certain of the lower mammals; for example, Keibel found in the pig differences which he regarded as equal to from 24 to 48 hours' growth, at such an early date as the 14th day of pregnancy. The computations must therefore be regarded as merely approximate; but as the total period considered is only 20 days, and the difference between the youngest and the oldest only 7 days, they may be regarded as fairly correct.

SUMMARY OF DATA REGARDING SELECTED OVA.

I.—Ovum of Peters.

Dimensions — external, about $2{\cdot}4 \times 1{\cdot}8$ mm.; blastocyst, internal, $1{\cdot}6 \times {\cdot}8 \times {\cdot}9$ mm.; embryo, ·19 mm. The specimen was obtained at sectio a few hours after death. The fixation is very good, and the details of its structure and imbedding have been very well worked out. The patient who had borne one child menstruated for the last time on 1st September, 1895. Towards the end of September, besides other symptoms, vomiting occurred. On the menstrual discharge failing to appear, she committed suicide on the 1st October by swallowing caustic potash. No definite data as to coitus could be obtained. Although this ovum is considerably more advanced in development than our ovum, it can scarcely be regarded as more than 15 days old, in view of the facts relating to Merttens' ovum, and the very great advance which occurs in the succeeding 7 days. Peters reckoned the age as 3 to 4 days, but this is obviously a great understatement. Estimated age, 13½ to 14½ days.

II.—Ovum of Jung.

This ovum, measuring 2·5 × 2·2 × 1 mm. in diameter, was obtained by curetting on account of leucorrhoea with retroflexion and prolapse of the uterus, from a multipara aged 28. Menstruation was irregular, occurring at intervals of from 5-6 weeks, and the last completed period began 4½ weeks prior to the operation. The last coitus occurred 4 days before the operation. The specimen is extremely well preserved, showing numerous mitotic figures. It was fixed while still warm in 70% alcohol. It presents a very close resemblance to that of Peters, but there are more definite villi. The case has not yet been published in full detail. This ovum probably comes next in point of age among other known ova to that of Peters, with the possible exception of Graf v. Spee's ovum of 1905. Estimated age, 14½-15½ days.

III.—Ovum of Merttens.

Dimensions—external, 4 × 3 mm.; internal, 3 × 2 mm. It was found in curettings sent for examination to Langhans' laboratory under suspicion of malignant disease—the presence of an ovum not being suspected. Only a few sections were mounted, 4 of which contained an ovum. The four sections were of practically the same dimensions, and were therefore regarded as representing the greatest diameter of the blastocyst. From the general characters of the ovum, it is distinctly, but not greatly, older than that of Peters. The villi, which averaged ·364 mm. in length, are somewhat thick columns of trophoblast with short mesoblastic cores containing no blood-vessels. The curetting was performed 21 days after the onset of the last menstruation, which lasted 5 days, leaving a clear period of 16 days, and this in all probability represents the maximum age of the ovum. Merttens regarded it as much younger than 16 days. It could hardly be less than 14½ days when compared with the present ovum or more than 15½ days when its history is considered.

IV.—Ovum of Beneke.

The cavity of the ovum measures 4·2 × 2·2 × 1·2 mm. and the embryo appears to be rather younger than that of ovum "v. Herff" of v. Spee. It was obtained by curetting on 30th March, 1903. The last menstruation extended from 5th to 10th March. There was no cohabitation after 22nd March. The period of 8 days between this and the operation is however unimportant, since by comparison with the present ovum the minimum age could scarcely be less than 15 days. The period of twenty days from the end of menstruation to the date of operation represents the maximum possible. Probably sixteen to seventeen days would be a fairly accurate estimate.

V.—Ovum "v. Herff" of Graf v. Spee.

This specimen was obtained in a decidual cast expelled by abortion 2 days after the onset of influenza, and, as we have ascertained from the author, exactly five weeks from the *end* of the last menstrual period. Allowing 5 days for the period, the abortion occurred 40 days after the date of last menstruation and 12 days from the expected menstruation. The implantation cavity measured 7 × 5·5 mm.—the external diameter of ovum 6 × 4·5 mm.—blastocyst 4 mm.—embryonic rudiment ·37 mm. There were definite but very short villi. The state of preservation is extremely good. The age of this ovum may be estimated as from 17 to 18 days.

VI.—Ovum No. 1 of Leopold.

The blastocyst measures externally 6 × 6·5 mm., internally 4 × 3·7 mm. It was found in a uterus which had been excised on account of carcinoma of the cervix. The patient was a married woman, Vpara, and her periods latterly had been somewhat irregular. The last extended from 14th to 19th August, 1887. On 20th August coitus occurred for the last time, and the operation was performed on the 29th August. Leopold regarded the ovum as of the 8th day on account of the history, but it is clearly much older. It is possible that the supposed menstruation was a haemorrhage due to the presence of the tumour, but it is also possible that it represented menstruation occurring during pregnancy. The embryo in this case was not recognised, but from the size of the blastocyst and the state of the villi, the age may be reckoned as about the same as that of ovum "v. H." of v. Spee, namely, 17 to 18 days.

VII.—Ovum of Reichert.

This ovum, the histological details of which are not very exactly known owing to the date (1873) at which it was described, measures internally 5·5 × 3·3 mm. It was obtained at a sectio upon the body of a young married woman who had not previously been pregnant. Her husband left Berlin "in the first days of November," and on 7th November the expected menstruation did not appear. During the night of 21st to 22nd November she died suddenly, her husband still being absent. Reckoning from the date of the missed period, and allowing an additional three days for the arrest of the menstrual process, the age of this ovum would be 17 days. The dimensions being very similar to those of the two preceding ova, it should probably be regarded as from 17 to 18 days.

VIII.—Ovum of Rossi Doria.

The ovum measures internally 6 × 5 mm., and the decidual chamber 9 × 8 mm. The patient was 30 years of age, had been 8 years married, and had 5 children. The last menstruation began on 30th January, and lasted between 3 and 4 days, as was usual. On the 23rd February, after dancing at a ball, she observed a few drops of blood, which she regarded as the return of menstruation almost a week too soon. This increased during 2 days into definite haemorrhage, and there were slight pains. Later she suffered very severe pains and returned for treatment on "7th February" (surely a misprint for 27th February?). A quantity of clots and a complete decidual cast were removed from the vagina. The ovum formed a projection like a pea. The decidua capsularis appears to have been ruptured, and the embryo is not figured. The preservation of the ovum is remarkably good. There are no useful data as to coitus. The interval between the cessation of menstruation and the first symptoms of abortion is about 21 days. Allowing 24 hours for the occurrence of fertilization, and assuming that development ceased soon after the appearance of symptoms, an age of 20 days is possible, and by comparison with Eternod's ovum, it might be stated as 18 to 19 days.

IX.—Ovum of Eternod.

This ovum, from the point of view of chronology, is one of the most important in the literature—as we have here the absolute maximum time occupied by development to a stage almost identical with that of ovum "Gle" of v. Spee. It is excellently preserved, and has been most carefully described and figured. It was obtained from a woman "worthy of belief" ("digne de confiance"), who, through force of circumstances, had coitus with her husband only on one occasion, namely, the night of 6th-7th November, 1891. Menstruation did not appear as expected on November 22nd. On November 28th she aborted. According to Eternod this "allows, reckoning upon possible delay of fertilization and of days preparatory to abortion, of the deduction that the specimen was of the end of the 2nd or beginning of the 3rd week." The ovum was of flattened disc shape, measuring with the villi 10 × 8·2 × 6 mm. The villi measured from 1·2 to 2 mm. in length, and the embryo 1·3 mm. in length by from ·18 to ·22 mm. in width. It is in much the same stage of development as ovum "Gle" of von Spee, but is slightly smaller in all respects. On the principles which have been applied to the present ovum, we have to deduct from the total period of 21 complete days and part of the 22nd day, about 24 hours for the occurrence of fertilization and rather more than one day for the abortion, leaving a probable maximum of 19 days. The age may therefore be stated as 18 to 19 days.

X.—Ovum of Frassi.

The ovum which is described as of less than 10 days was obtained by hysterectomy on account of persistent menorrhagia due to metritis. The patient was 40 years of age and had had 11 children—the last 2½ years previously. Menstruation occurred regularly every 28 days. Her last period was believed to have occurred 2 weeks before the operation, but she afterwards confessed that that period had been omitted; she had concealed the fact for fear the operation would be put off if it was known she was pregnant. She had suffered greatly in her later pregnancies. The uterus was fixed whole in 5% formalin, and the preservation of the ovum is very good. The implantation cavity is wholly surrounded by decidua, and there is no "cicatrix." There are villi all over the circumference, measuring from ·5 to 1·9 mm. in length, but they are best developed round the sides, and least over the apex of the vesicle. Blood-vessels are seen in the base of the cord, but there are none in the villi. The implantation chamber measures 13 × 5 mm., and the cavity of the ovum 9·4 × 3·2 mm. The embryonic rudiment measures 1·17 × ·6 mm., and it is regarded by Frassi as slightly younger than that of the ovum "Gle" of v. Spee. The ovum is very similar to that of Eternod, and may be considered to be of the same age, namely, 18 to 19 days.

XI.—Ovum "Gle" of Graf v. Spee.

This was a perfectly fresh aborted ovum in a complete decidual cast, expelled 5 weeks after the *termination* of the last menstruation. The preservation of the specimen is excellent, numerous karyokinetic figures being recognisable. The patient had been healthy, menstruating regularly every 4 weeks, and the abortion was regarded as the return of the period a little after its usual date. The internal dimensions of the chorion are 10 × 8·5 × 6·5 mm., and the embryo measures 1·54 mm. The stage of development of the embryo is slightly more advanced than that of Eternod, and the age may be stated as 19-20 days.

If the foregoing summary of the facts regarding these eleven ova be analysed, it will be found that the most precise data are supplied by the cases of Merttens, Beneke, Rossi Doria, Eternod, and Reichert. In the case of Merttens 16 days, in that of Beneke 20 days intervened between the end of last menstruation and operation; in the case of Rossi Doria 24 days elapsed between the beginning of the last period and the commencement of symptoms of abortion; and in Eternod's case the ovum was expelled 21 days after a single coitus. Eternod's case supplies us with a fairly precise upper limit, on our method of estimating, and at the same time justifies us in excluding the possibility that in the first three cases fertilization occurred before menstruation. The case of Merttens may be taken as defining the maximum possible age of an ovum slightly older than that of Peters. The circumstances of Reichert's case were very similar to those of our own; fertilization in all probability occurred shortly before an expected period which was arrested.

By utilising these data we can arrange the ova in a series in which dimensions and ages gradually increase. The results of the rule of His applied to these ova are brought out in the column in the table under the head of "days elapsed from the omitted period." It will be seen at once how contradictory the results are in the cases to which it can be applied, and it will be noticed that it is not applicable at all to five cases out of the twelve. This is of course due to the admitted error of three weeks under the rule. In dealing with these young ova it seems therefore necessary to proceed on the basis of some such "normentafel" as here given, and we submit our table as a tentative in that direction. That it is absolutely correct is not pretended, but that it is fairly correct in a relative sense is probable, because it is consistent in itself and with the data of comparative embryology.[1]

Having now obtained a chronological sequence in which the age is calculated from fertilization, a second table was constructed, to see at what periods of the month fertilization and imbedding would have taken place in these twelve ova, on the basis of the first table. The termination of pregnancy being known, the date of fertilization was arrived at by

[1] The table does not affect the ordinary obstetric reckoning, the basis of which is statistical.

TABLE I.

Author.	Dimensions in mm. Blastocyst. External.	Internal.	Embryo.	Days Elapsed from Last Period. Beginning.	End.	Omitted Period.	Age in days.	Remarks. How obtained.
1. Teacher-Bryce	1·95 × ·95 × 1·10	·77 × ·63 × ·52	About ·15	38	34	10	13–14	Abortion 16½ days after coitus.
2. Peters	2·4 × 1·8	1·6 × ·8 × ·9	·19	30		2	14–15	Suicide. Sectio.
3. Jung		2·5 × 2·2 × 1·0		32			14½–15½	Periods 5–6 weeks. Curetting on account of leucorrhoea.
4. Merttens	4 × 3	3 × 2		21	16		14½–15½	Curetting.
5. Beneke		4·2 × 2·2 × 1·2	Like No. 6 but younger	25	20		16–17	Curetting.
6. v. Spee, "v. H."	6·0 × 4·5	4·0	·37	40		12	17–18	Abortion two days after onset of influenza.
7. Leopold	6·0 × 6·5	4·0 × 3·7		15	10		17–18	Hysterectomy; cancer of cervix. Menstruation during pregnancy (?).
8. Reichert		5·5 × 3·3		42		14	17–18	Sudden death. Sectio.
9. Rossi Doria	9·0 × 8·0	6·0 × 5·0		28	24		18–19	Abortion; sudden onset. Retention three days.
10. Eternod	10 × 8·2 × 6·0	6·0 × 4·8 × 3·6	1·3	34		6	18–19	Result of single coitus 21 days before abortion.
11. Frassi	13 × 5	9·4 × 3·2	1·17	42		14	18–19	Hysterectomy. Chronic metritis.
12. v. Spee, "Gle"		10 × 8·5 × 6·5	1·54	40		12	19–20	Perfectly fresh abortion.

