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On the Structure of the Human Placenta, with Special Reference to the Origin of the Decidua Reflexa.

By D. Berry Hart, M.D., F.R.C.P.Ed., F.R.S.E., and G. Lovell Gulland, M.D., F.R.C.P.Ed.

In investigating the structure of the advanced extra-uterine placenta, one of the authors was struck with the fact that the placenta developed there entirely in connective tissue. In the placenta of advanced normal gestation, it has been supposed by many good observers that the fœtal villi, in addition to their own epithelium, derived a covering from the maternal epithelium,—from the surface epithelium of the serotina, or from that of the uterine glands. The generally accepted view in regard to the human placenta has been that the villi of the fertilised ovum grafted themselves on a portion of the hypertrophied mucous membrane, this portion being now termed the decidua serotina; that by the mutual ingrowth of the serotina and villi the placenta was formed; while round the developing ovum there very early grew coalescing folds of decidua, the so-called decidua reflexa. On the one hand were the chorionic villi covered by the fœtal epithelium, on the other the connective tissue of the serotina with its special layer of epithelium,—these forming as it were the elements from which the complex placenta was to evolve.

This view is highly unsatisfactory, so far as the human placenta is concerned. It does not explain the overwhelming frequency with which the human fertilised ovum grafts itself on a certain area of the genital tract, viz. in the uterine cavity proper; it assumes a function for the surface epithelium which has never been proved; and, finally, it leaves the origin of the decidua reflexa a complete mystery. Why should decidual folds at the edge of the serotina rise and cover

in the ovum, however various its site within the normal limit?

The present investigation was therefore begun to ascertain the part played in the development of the human placenta by the surface epithelium of the decidua serotina; to discover if possible a feasible explanation of the overwhelming frequency with which the fertilised human ovum grafts itself in the cavity of the uterus proper; and, finally, to investigate the nature of the reflexa.

In approaching these questions, we found the greatest help in the invaluable monographs of Sir William Turner, *On the Comparative Anatomy of the Placenta.* The microscopic investigations of Hubrecht, Duval, Langhans, Kastschenko, Minot, Frommel, Gottschalk, and many others, gave us not only valuable facts, but enabled us to compare our own results with theirs.

One of the most important factors in such an investigation as the present is the material at the disposal of the workers, its freshness, and the methods employed for its preservation and examination. In the lower animals, as a rule, the specimen can be obtained immediately after the animal's death, and at once prepared for microscopic examinations in the best manner possible. In the case, however, of human uteri it is different, as the specimens are usually obtained from twenty-four to thirty-six hours after death, and thus their value is greatly deteriorated, especially as regards free mucous surfaces, where the epithelial covering soon becomes lost. The authors were specially fortunate in their specimens, as one early pregnant uterus, about the sixth or seventh week, was extirpated from a patient, owing to cancer of the vaginal portion of the cervix, and placed in corrosive sublimate solution a few minutes after its removal. A second specimen of a full time pregnant uterus was re-obtained from a patient who died suddenly, and on whom post-mortem Cæsarean section was performed in the child's interest. The uterus was also removed at the same time, and very shortly afterwards hardened in corrosive sublimate and alcohol. The specimens examined were as follows:—

Rabbit.—(1) Unimpregnated uterus; (2) impregnated ovum at fourth day; (3) impregnated ovum at eighth; (4) impreg-

nated ovum at eleventh; (5) impregnated ovum at fourteenth; (6) impregnated ovum at twentieth day; (7) placenta at full time; (8) post-partum uterus.

Sheep.—Unimpregnated uterus, and many very early pregnancies, the dates of which could not be ascertained.

Rat.—One near full time (white rat).

Human.—(1) Several early abortions; (2) six weeks' pregnant uterus in complete preservation; (3) two months' aborting uterus; (4 and 5) three months' pregnant uteri with fœtus expelled (two specimens); (6) four months' uterus; (7) four and a half months' uterus; (8) two six months' uteri; (9) full-time pregnancy; (10) two third-stage uteri (full time). All of these were in a good state of preservation, while 2, 8, and 9 were quite perfect.