Chronological Table of twelve recorded early pregnancies. The table is constructed on principles explained in the text. Fertilization is assumed to be effected about 24 hours after insemination, and 24 to 48 hours is allowed for the completion of abortion. The leading data are supplied by the histories of Nos. 1, 4, 5, 8, 9, 10, and the position of the remainder is adjusted according to their dimensions and state of development. The ages, according to the convention of His, are shown in the column headed "Days Elapsed from Omitted Period."

TABLE II.

Fertilization.		Imbedding.
	I.	
	2	
	3	
	4	
	5	
Merttens	6	
Rossi Doria	7	
Beneke	8	
	9	
	10	
	11	
	12	
	13	Merttens
Eternod	14	Rossi Doria
	15	Beneke
Peters	16	
Jung	17	
	18	
v. Spee, "Gle"	19	
	20	
v. Spee, "v. H."	21	Eternod
	22	
Frassi	23	Peters
Teacher-Bryce and Reichert	24	Jung
Leopold	25	
	26	v. Spee, "Gle"
	27	
	28	v. Spee, "v. H."
	II.	
	2	Frassi
	3	Teacher-Bryce and Reichert
	4	Leopold
	5	
	6	
	7	
	8	
	9	
	10	

Table showing the relation of the dates of Fertilization and Imbedding to the menstrual cycle, calculated from the data given in Table I. The higher figure in the age column is arbitrarily chosen in each instance, and allowance is made for the special circumstances of each case. The Roman numerals indicate the first days of two successive menstrual periods.

subtracting the age of the ovum in each case. As a definite figure was required the higher figure was arbitrarily selected in each instance, allowance being made for the various circumstances under which the ova were obtained. The date of imbedding was fixed by assuming that seven days elapse between fertilization and implantation of the ovum in the endometrium.

The second table is the complement of the first, and it shows that, if the ages of the ova be correct, fertilization may occur at any time during the intermenstrual interval, and that imbedding may take place either in the period of quiescence or in the period during which, without the occurrence of pregnancy, the premenstrual and menstrual changes would have been progressing.

This result of our seriation of these early cases is not consistent with the older views regarding menstruation and its relations to imbedding, for it carries with it the conclusions that the menstrual decidua is not a preparation for the reception of an ovum (in the old sense of the words); that menstruation is not an abortion of an unfertilized ovum; and that ovulation does not necessarily coincide with menstruation. The conclusion is not inconsistent, however, with the recent views on menstruation as developed by Heape, and supported by a considerable number of comparative researches. It is this consideration which gives weight and interest to our argument.

It is now generally admitted that the menstrual cycle in man and monkeys is homologous with the oestrus cycle of the lower mammals. The oestrus cycle is divided by Heape into *pro-oestrum*, *oestrus* and *dioestrum*, and this division has been confirmed for many mammals by his own researches and those of F. H. A. Marshall. During pro-oestrum the generative organs of the female show signs of special activity, such as swelling of the vulva, coloration or flushing of the surroundings, and a discharge of blood or mucus from the vagina. This is immediately followed by the "oestrus," or "period of desire," during which alone the female is capable of impregnation and will receive the male. If pregnancy does not occur, oestrus, after a brief space in which desire subsides (metoestrum), is succeeded by a period of quiescence or dioestrum, which lasts till pro-oestrum again sets in. In polyoestrous mammals several cycles of this kind may follow one another. Menstruation in the human female is homologous with pro-oestrum, as first pointed out by Heape. Though there is no fixed "period of desire" there is an indication that a vestige of this persists, in the fact that a phase of more pronounced oestrus commonly succeeds the cessation of menstruation.

The accompanying table, which is borrowed from Heape's papers, but has been slightly modified and adapted to our present purpose, will explain at a glance the general relation of the oestrus cycle of a poly-oestrous mammal to the menstrual cycle.

It is quite clear from the results of the comparative method that the significance of menstruation does not lie in the mere periodic growth and subsequent destruction of the mucous membrane, but in the cycle as a whole. The essence of the process is not the preparation of a menstrual decidua, but the formation of a new endometrium; in other words, the growth and swelling which precedes "discharge," does not represent a preparation for the ovum; it is merely a phase in that reconstitution of the new endometrium which is the real preparation for the reception of the ovum. In the case of most lower mammals, the generative organs lie dormant through a large part of the year, and when the breeding season approaches, the endometrium undergoes in the pro-oestrum a species of regeneration resulting in the development of a new surface on which the ovum may implant itself. In the case of the human female there is no longer this regular breeding period, but desire and the possibility of impregnation occur at irregular periods all the year round. Instead therefore of an annual (or in some mammals a seasonal) renewal of the endometrium, and the preparation of a new surface on which the ovum may be engrafted, we have in the human subject a monthly regeneration and preparation of the endometrium for the same purpose.

Much of the difficulty regarding the decidua disappeared when it was shown that it had no part in the formation of the placenta. The services performed by the decidua in the imbedding of the ovum require that its connective tissue elements shall be in a condition of special

TABLE III.

Oestrus Cycle.	Day	Menstrual Cycle.	
	I.		*Appearance of Discharge.*
Pro-oestrum	2		
	3	*Menstruation.*	
	4		
	5		*Cessation of Discharge.*
Oestrus	6	Period of Repair.	
	7		
	8		
(Metoestrum)	9		
	10		
	11		
	12		
	13		
	14		
Dioestrum	15	Period of Rest.	
	16		
	17		
	18		
	19		
	20		
	21		
	22		
	23		Proliferation.
	24	Period of Swelling.	Congestion.
	25		Increase of Vessels.
	26		
Pro-oestrum	27		Breaking down of Vessels.
	28	Period of Degeneration.	Formation of Lacunae. Rupture of Lacunae.
	II.		*Appearance of Discharge.*
	2		
	3		
	4		
	5		*Cessation of Discharge.*
Oestrus	6	Period of Repair.	
	7		
	8		
	9		
	10		

Table similar to No. II illustrating the division of the menstrual cycle of the human female and its homology to the oestrus cycle of a polyoestrous mammal unaffected by pregnancy, modified from Heape. The chronological division of the cycle is founded on that of Milnes-Marshall, 1893. The complete cycle is shown extending from the 10th day of one lunar month to the 10th day of the next.

activity. The cellular "primitive" structure of the endometric stroma permits that special and ready reaction which constitutes the conservative function of the decidua, and by a recurrence of the menstrual cycle the mucous membrane is maintained in the necessary condition of immaturity.

Accepting this interpretation of menstruation our Table II no longer presents the difficulties which it presents to the older views regarding the process. In the lower mammals ovulation takes place apparently during oestrus or in late pro-oestrum, and in most animals fertilization of the ova occurs forthwith. It is quite possible that in the human subject considerable delay may occur between insemination and ovulation on the one hand, and between insemination and fertilization, or the actual union of the male and female element on the other, as there is no fixed period corresponding to "heat." But it seems reasonable to suppose that the most favourable condition for successful impregnation lies in the occurrence of insemination and ovulation simultaneously, or at no great distance of time, and the occurrence of fertilization immediately the two elements meet, just as in the lower animals.

Looking now at Table II, it is apparent on these premisses that fertilization of the twelve ova concerned must have taken place at wide intervals during the month, and comparing it with Table III it will be noticed that the first three must have been fertilized while repair was possibly not yet complete, and the next three clearly during the period of quiescence. Von Spee's two ova may, and the last four certainly must, have been fertilized in the period of swelling, if we assume that the swelling continues in spite of the occurrence of fertilization.

Most probably also ovulation corresponded more or less closely with fertilization, and occurred at intervals throughout the month, perhaps not even excepting the latter days of the actual period of menstrual discharge. A further inference is that ovulation and menstruation may, but do not necessarily, coincide. This is supported by the researches of Bland-Sutton on menstruation of Macaque monkeys and baboons, and of Heape on menstruation in Semnopithecus entellus and Macacus rhesus. They have shown that in these animals menstruation and ovulation do not necessarily coincide. Further, it is supported by the observations made by gynaecological surgeons in the course of operation, viz., that apparently ripe or recently ruptured Graafian follicles are found in the ovary at any point of the intermenstrual period, and that, on the other hand, there is frequently no trace of either ripe or recently ruptured follicles immediately before or immediately after the menstrual period. It would therefore appear possible that the disappearance of a fixed oestrus in the human female has been associated with severance of ovulation from oestrus, but it is probable that the most favourable circumstances for successful impregnation, are ovulation about the period of menstruation, and insemination shortly before or after the period of discharge.

On the other hand it is absolutely certain that if the table be correct, imbedding occurs quite independently of the menstrual growth, and at any period in the cycle save the destructive phase.

In the menstruation of monkeys, according to Heape, "the stage of growth" is characterised by, firstly, swelling of the endometrium, proliferation of the inter-glandular tissue elements, congestion, and later an increase in the number of the leucocytes visible in the blood-vessels. In the first stage of degeneration all these phenomena become more pronounced, and extravasation of blood takes place into the tissues with migration of leucocytes. In other words, the phases represent the early stages of that reaction of the tissues in response to stimulus which is called inflammation. In the later stages the degenerative changes in the tissue elements, the haemorrhage, and the disintegration of the membrane which follows, constitute a form of ulceration of the endometrium which can scarcely be characterised as other than severe. The discharge contains red-blood corpuscles, masses of uterine stroma, fragments of uterine epithelium, squamous cells from the vagina, leucocytes and blood-clot in somewhat varying amount; in short, the elements are the same as are found in a human menstrual discharge, where the reaction has been intense, and accompanied by the shedding of membrane.

The swollen endometrium is described by Heape as menstrual decidua, following the usual custom of obstetricians and pathologists. The decidua of pregnancy, so far as we can judge from the limited amount of material belonging to the early stages which we possess, is very similar in structure to menstrual decidua; in fact many authorities deny the possibility of distinguishing between them, and doubtless the processes concerned in their formation are similar. But although the processes are similar, it does not follow that their purpose is identical. As already pointed out, it is apparent from the tables that the ovum can imbed itself during the period of quiescence of the endometrium, and the case of ovarian pregnancy described in the second part of this memoir demonstrates that the presence of decidua is not necessary to imbedding. In the mouse and guinea-pig there is no change in the endometrium until it is attacked by the ovum. In the human subject, no doubt, in certain instances, menstruation is arrested and degeneration is checked before imbedding takes place; but it is not essential that actual development of the endometrium into decidua should precede its invasion by the ovum. Indeed, the analogy of the guinea-pig and other mammals makes it probable that the development rapidly takes place immediately after the invasion, and that it may in the first instance be of local occurrence only. This apparently is what occurred in the case of Peters, where a definite decidual reaction is said to be limited to the immediate neighbourhood of the ovum. On the other hand, should an ovum be fertilized after the pre-menstrual changes have set in, there is no reason to suppose that they would offer any obstacle to its implantation; indeed, as the early changes in the formation of the menstrual swelling are identical with those of decidua formation, it might be favourable to the process. We have no evidence, however, to show whether fertilization may not completely arrest the whole menstrual changes.

Menstruation on the premisses detailed above is thus a cyclical process which provides for the maintenance of the endometrium in a suitable condition for producing the decidua of pregnancy, but the ovum is not dependent upon the development of a menstrual decidua for a suitable nidus in which to become imbedded. The uterus is capable of developing a decidua of conservation whenever its integrity is threatened by the growing ovum.

II

AN EARLY OVARIAN PREGNANCY

By T. H. BRYCE, J. M. MUNRO KERR and JOHN H. TEACHER

AN EARLY OVARIAN PREGNANCY

INTRODUCTION

The literature of ovarian pregnancy takes us as far back as 1614, when Mercer first suggested the possibility of its occurrence. There seems to have been a common belief that the ovum might be implanted and could for a certain time develop within the ovary. No demonstrative histological evidence was however forthcoming, and as data regarding tubal pregnancy, and the varieties it may assume, accumulated, it became increasingly doubtful whether the early records were not due to inaccurate diagnosis. This opinion was expressed by such authorities as Lawson Tait and Bland-Sutton. In 1899, however, a careful histological description of an early case was published by Catherine van Tussenbrœk, by which she demonstrated beyond question that the ovum could be imbedded in the ovary. Since then her main conclusion has been confirmed by a number of observers, and it is now universally admitted that such an implantation, remarkable as it may seem, does occasionally occur.

The details of the process of imbedding in the substance of the ovary are not however fully known, nor completely understood. The desideratum is a still earlier chorionic vesicle than any yet described implanted in the gland. Catherine van Tussenbrœk considered that her case proved that the essence of ovarian pregnancy was implantation of the ovum in a Graafian follicle, but other cases since published do not all bear out this conclusion. The specimen which we have to describe shows that imbedding may occur outside the follicle, and it is especially valuable in respect that the stage of development reached by the chorionic vesicle, is earlier than in any of the cases hitherto recorded. It serves to reconcile the data of previous observers, its histological details throw light on some of the points still at issue, while comparison with the very early ovum described in the first paper helps to explain more clearly the nature of the processes involved.

Catherine v. Tussenbrœk justly claims that her investigations furnish incontestible proof that the plasmodium, which covers the villi of an ovum imbedded in the ovary, just as it does those of an ovum imbedded in the uterine mucous membrane, cannot be a derivative under any circumstances of the uterine epithelium. The corollary however, that her specimen provides a proof of the foetal origin of the layer, is not fully warranted. Her case affords strong presumptive evidence that the plasmodium is foetal, but it carries us little further than the data on the subject accumulated by Peters. A combination of the data from the two cases described in the present memoir furnishes more decisive proof.

HISTORY OF THE CASE.

The patient was 27 years of age, had been married for two years, and had one child born eleven months before the present occurrence. During lactation, and subsequently, menstruation was regularly repeated. On November 20th, 1903, she became unwell for the last time, and as menstruation did not recur in December she believed that pregnancy had supervened. On January 1st, 1904, she made complaint of pain in the back and lower part of the abdomen. This recurred at intervals during the succeeding days, and was associated with abdominal tenderness and inclination to faint. On the night of January 8th she had a more severe attack of pain, and on January 9th was seen by Dr. Munro Kerr, who made a diagnosis of extra-uterine pregnancy with the tube probably as yet unruptured. For certain reasons the operation was postponed till January 13th, when the symptoms pointed to rupture having taken place. When the abdomen was opened two or three pints of blood were found in the cavity. On drawing up the right appendages Dr. Kerr was surprised to find that the Fallopian tube was to all appearance normal, but projecting from the free margin of the ovary he observed a haemorrhagic mass about the size of a walnut, which he diagnosed as an ovarian pregnancy. The tube and ovary were removed in the usual way, and the patient made an uneventful recovery. The uterus at the time of operation was considerably enlarged, soft and globular, and the presence of an intra-uterine pregnancy was suspected. This surmise proved correct, the pregnancy went on to term, and on August 19th, 1904, she was delivered of a full-time child.

The simultaneous occurrence of an intra-uterine and ovarian pregnancy is of considerable interest. It will be noticed that labour supervened 8 days prior to the day anticipated by the ordinary obstetric tables, and the cessation of menstruation had probably relation to the uterine gestation. If 28 days be counted from the 20th of November we reach the 18th of December as the day from which the duration of pregnancy is calculated according to His' rule. The first symptoms of the extra-uterine pregnancy set in on January 1st, and the final rupture came on January 8th. If we assume that fertilization of both ova took place as the result of the same insemination, the age of the ovarian pregnancy may be anything between 14 and 22 days according to His' convention. The stage of development of the chorionic vesicle and embryonic rudiment points to the age as being (still according to the convention) from 12 to 15 days, so that we must assume that growth and differentiation ceased on the occurrence of rupture of the implantation sac and commencement of haemorrhage from the ovary on January 1st. If this were not the case we must conclude, either that the ovarian ovum was fertilized later than the uterine, or that development was retarded owing to the site of implantation.

Dr. Munro Kerr, having taken special care in removing the parts to avoid injuring the specimen, placed it in formalin immediately after the operation, and took it to the Pathological Department of the University where Professor Muir sliced the ovary longitudinally from the free margin to the hilum. The specimen was then placed in the hands of Dr. Teacher, who made a sketch of it to scale while it was still in the fresh condition. In the subsequent fixation and hardening it unfortunately became somewhat distorted, so that it was impossible to obtain a single section of the entire gland and the interesting structures it contained. Even under the most favourable circumstances however, the great mass of hardened blood clot proves an insuperable obstacle to perfect sectioning in specimens of this kind, and it is practically impossible to get entire sections. It was therefore necessary, as it has been in all other cases described in the literature, to examine separate slices through the ovary and make a reconstruction therefrom.

NAKED-EYE DESCRIPTION OF THE SPECIMEN.

The Fallopian tube appeared to be slightly thickened and congested, but was in other respects normal. Subsequent microscopic examination revealed slight oedema of the subperitoneal tissue at some places, but the mucous membrane presented quite a normal appearance and showed no decidual changes. There was no adhesion either of the ampulla or of the fimbriated end of the tube to the ovary. The ovary was considerably enlarged, chiefly in an axis running from the free margin to the hilum. It was somewhat sharply marked off into two portions in this axis. The portion next the broad ligament was of about normal size, and presented the appearance of a healthy ovary of a woman in the child-bearing period. The surface was fairly smooth, free from cicatrices, and there was no indication externally of a corpus luteum.

The posterior portion of the gland, corresponding to the haemorrhagic mass mentioned above, was directly continuous with the other, but sharply delimited from it by change of colour. While the greater part of the mass appeared to consist of blood clot, the base of the clot, and a considerable portion of its circumference, was bounded by blood-infiltrated ovarian stroma. The blood clot was thus obviously protruding from a rent in the surface of the gland, and rather towards the lower end of the clot was a small fissure between the lips of which projected a mass of villi which proved to be one end of a young chorionic vesicle.

Figure IX is a drawing of the gland split open, copied from the original sketch. On the cut surfaces a large corpus luteum is seen occupying the lower end of the ovary close up to the hilum. Fully half the section is constituted by apparently normal ovarian tissue. The marginal portion, however, more deeply shaded in the figure, consists of blood-infiltrated stroma and blood clot. Within this portion of the gland, in a small cavity of irregularly oval shape, lies the chorionic vesicle separated from the corpus luteum by a considerable zone of blood clot. The knife has cut both the

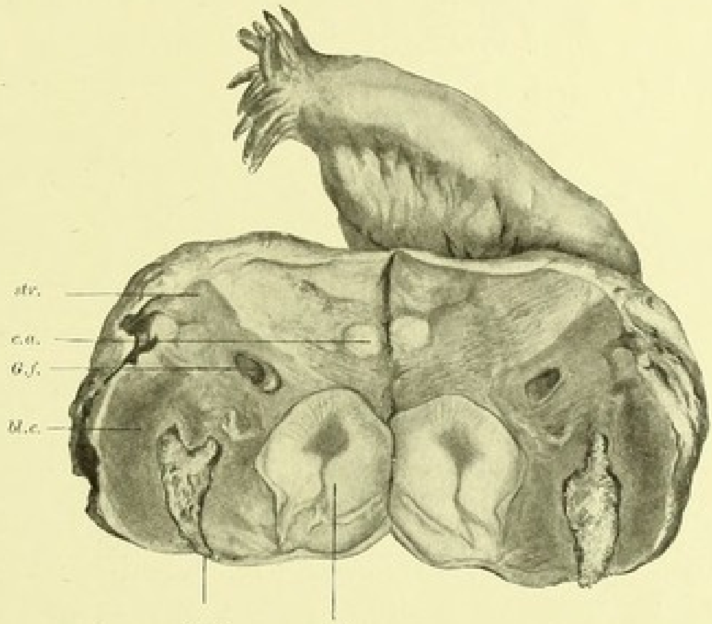

FIGURE IX. DRAWING OF THE FALLOPIAN TUBE AND OVARY, FROM DR. MUNRO KERR'S CASE OF OVARIAN PREGNANCY. NATURAL SIZE.

The ovary has been divided longitudinally. *c.l.*, corpus luteum; *chor.*, chorionic vesicle; *bl.c.*, blood clot; *str.*, blood infiltrated stroma; *c.a.*, corpus albicans; *G.f.*, Graafian follicle filled with blood.

corpus luteum and vesicle unequally, the greater portion of each remaining in the lateral segment to the left in the figure. A complete series of sections through the whole ovary being, in the circumstances, impossible, a slice of about 3 mm. thick was taken from the outer portion, including the greater part of the corpus luteum and a complete section of the chorionic vesicle. This block of tissue was converted into a complete series of sections 8 microns thick, and stained in various ways. A second portion of tissue was then taken out from above the corpus luteum to complete the section of that structure in this plane, and to establish its relation to the rest of the ovary and the blood clot in which the vesicle lay. From a careful study of the sections from the first block, and adjustment to them of the sections from the second, an accurate picture was obtained of the relations of the corpus luteum, the unaltered part of the ovary, and the vesicle to one another in the longitudinal plane (Figure x). The gland was then cut at right angles to this plane, and two supplementary slices (one from the lateral and one from the mesial half) through corpus luteum and chorionic vesicle were removed and sectioned. By this means a complete picture of the relations of parts in the transverse plane was obtained (Figures XI and XII).

DESCRIPTION OF THE SECTIONS.

It has been noticed above that the embryonic vesicle appeared to occupy a small cavity of irregularly oval shape. The sections reveal that this is a space with walls largely composed of recent blood clot, but in part lined by a thin irregular layer of fibrin and ovarian tissue in a state of coagulation necrosis. To this the villi are attached by characteristic broad trophoblastic masses. The cavity represents the normal intervillous space, for the most part empty of blood. The chorionic vesicle occupies the centre of the implantation cavity. It is collapsed and much folded. Its longest measurement is 1·35 cm., but when rounded out its diameter could not have reached a centimetre The villi measure from 2 to 3 mm. in length, and are covered by the characteristic two-layered epithelium identical in all respects with that of a uterine ovum of corresponding age (Plate X, Figs. 13 and 14). They contain vessels filled with nucleated red-blood corpuscles. Numerous karyokinetic figures occur in the epithelium.

Remains of an embryo were found within the collapsed chorion, but in so damaged a state that it was not considered worth while to give the time necessary for reconstruction. There is a thick abdominal stalk containing vessels full of nucleated red corpuscles, the yolk-sac is much folded, but shows the development of vessels in its walls. The germinal disc is cut very obliquely, and the presence of a primitive streak or neurenteric passage could not be determined. Its general characters indicate however that the embryo cannot have been further advanced than Graf v. Spee's embryo "Gle," and it is probably even younger.

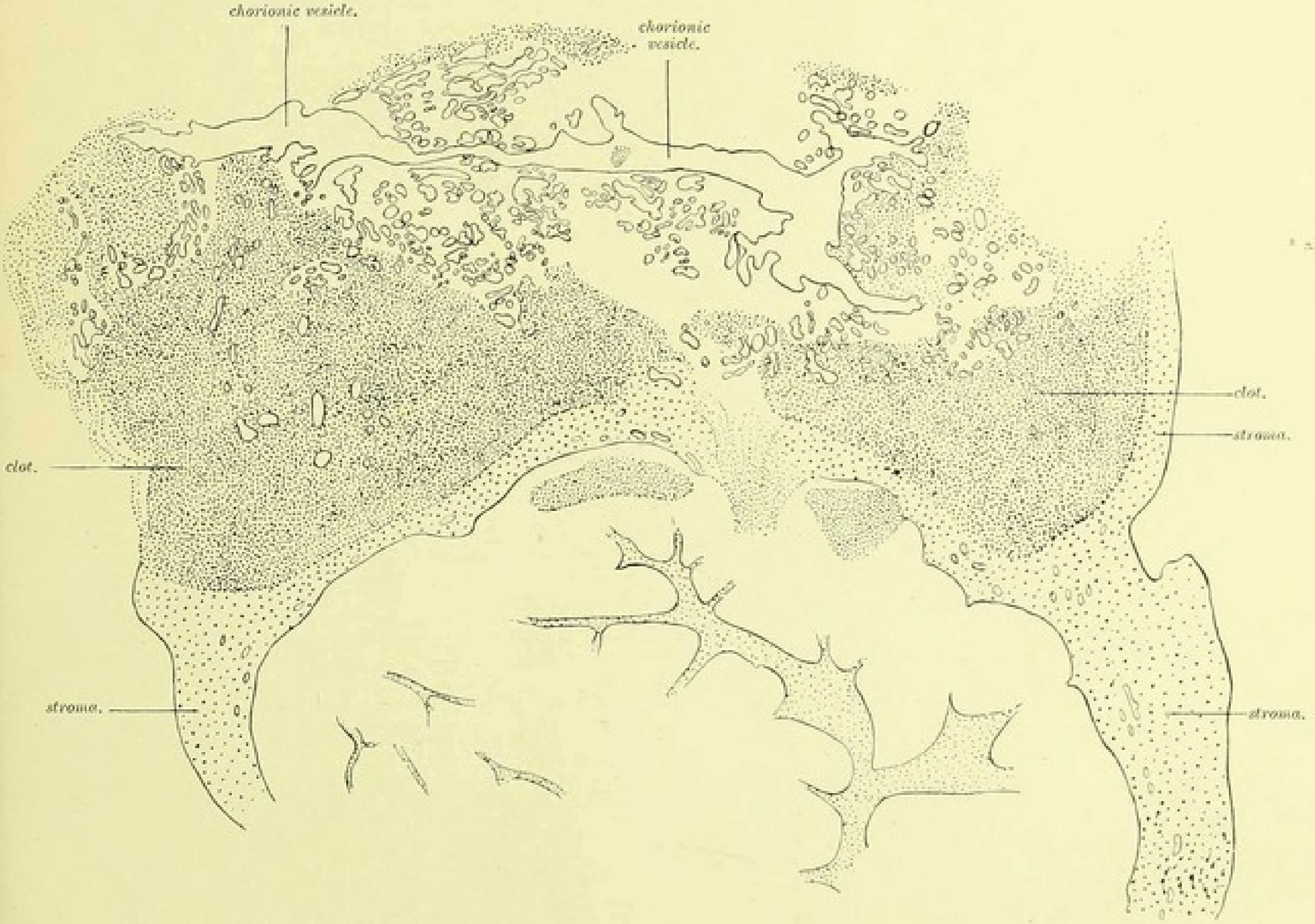

FIGURE X. LONGITUDINAL SECTION THROUGH A PORTION OF THE CORPUS LUTEUM AND CHORIONIC VESICLE. (T. H. B. DEL.)

The section passes through the mouth of the follicle; the shaded masses on each side of this are necrotic portions of lutein tissue.

The relations of the chorionic vesicle to the ovary are shown in Figures X, XI, XII, which are drawn from the actual preparations by means of Edinger's projection apparatus.

Figure X is a reconstruction in the longitudinal plane from sections of the two series above mentioned. Figs. XI and XII represent each a section of one-half of the gland in the transverse plane, and an imaginary interval between them of 3 mm. would correspond to the slice of tissue cut out for the longitudinal series. From these figures it will be at once apparent that the vesicle is almost entirely surrounded by recent blood

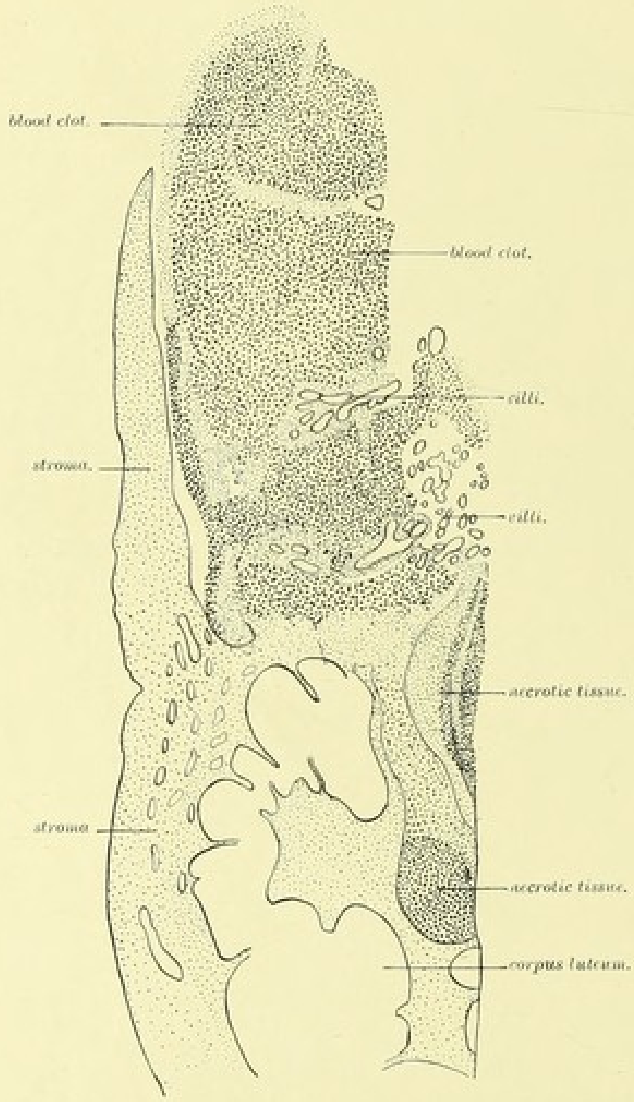

FIGURE XI. TRANSVERSE SECTION THROUGH A PORTION OF THE CORPUS LUTEUM AND CHORIONIC VESICLE. (T. H. B. DEL.)

The areas marked necrotic tissue occupy the mouth and centre of corpus luteum.

clot. Only at one point does the chorion come close to the ovarian stroma, and that is opposite a gap in the wall of the corpus luteum.

The sections corresponding to Figures XI and XII show that the sides of the blood clot are clothed for a distance of about 1 cm. from its base by a layer of ovarian stroma more or less infiltrated with blood. This lamella of ovarian tissue ends distally in a free edge, leaving an interval between its lips of about 2 cm., in which the blood clot is exposed on the

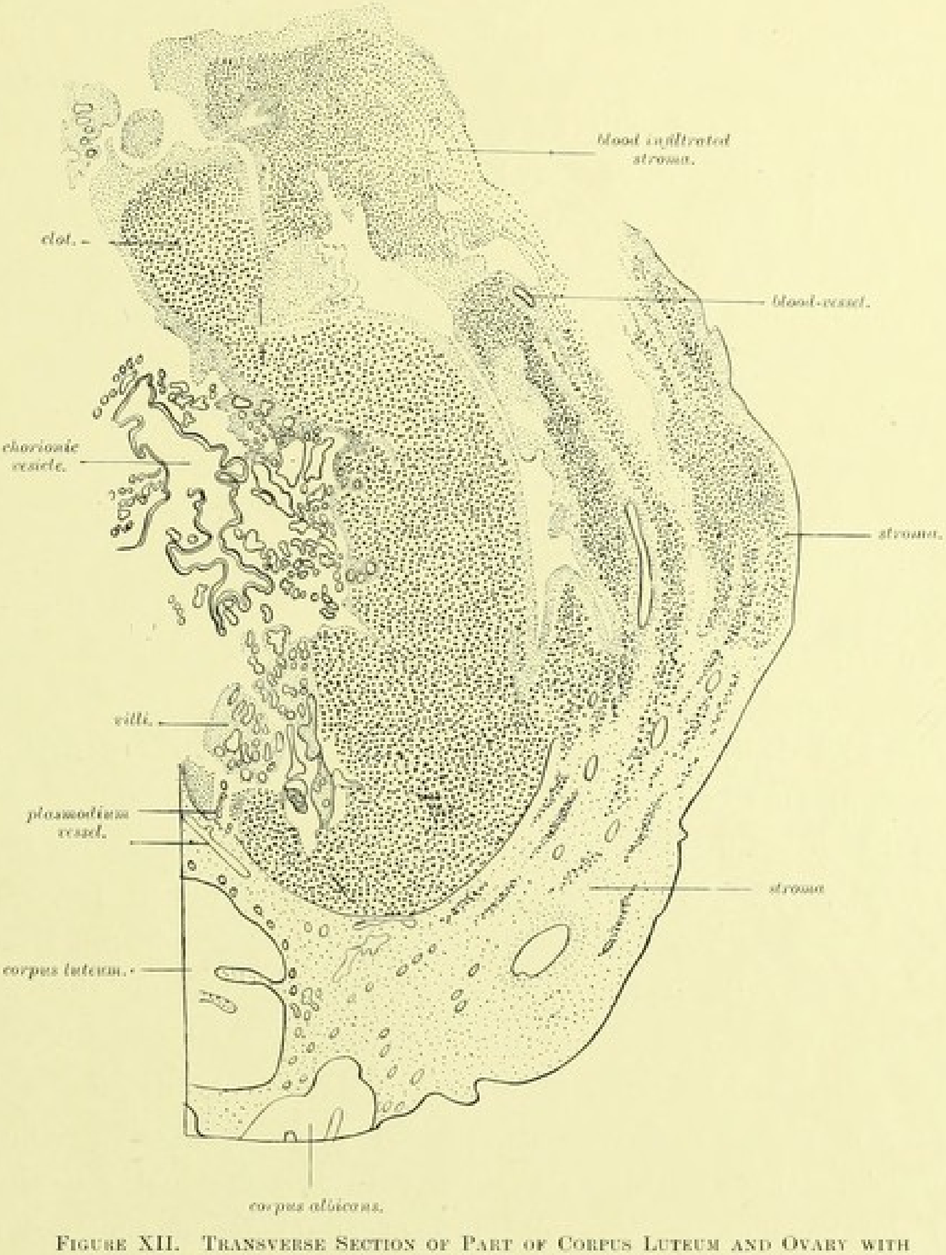

FIGURE XII. TRANSVERSE SECTION OF PART OF CORPUS LUTEUM AND OVARY WITH CHORIONIC VESICLE. (T. H. B. DEL.)

surface of the ovary. It is apparent from a study of the sections that considerable haemorrhage had taken place shortly before the operation, and that the blood had more extensively infiltrated the tissue intervening between a layer of necrotic tissue immediately applied to the villi, and the more healthy, living ovarian tissue forming the outer lamella of the wall of the cavity. A large coagulum was thus formed round the chorionic vesicle, and the whole constituted practically a "fleshy mole," which would doubtless in a short time have been extruded from the ovary into the peritoneal cavity.

The relations of the villi to the ovarian stroma are shown in our coloured drawing (Plate IX, Fig 12). It represents a portion of the same section as figured in Figure XII, at a point where the villi have remained in close association with the connective tissue of the gland. An apparently normal villus showing both cyto-trophoblast and plasmodi-trophoblast, and some irregular masses of plasmodium are seen attached to the ovarian tissue. The connective-tissue lamella applied to the trophoblast is completely necrotic, and the deeper layers of the stroma show degenerative changes; at a still deeper plane the signs of degeneration gradually fade away, and normal connective tissue is reached. There is no reaction corresponding to the formation of the thick decidua in the uterus, and the destructive changes are much more pronounced; in fact, the appearances suggest the persistence of the early acutely destructive phase represented by the ovum which is described in the first paper. There are a number of mononuclear cells with large cell-bodies scattered through the ovarian tissue in the zone of attachment of the villi (Plate IX, Fig. 12). While some of these are probably of foetal origin, representing cells which have been cast off from large masses of Langhans' layer cells, spread out over the surface of the necrotic zone of ovarian stroma, many are undoubtedly maternal cells. They may be swollen connective-tissue cells, or interstitial cells of the ovary. They are not unlike decidua cells, and if they be swollen connective-tissue elements they would be analogous to the decidual cells in their mode of development, and would represent an effort on the part of the ovarian tissue to react as the endometrium does, but they are relatively so few in number that they do not constitute anything resembling a real decidua.

The relation of the chorionic vesicle to the corpus luteum constitutes the most important point in the specimen. This body presents the usual characters of a corpus luteum of the 2nd month of pregnancy. Although it approaches quite closely to the surface of the ovary at the lower end, it has clearly not ruptured upon this aspect of the gland, for its walls are here quite intact. The only break in its contour is directed towards the mass of blood clot enclosing the vesicle. Figure X shows the margin of the opening in longitudinal sections, while Figure XI shows a portion of it cut transversely. The corpus luteum is approximately globular, but somewhat flattened in the transverse plane of the ovary. The circumference can be seen rounding in on all sides towards the opening. The centre of the body is occupied by the usual irregular mass of young connective tissue and partly organised blood clot. This is continued outwards as a hyaline fibrinous band, through the break in the capsule into the necrotic stroma and blood clot surrounding the chorion, while the normal stroma investing the corpus luteum passes inwards between it and the blood clot, as far as the margins of the fibrin mass protruding through the gap. The apparent width of the gap is considerably diminished if allowance be made for the darker masses represented as occupying its lips in the figures; these are necrosed portions of the corpus luteum.

It is quite evident from this description that the chorionic vesicle is situated opposite the break in the capsule of the corpus luteum, and that it lies entirely outside it. The vesicle obviously lies in an implantation cavity excavated in the ovary and now greatly distended by recent haemorrhage.

It may be taken for granted that the spermatozoon which effected fertilization obtained access to the Graafian follicle through the opening on the surface formed by the rupture of the follicle. The only other alternative is that the fertilized ovum adhered to the ovary and implanted itself therein from without. The appearances do not at all suggest such an occurrence; it is, moreover, highly improbable. On the other hand, from what we know of the powers of movement of the spermatozoon, the first alternative is by no means far-fetched. We assume therefore that after fertilization the ovum was retained within the follicle by the closure of the rent in its wall. During the early stages in the formation of the corpus luteum, the ovum went through the segmentation phases, and as an early blastocyst found itself within the contracting follicle just as normally the blastocyst finds itself, after its passage through the Fallopian tube, in the uterine cavity. It now behaved as a uterine ovum would have done. It attacked the wall of the follicle and imbedded itself in the vascular connective tissue immediately without the capsule. This sequence of events is indicated by the large size of the break in the wall of the corpus luteum, which is considerably larger than that found in the wall of a normal corpus luteum a few weeks after the escape of the ovum from the follicle, and also by the necrosed tissue in the lips of the opening. The fibrinous and partially necrotic mass in the mouth of the corpus luteum we take therefore to correspond to the fibrin cone in the aperture of entrance in the early uterine ovum, or the later cicatricial tissue known as Reichert's scar. Having lodged itself in the narrow band of stroma between the corpus luteum and the surface, the further growth of the ovum has resulted in the extensive destruction of the ovary which is now visible. We have seen in the first paper that the ovum tends to produce in the first instance an implantation cavity of transversely elongated shape. Here there seems likewise to have been greater extension of the destructive changes in a lateral direction, and the ovarian stroma had yielded place to the growing blastocyst rather than the corpus luteum; this is probably due to the nature of this tissue. What the blastocyst requires is a vascular connective tissue, and this it must have found more readily in the stroma of the gland.

DISCUSSION OF DATA

As has been already indicated in the introduction, the early records in the literature of ovarian pregnancy do not, from the absence of histological detail, bring critical evidence to bear on the points which concern us in this paper. It is unnecessary therefore to deal with them here. Since the publication of Catherine van Tussenbrœk's paper a number of well authenticated cases have been put on record. The majority of these have been summarised by Kelly and M'Ilroy. In a number of the cases reported, the state of the specimen did not permit of an accurate determination of the precise relations of the chorionic vesicle to the ovary. We shall therefore in the following discussion refer only to those cases in which such determination was possible, referring the reader for the details of other cases to the paper by Kelly and M'Ilroy.

I.—Case of C. van Tussenbrœk.

The "ovisac" in this instance was a reddish brown mass about the size of a small plum, and it occupied the greater part of the right ovary. The Fallopian tube was in no way attached to the ovary, and being normal was obviously not the primary seat of implantation of the ovum. The mass representing the ovisac had everywhere a smooth surface like that of the rest of the ovary, but at the pole opposite the pedicle there was a small rupture from which hung a shred of blood clot. A section across the ovisac and surrounding tissue, and passing through the point of rupture, showed a chorionic vesicle imbedded in fibrinous masses, and enclosed in a thin envelope of ovarian tissue all round its free surface. On the deep aspect of the ovisac and somewhat spread out round its base, there was a large corpus luteum. This enclosed a large cavity filled with organising blood clot and fibrin, and on one aspect came into direct contact with the foetal tissue. Here the wall of the body diverged so that the chorionic vesicle appeared to rest in its widely splayed-out mouth. All round the circumference of the ovisac portions of lutein tissue were found, though always in the form of a thin interrupted layer. This layer of lutein tissue was not however in contact with the villi of the chorion; it was everywhere separated from them by a thin lamella of fibrous tissue which formed the actual investment of the chorion. The lutein tissue did not behave like decidua, and indeed played no part in the attachment of the ovum. As the authoress rightly points out, the tissue in which the ovum was imbedded represented the young connective tissue which is formed within the lutein tissue or theca interna, in the first stage of organisation of the contents of the ruptured follicle. No formation like a decidua was present, though at first, until she recognised its true nature, the authoress thought that the broken layer of lutein cells represented decidua; the only reaction on the part of the ovary to the needs of the growing ovum, was a great increase in the vascularity of the stroma.

The chorionic vesicle was covered all over by villi which showed precisely the same structure as those of an intra-uterine vesicle of the same stage. The embryo measured 12 mm. and was perfectly normal in appearance.

II., III.—Cases of Kelly and M'Ilroy, and of Mendes de Leon and Holleman.

In the specimens described by these authors there was no formed corpus luteum, but lutein cells were found in the wall of the implantation cavity. In the first-mentioned case the lutein tissue was separated from the villi by a thin layer of fibrous tissue, and the conditions of implantation were practically identical with those in van Tussenbrœk's case, but the corpus luteum had apparently been distended and spread out over the mass of blood enclosing the remains of the chorionic vesicle. The difference is accounted for by the much larger size of the mass of clot and tissue enclosed in the implantation sac.

IV.—Case of Thompson.

In this case the ovary (left) was enlarged, and a dark red body about "the size of a horse chestnut" projected from its free margin. There was no adhesion of the Fallopian tube to the gland. The marginal swelling was somewhat separated from the ovary proper during the operation, but the relations of the two parts were quite distinct, and there was complete continuity of tissue between them. The red mass enclosed the chorionic vesicle which contained a normal embryo of 12 mm. length. The villi were for the most part in a state of degeneration, but on the better preserved the usual two-layered epithelium was readily made out. About two-thirds of the vesicle projected from the ovary, the remainder being imbedded in a shallow depression within the gland. The projecting portion of the chorion was covered by a thin layer of fibrous tissue, which the author calls the theca externa, but at no point could he recognise lutein cells. On the deep aspect of the excavation within the substance of the ovary, there was well preserved corpus luteum tissue, which extended to the edge of the thin fibrous sac above mentioned. The villi and masses of trophoblast on the deep aspect of the vesicle were attached to ovarian tissue, while masses of plasmodium were seen lying in contact with the theca interna. Nothing resembling decidua was seen. The author regarded the ovum as having developed partly within and partly without the ovary.

V.—The Case of Hewetson and Jordan-Lloyd.

These authors describe a specimen which, in its relation to the corpus luteum differs somewhat from the preceding. The chorionic vesicle was found lying in a mass of firm blood clot in the pouch of

Douglas. The Fallopian tube was normal from end to end. The mass of blood clot was "as large as a fist"; the enlarged ovary was incorporated with it, and formed part of the walls of a sac in which the clot lay. Microscopical examination revealed the presence of villi scattered through the clot, and also imbedded in the ragged walls of the cavity, which was thus proved to be a gestation sac. The walls of the sac, where formed by the ovary, consisted of intensely vascular ovarian stroma, which was even more reticular than in the remainder of the gland, the fibres running parallel to the surface. The vessels were greatly enlarged and thin walled, and many of them opened directly into the gestation sac. The cavity of the sac was ragged and irregular, large areas having the appearance of fibrin with villi imbedded in it. At no point did the villi actually penetrate to the ovarian stroma.

The membrane lining the sac presented a striking resemblance to the necrotic layer of the decidua of a 3rd or 4th month pregnancy, but there was no trace of decidual cells in any part of the wall. Bulging into the sac from the lower part of the ovary was a large corpus luteum, which was perfectly intact and separated from the gestation sac by a thin lamella of loose and very vascular ovarian stroma. In the fibrin layer covering this part of the wall of the sac the imbedded villi were present in relatively greater number. There were no lutein cells visible anywhere except in the intact corpus luteum.

VI.—The Case of Franz.

In this instance the gestation sac took the form of a fleshy mole situated alongside a large corpus luteum, which showed an interval in its wall next the chorionic vesicle. There was no lutein tissue round the mole, and the general relations were very similar to those in the present case, but owing to the size of the chorionic vesicle they are less well defined.

In addition to the above six, a number of other cases have been published with detail insufficient for the purposes of our present comparison, but it may be noted that in some instances the absence of a corpus luteum has been recorded, while one or two observers state that they were unable to find any lutein tissue round the gestation sac.

It is apparent from the analysis of these six cases, and the description of the present specimen, that considerable variety occurs in the imbedding of the blastocyst in the ovary, more especially in respect to its relations to the corpus luteum. Upon one point all observers are agreed, viz., that the layer next to the foetal tissue is connective tissue in some form, and that the lutein cells do not play the part of decidua; indeed, histologically they appear to take no share in the imbedding of the ovum. The published cases may be divided into three categories according to the relationships of the lutein tissue. (1) It may occur all round the gestation sac, as in two of the cases cited and several others referred to by Kelly and M'Ilroy; (2) it may appear only on one aspect of the gestation sac, as in four of the instances given above; and (3) it may be absent altogether either as a separate layer or as an intact corpus luteum, as in several cases not here summarised, *e.g.* the cases of Freund and Thomé. The second group of cases may be further subdivided into a group in which the corpus luteum is quite intact, *e.g.* Hewetson and Jordan-Lloyd's case, and a group in which there is a defect in the wall adjoining the gestation sac, *e.g.* in the present case and that of Franz.

Before proceeding to explain the differences which the analysis of the cases reveals, the structure and development of the normal corpus luteum may be briefly considered.

The origin of the lutein cells is still a matter of controversy,[1] but as regards the human subject the preparations of one of us (J. H. T.) seem quite clearly to indicate that, whatever the source of the cells may be in lower mammals, they do not in man arise from the membrana granulosa. In a Graafian follicle which is approaching maturity, the membrana granulosa forms a fairly thick layer of cells even apart from the discus proligerus. Outside this there is seen a layer of large oval

[1] See a Review by F. H. A. Marshall in *Q.J. of Micro. Sc.* 1905.

cells enclosed in the meshes of the innermost layer of connective tissue (theca interna). These are clearly the progenitors of the lutein cells of the corpus luteum, and in a perfectly ripe follicle the layer has developed into a zone of considerable thickness. At either of these stages, a distinct basement membrane can, in favourable preparations, be made out between the young lutein tissue and the membrana granulosa. On the outer side of the lutein layer there are numerous vessels, and as the follicle is about to rupture vessels appear on its inner aspect also. When rupture takes place the greater part of the membrana granulosa is probably shed with the ovum, but shreds of it remain within the follicle, more or less detached from the theca interna. Haemorrhage and serous exudation now take place into the cavity of the follicle, and it becomes occupied by a mass of coagulum, consisting of a delicate fibrinous reticulum and blood clot in varying proportions. The lutein tissue now develops with great rapidity into a thick layer, the blood-vessels both within and without this layer enlarge, and the coagulum is invaded by numerous leucocytes, fibroblasts, and young blood-vessels. The point of rupture on the surface of the ovary is recognisable for a long period, but communication with the cavity of the follicle is frequently, if not always, closed by the formation of young connective tissue internal to, or between the lips of the torn lutein layer. Data as to the rapidity with which this occurs are wanting, for owing to the fact that ovulation and menstruation do not necessarily coincide, the date of last menstruation cannot be taken as a point from which to estimate the age of an ordinary corpus luteum. Taking however the analogy of a healing wound, there would be a thin layer of vascular connective tissue between the lutein tissue and the contents of the follicle within seven days. If we now apply these data to the matter in hand, it will be seen that there are two possible situations in which an ovum impregnated within the Graafian follicle may become imbedded.

There is very good reason for believing, from the data provided by the early ovum described in the first paper, that imbedding commences while the ovum is still a very minute object, little if any larger than the mature unfertilized ovum, that is about ·2 mm. Such a minute body might readily find a suitable nidus in the thin layer of young connective tissue within the follicle. Van Tussenbrœk's ovum must have lain to one side of the central coagulum, as she herself concluded; in its growth it disturbed the outer part of the corpus luteum and to a great extent broke it up, while the inner portion remained intact.

On the other hand, if it be admitted, as we believe it must, that the primary and essential factor in determining the effective implantation of the ovum be a rich supply of blood, the conditions just external to the layer of lutein tissue are still more favourable, and accordingly it appears that in the present case and that of Franz the ovum has burrowed out of the follicle into this lamella, and lies separated from the corpus luteum by a narrow zone of ovarian stroma except at one point. Here the wall of the gestation sac is directly continuous with the interior of the corpus luteum by a band of tissue of doubtful character and more or less in a state of necrosis. This strand is perfectly comparable with the cone of fibrinous material occupying the point of entrance in the Teacher-Bryce ovum (Plate III, Fig. 3), and may, as has been already explained, be interpreted in the same way. Whether this point of perforation correspond to the region of rupture of the follicle or to some other point is immaterial, because we know that the process of imbedding cannot begin till at least seven days after fertilization, by which time the follicle would be again closed. While this interpretation satisfactorily explains the position of the ova in these cases, another possibility may be admitted, viz., that the ovum was arrested between the lips of the wound in the follicle, was there fertilized, and was then imbedded in the vascular stroma outside the follicle. If this were so the fibrinous and necrotic tissue occupying the gap in the follicle wall might be due to the destructive process extending inwards towards the heart of the follicle. The imbedding in the case of Thompson's ovum, which lay in the splayed-out mouth of the follicle with no lutein tissue either on its free surface or between it and the corpus luteum, may have occurred in this way.

The fact that in our younger stage the chorionic vesicle lies wholly without the follicle is in favour of the first alternative, which moreover presents a more complete analogy to the conditions in a uterine implantation. The further growth of the ovum and extension of the destructive activity of the trophoblast would obviously have brought about the same condition of things as in Thompson's case. If the case had proceeded further without rupture of the ovary, the ultimate result would presumably have been destruction of the corpus luteum. The series of cases in which intra-follicular imbedding had occurred show that in these also the final result would be disappearance of the lutein tissue, so that in the final issue the initial differences due to variation in the site of implantation would disappear, after a few weeks or months. Variation in the site of implantation is due then only to differences in the degree to which the ovum burrows into the connective tissue of the ovary, and the cases readily arrange themselves in series on that basis.

The case of Hewetson and Jordan-Lloyd forms the extreme term of a series of which the case of van Tussenbrœk is the first term. It represents a case in which, probably at a comparatively early stage, the gestation sac had ruptured and abortion had taken place into the pouch of Douglas. The present case is an instance of a chorionic vesicle caught in the course of such an ovarian abortion. While Hewetson and Jordan-Lloyd conclude that the case is one of primary implantation in the substance of the ovary, they are inclined to the view that the ovum, either fertilized or unfertilized, reached the surface of the ovary, but being prevented, possibly by adhesions from reaching the Fallopian tube, burrowed back, as it were, into the substance of the gland. While the possibility of such an occurrence cannot be excluded, the case fits in with the other recorded cases, and with the present specimen much better if considered as a further stage of burrowing from within. The conditions of imbedding revealed in the early ovum described in the first paper embodied in this publication—its complete inclusion, the excessively minute size of the sealed point of entrance, indicating the very early stage at which imbedding occurs—seem to remove the difficulties, which, on account of the continuity of the thin layer of stroma intervening between the gestation sac and the corpus luteum, impelled Hewetson and Jordan-Lloyd to interpret the appearances in their case as due to burrowing of the ovum into the ovary from without.

The factors of ovarian pregnancy appear, in short, to be fertilization and retention of the ovum within the Graafian follicle, or in its immediate neighbourhood, until such time as it becomes capable of imbedding itself by its own activities, when it may do so in any patch of connective tissue which is sufficiently large to accommodate it and sufficiently vascular to meet the demands of its nutrition.

In the present case, as in all others recorded, there is no formation resembling decidua. In this matter the early uterine ovum sheds light on the facts of ovarian pregnancy. It has revealed a stage in the process of imbedding in which destructive changes exceed, or perhaps better precede, constructive decidual changes. The formation of a decidua in the immediate neighbourhood of the ovum is not essential to its imbedding. The blastocyst implants itself in the tissue of all others best capable of reacting to the stimulus of an irritant or foreign body, viz., connective tissue. In uterus, tube and ovary alike, the reaction is manifested, in the first instance, by enlargement of the vessels. In the uterus there is soon extensive formation of decidua, but in the ovary the actively destructive changes persist to a later stage than in the uterus. This fact, along with the absence of a decidua, points to the conclusion that decidua formation is a provision of a conservative nature, by which during the early months the activities of the trophoblast are limited and controlled until such time as placentation is complete.

Lastly, ovarian pregnancy finally excludes the theory that the uterine epithelium can have any part in the formation of the plasmodium. The fact that neither the membrana granulosa nor the lutein tissue has any part in the formation of the investment of the villi in an ovum imbedded in the ovary, limits the possibilities of a maternal origin of the layer of syncytium to the connective tissue. The wholesale destruction of tissue in the ovary and the characters of the early stages of an ovum imbedded in the uterus quite put out of court any theory which has as its basis the idea of an interlocking of foetal and maternal tissue, and with it the derivation of the plasmodial layer from maternal endothelium. The fact that the tissue round the chorionic vesicle in the ovary is everywhere clearly recognisable as necrotic connective tissue, while it is strong presumptive evidence in favour of the wholly embryonic origin of the plasmodium, cannot be admitted as a decisive proof of that contention. When we consider, however, the nature of the processes involved in the implantation of the blastocyst, more especially in the early stage revealed by our uterine ovum, it may safely be affirmed that, if further proof were needed, the results of our investigations establish beyond all doubt that the plasmodium is in the human subject a product of the foetal ectoderm.

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I. AN EARLY HUMAN OVUM IMBEDDED IN THE DECIDUA

PLATE I.

Fig. 1. Section through the Decidual Lobule, figured on page 10. Photograph at a magnification of 27 d. *a*, upper border; *b*, lower border of lobule; *m.g.*, mouth of a gland; *p.e.*, point of entrance.

The section cuts the lobule in the long axis of the shred of decidua. The free surface of the mucous membrane lies to the left, the deep surface to the right. In the centre is seen the cavity of the blastocyst. Round it is a mass of irregular plasmodium occupying the blood-filled implantation cavity. The swollen decidua shows dilated glands, and much enlarged vessels. Near the deep surface the vessels are dilated into almost sinus-like channels. There is a haemorrhage in the upper part of the section.

The photograph represents at a lower magnification the same section as drawn in colour on Plate III.

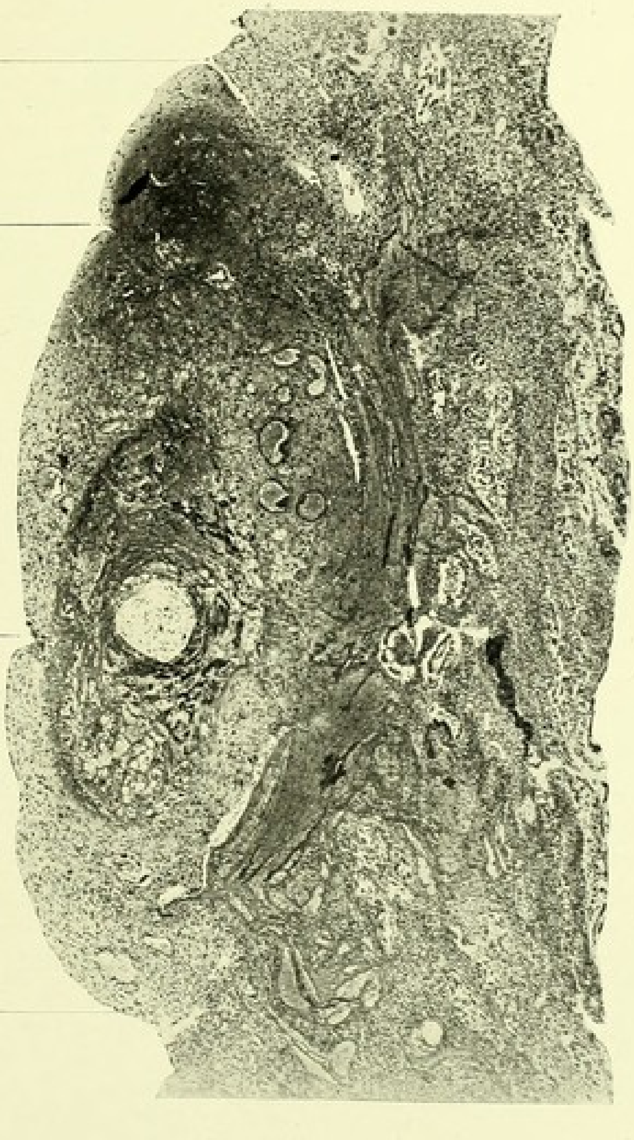

Fig. 1.

J. H. Teacher, phot.

PLATE II.

PLATE II.

FIG. 2. SECTION THROUGH THE BLASTOCYST AND IMPLANTATION CAVITY. Photograph at a magnification of 85 D. *D*, on the free surface of the decidua, indicates a hollow corresponding to the dimple in the figure on page 10. The appearance of a dimple on the surface is due to the relative thinness of the decidual wall of the implantation cavity directly over the blastocyst. It does not correspond to the point of entrance, which lies nearer the left margin of the lobule (see Plate III, Fig. 3). The section shows the decidual wall of the implantation cavity; the darker band represents the necrotic zone of the decidua. The blastocyst is at this point somewhat folded and irregular. Its interior is filled with mesoblast, and in the centre is a cavity of retraction in which a portion of the torn amnio-embryonic vesicle is seen. The cyto-trophoblast can be made out and the plasmodi-trophoblast here forms a very irregular reticular formation, more especially at one end, below in the section. Above this is a considerable mass of effused blood which has partly torn up the formation, in part pressed it down on the cyto-trophoblast. Within the necrotic layer of the decidua, especially below and to the left, a lamella of large free cells is seen. The decidua is crowded with leucocytes.

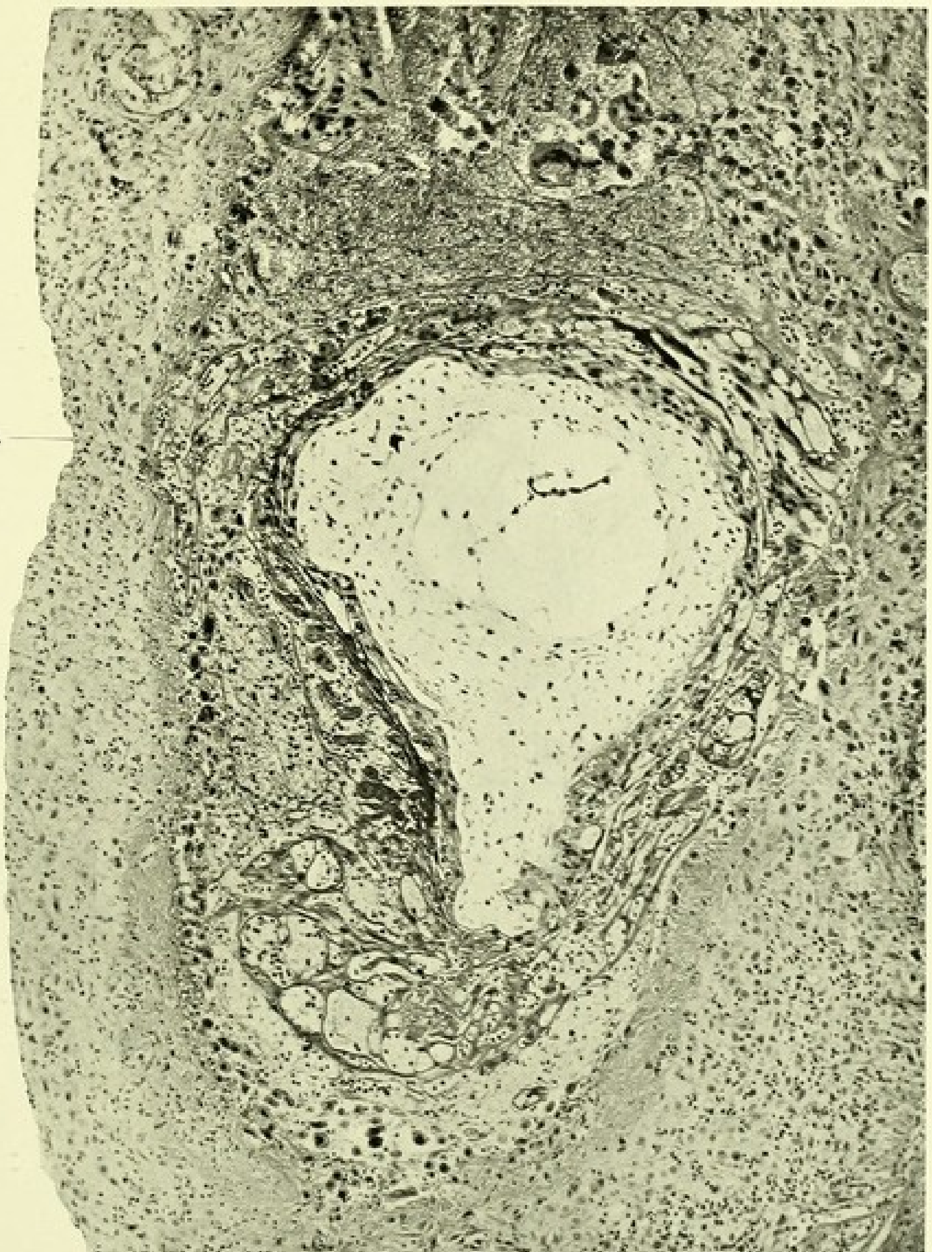

Fig. 2.

J. H. Teacher, phot.

PLATE III.

FIG. 3. SECTION THROUGH BLASTOCYST AND IMPLANTATION CAVITY at the level of the point of entrance. × 100 D. *dec.*, decidua ; *n.z.*, necrotic zone of decidua ; *P.E.*, point of entrance ; *gl.*, gland ; *bl.v.*, maternal capillaries : *hg.*, haemorrhage.

The cavity of the trophoblast is at this point filled with mesoblast. The *cyto-trophoblast* appears as a blue-pink lamella ; the *plasmodi-trophoblast* as bands and threads of protoplasm stained of a dusky-red colour enclosing nuclei. The spaces in the plasmodium are occupied by maternal blood corpuscles. These come from maternal capillaries opened up as the implantation cavity enlarges. In the upper part of the section there has been a considerable haemorrhage into the decidua ; this has in part broken down the necrotic zone, and the mass of effused blood has partly torn up the plasmodial bands. The implantation cavity is lined by a necrotic zone of the decidua distinguished by its pink colour ; the unaltered parts of the decidua have a grey-blue tint. Within the necrotic zone are seen numbers of free cells. The glands of the decidua are dilated ; their epithelium is desquamating, and their lumen contains red and white blood corpuscles. The blood-vessels are much dilated, more especially on the deep aspect of the decidua, where they form almost sinus-like spaces ; to the right and below, the endothelium of one wall of such a vessel is seen covering the decidua. The decidua is crowded with leucocytes. The point of entrance shows a depression filled with a mass of fibrin ; continuous with this and with the necrotic tissue, a fibrinous spur projects into the implantation cavity.

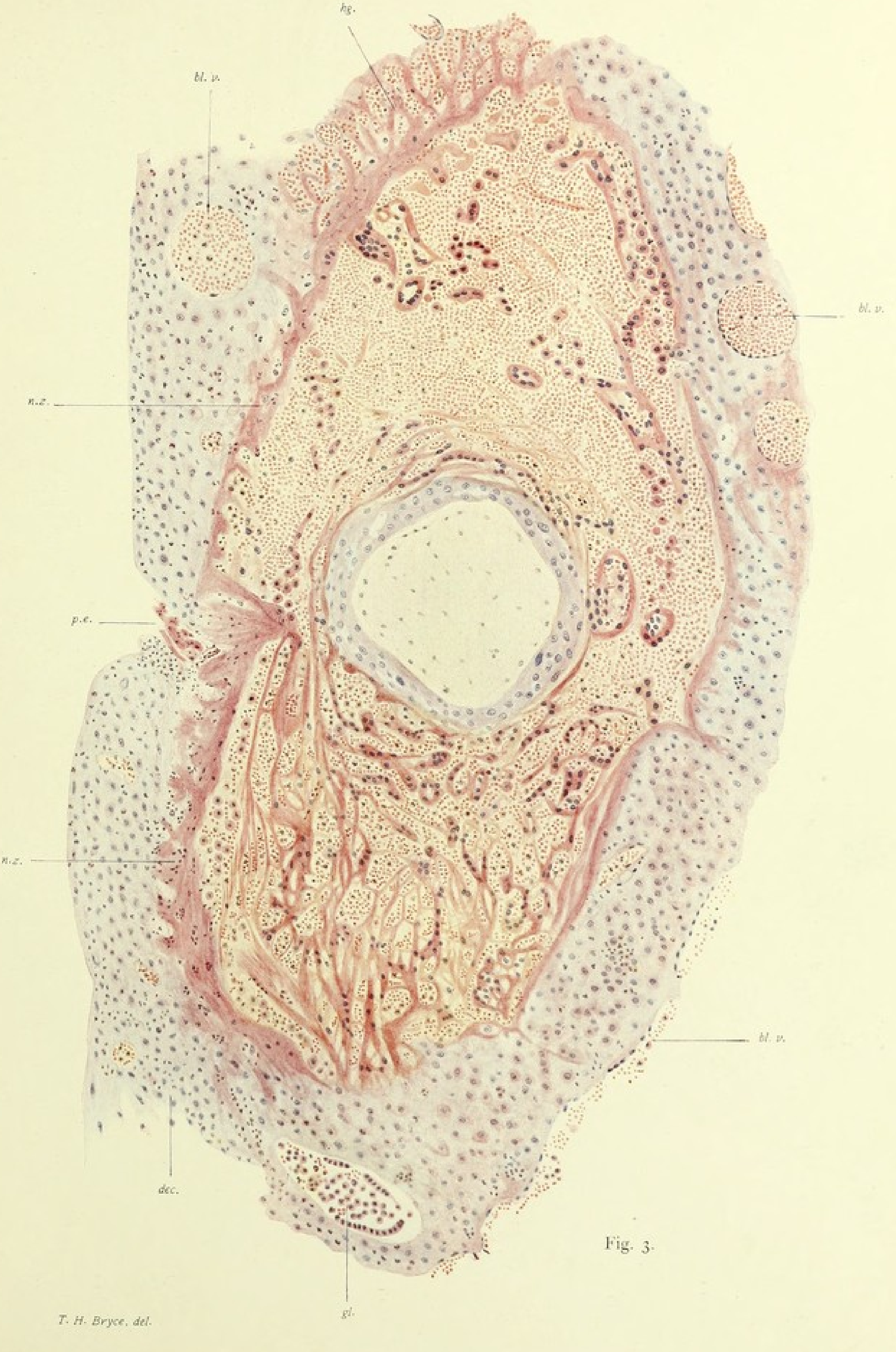

Fig. 3.

T. H. Bryce, del.

Plate IV.

PLATE IV.

FIG. 4. SECTION OF BLASTOCYST. × 200 D.

The cyto-trophoblast appears as a blue-pink lamella with irregular nuclei. Directly continuous with it are strands of plasmodium ; only the central strands of the plasmodium are represented. The mesoblast is shown as a mass of mucous tissue. The delicate blue reticulum which forms its base is largely a precipitation product ; in it are numerous small rounded or spindle-shaped cells, which form a very loose syncytial tissue. The mesoblast has shrunk away from the cyto-trophoblast on the left, and in the centre is the retraction cavity containing a portion of the torn amnio-embryonic vesicle.

Fig. 4.

T. H. Bryce, del.

Plate V.

PLATE V.

FIG. 5. SECTION OF A PORTION OF THE WALL OF THE BLASTOCYST, showing cyto-trophoblast and plasmodi-trophoblast, with portions of decidua, and the opening of an enlarged sinus-like capillary into the implantation cavity. × 350 D. *cyt.*, cyto-trophoblast; *dec.*, decidua; *end.*, endothelium of maternal capillary; *pl.*, plasmodium; *n.z.*, necrotic zone of decidua.

The cytological characters of cyto- and plasmodi-trophoblast are here brought out. The section passes through an opening, eroded by the plasmodium, in the wall of a large sinus-like capillary. The endothelium is still partly preserved, and covers the upper portion of decidua. The vessel opens by a wide gap into the implantation cavity, and the opening is partially occupied by a large mass of irregular vacuolated plasmodium. This is continuous with the necrotic zone of the decidua, from which it is distinguished by a difference in colour. The plasmodium is not continuous with the other portion of decidua; between them there is a narrow space containing a few leucocytes. Under the endothelium there are several large apparently degenerated decidual cells. The guiding line to the endothelium touches one of these cells.

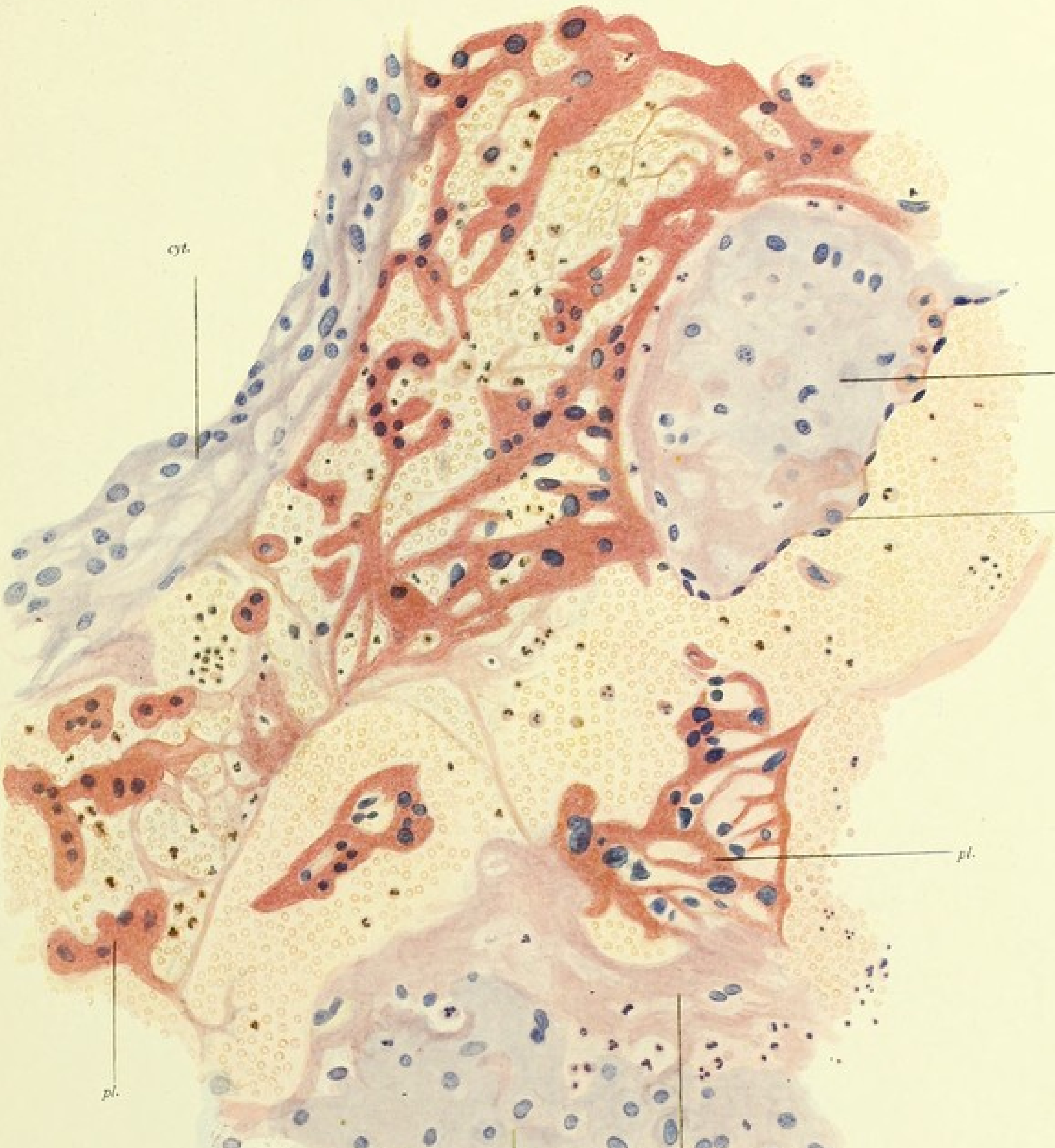

Fig. 5.

T. H. Bryce, del.

Plate VI.

PLATE VI.

Fig. 6. Section of a Portion of the Necrotic Zone of the Decidua, and of the Layer of Large Cells on its Inner Aspect. × 500 d. *n.z.*, necrotic decidua; *m.c.*, large, probably maternal, cells in various stages of degeneration, some lying free in the implantation cavity, others embedded in the necrotic tissue; *cav.*, blood-filled implantation cavity.

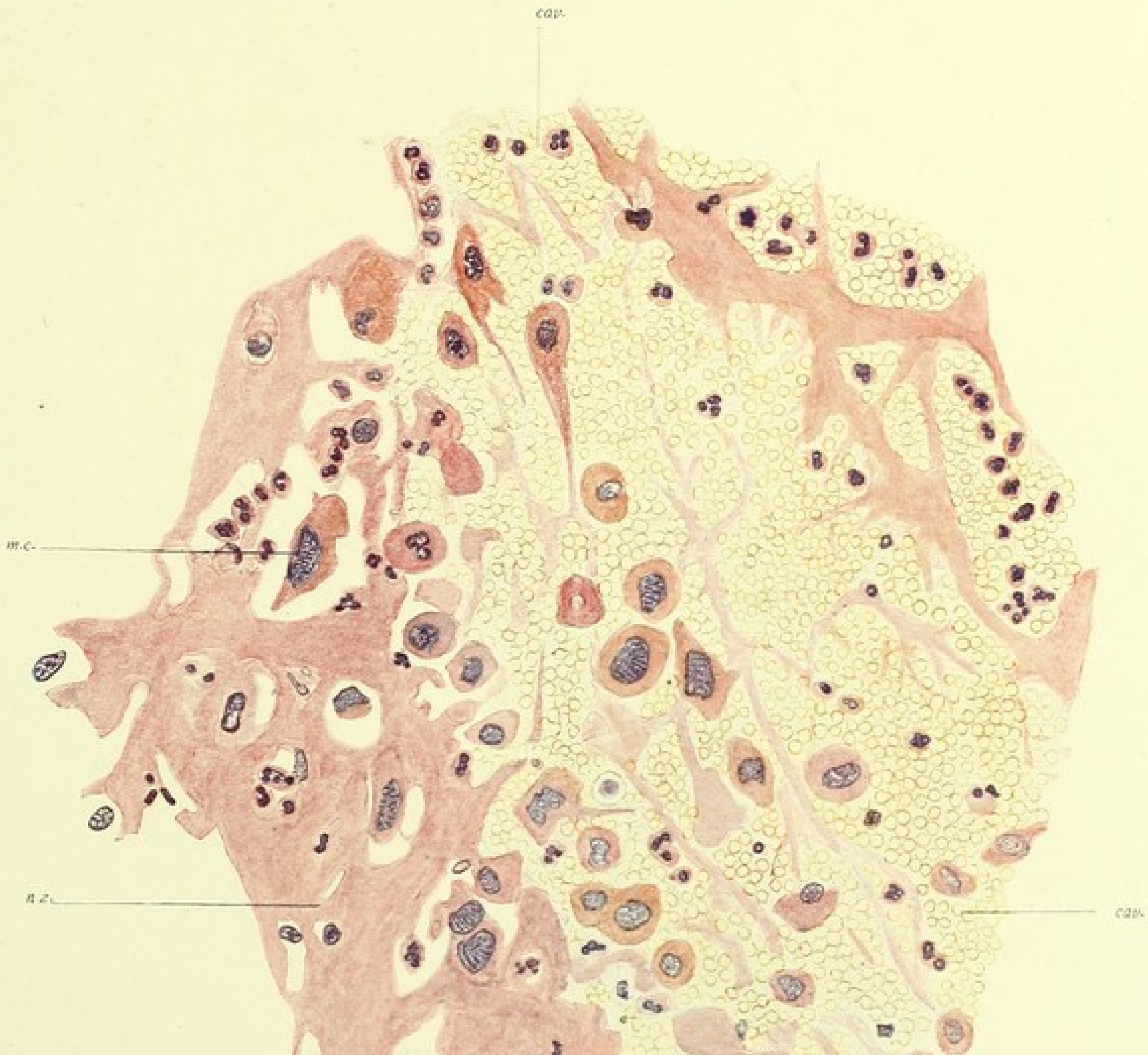

Fig. 6.

T. H. Bryce, del

PLATE VII.

PLATE VII.

FIG. 7. TANGENTIAL SECTION THROUGH THE BLASTOCYST WALL, showing cyto-trophoblast and plasmodi-trophoblast. × 320 D. *pl.*, plasmodium ; *nuc.*[1], cell with large single nucleus ; *nuc.*[2], cell with two nuclei.

The cellular layer shows great irregularity in the size of the nuclei ; many cells show two, others three, some multiple nuclei.

FIG. 8. SECTION OF THE AMNIO-EMBRYONIC VESICLE. × 320 D.

The drawing represents the walls of the vesicle restored by the superposition of three successive sections. The mesoblast is slightly indicated, and the vesicle is seen to be attached more closely and firmly at one point.

FIG. 9. SECTION OF THE ENTODERMIC VESICLE. × 320 D.

Some of the surrounding mesoblast cells and threads are represented.

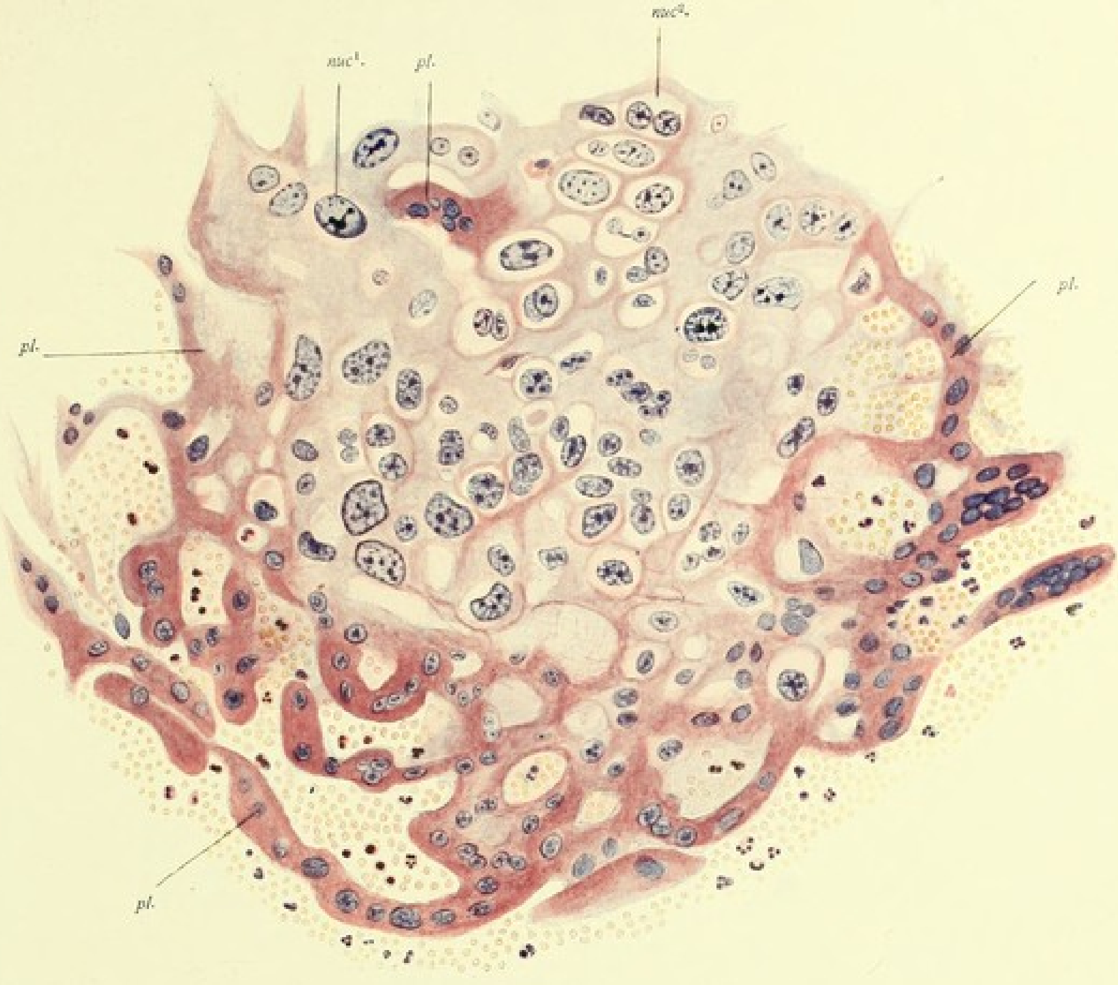

Fig. 7.

Fig. 8.

Fig. 9.

T. H. Bryce, del.

Plate VIII.

PLATE VIII.

Fig. **10.** Section showing a Mass of Vacuolated Plasmodium Invading the Decidua. Photograph. × 350 D. *pl.*, plasmodium ; *dec.*, decidua ; *n.z.*, necrotic zone of decidua.

The mass of plasmodium shows a number of small vacuoles. It lies in a bay of the necrotic zone, and between the two are several large free, probably maternal, cells. The decidua is crowded with leucocytes. The decidual cells adjoining the necrotic zone show the early stages of degeneration ; further out they are more normal.

Fig. **11.** Tangential Section of the Opposite Pole of the Cyto-trophoblastic Sphere from that figured in Fig. 7, Plate VII. Photograph. × 350 D.

The nuclei are very irregular. The well-defined central cells belong to the innermost layer of the cyto-trophoblast.

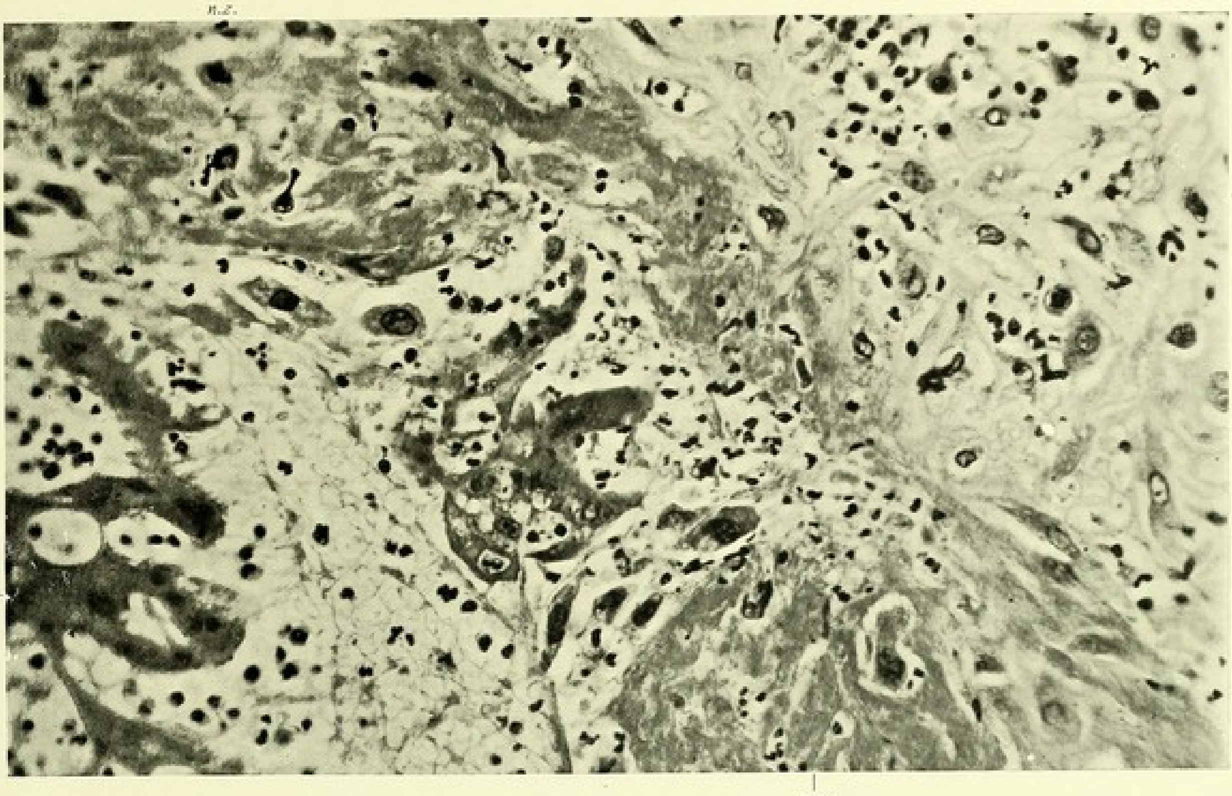

Fig. 10.

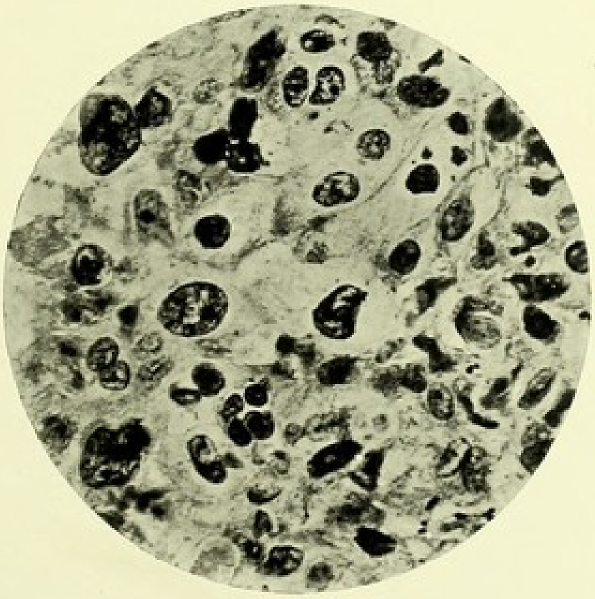

Fig. 11.

J. H. Teacher, phot.

II. AN EARLY OVARIAN PREGNANCY.

PLATE IX.

FIG. 12. SECTION OF A PORTION OF THE OVARIAN STROMA AND VILLI OF THE CHORION. × 200 D.

V, villus; *Tr.*, mass of Langhans' layer cells; *pl.*, plasmodium; *bl.c.*, blood clot; *hg.*, haemorrhage; *str.*, stroma of ovary; *bl.v.*, blood-vessel in stroma.

A portion of the stroma has been selected in which runs a large vessel; this, when traced through the sections, was found to open out into the gestation sac. The stroma adjoining the cavity is necrotic. Masses of plasmodium are seen attached to it, both on the right above the haemorrhage, and to the left above the blood-vessel.

Fig. 12.

T. H. Bryce, del.

Plate X.

PLATE X.

Fig 13. Section of the Villi and Edge of the Chorion. Photograph. × 140 d.

The section demonstrates that the villi are covered by a double-layered epithelium (cellular layer and plasmodial layer).

Fig. 14. Section of a Single Villus and Mass of Langhans' Layer Cells, more highly magnified than in the last figure. Photograph. × 240 d.

The two-layered epithelium covering the mesoblastic core of the villus is well seen. The mass of Langhans' layer cells is covered by a very distinct plasmodial layer (syncytium of authors).

Fig. 13.

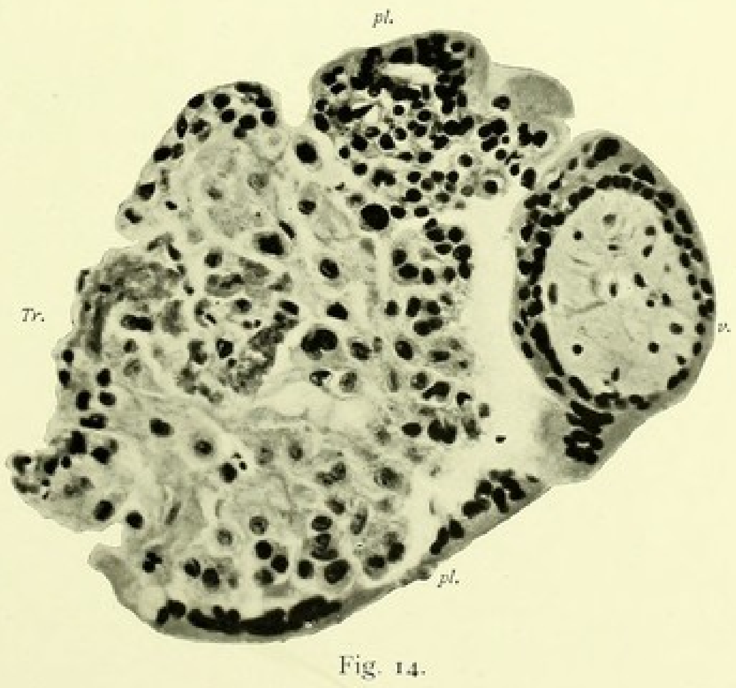

Fig. 14.

J. H. Teacker, phot.