The method of preparation employed varied in different cases. As fixing agents, Flemming's "strong" solution, a saturated watery solution of picric acid, and a watery solution of corrosive sublimate saturated by boiling, were used in different cases, and to control one another. The early rabbits' uteri were fixed, after cutting them into segments, either unopened in the case of the fourth day uteri, or in the eight days' uteri, after a window had been made in the side away from the mesometrium to allow the escape of the amniotic fluid and the entrance of the fixing agent. The later rabbits' uteri were all opened before fixing, as were also the sheeps', rat's, and human uteri. All the specimens were hardened in alcohol, and cut in paraffin, the smaller uteri and placentæ being cut in series. The sections were fixed on the slide by the method described by one of the authors (*Journal of Anatomy and Physiology*, 1891); stained, as a rule with hæmatoxylin and eosin (though gentian violet, iodine green, and other anilines, were sometimes used), and mounted in balsam.

Results of Examination of Impregnated Ova of Rabbit, Rat, and Sheep.

We do not propose to give a detailed description of the appearances found in these placentæ. This will more appropriately appear at another time; for, while the pregnant uteri

of these mammals present many interesting features, the structure of their placentæ differs too much from that of the human placenta to allow of any very profitable comparison. For example, the villi of the rabbit's placenta are totally unlike the human villi; the so-called decidua reflexa of the rat is merely a cup-shaped elevation in which the placenta lies, and though the villi of the sheep's placenta have some points of resemblance to those of the human chorion, the manner of their implantation, in specially differentiated parts of the uterine surface, is so unlike what takes place in the human uterus, that it is doubtful how far one is entitled to institute a comparison.

The following points are the main ones which can be brought into line with facts in the history of the human placenta:—

Rabbit.—Here, as Duval, Minot, and others have already shown, the uterine epithelium becomes immensely hypertrophied and degenerated over the two folds of the mucosa next the mesometrium, the site of the future placenta. At that point on the circumference of the blastoderm, which comes in contact with these projecting folds, the fœtal ectoderm becomes thickened, and before the mesoderm has grown up to support it, it becomes attached to the degenerated uterine mucosa, which rapidly disappears before it (see Plate IV. fig. 6); very possibly the degenerated epithelial cells are utilised for the nutrition of the "ectoplacenta," as Duval proposes to call this epiblastic proliferation. The mesoderm soon grows into the ectodermic projections, and villi of a sort are formed, but these differ so much from the villi of the human placenta that their history need not be further traced. We need only say that the ectoplacenta loses its distinctness very soon, and seems mainly to be employed to remove the superficial parts of the serotina, if we may so call it.

Rat.—The only point of special interest is the ease and completeness with which the decidual cells, which are here very large, can be shown to be derived from the ordinary connective-tissue corpuscles of the serotina. All intervening stages can be found in the layers of cells lining the so-called decidua reflexa. In other respects the placenta of the rat

greatly resembles that of the rabbit, and is not further available for our present purpose.

Sheep.—Here the structure of the placenta is modified by pre-existence of the projections on the uterine wall, which combine with the fœtal parts to form the cotyledons. These projections, in the non-pregnant uterus, are low, round cylinders with a slightly excavated summit, and are irregularly scattered over the uterine mucous membrane. They consist of a delicate connective tissue whose strands run mainly parallel to the surface, and which is traversed by numbers of long capillaries running mainly at right angles to the surface. They are covered by a single layer of cubical epithelium, and there are no glands, though in the rest of the uterine mucous membrane these are numerous and well-formed. When pregnancy occurs, the blastoderm very rapidly fills up the uterus, and on the parts applied to these projections the epiblast (which has usually two layers) and mesoblast simultaneously form villi, at first very short. The application of these to the surface of the uterine projections is soon followed by the degeneration and disappearance of the uterine epithelium; and the further history of the placenta, so far as we traced it, is comprised in the growth of the villi into the cotyledon and the disappearance of the connective tissue forming this before their growth. No special decidual cells are formed, and the connective tissue does not show any marked appearances of degeneration before its removal. The villi retain their original character.

The only point in which the placentæ of the rabbit and sheep agree is in the way in which the uterine epithelium is removed by the fœtal epithelium. The uterine epithelium becomes absorbed or destroyed by the villi which then come in contact with the connective tissue of the mucous membrane. It is possible that the altered epithelium may have a nutritive function for the early ovum.

Human Pregnancy (Sixth Week).

(Fœtus one and a quarter inches long.)—As already explained, this specimen was exceptionally well preserved.

Decidua Vera.—Two portions were specially examined (*a*) at the placental edge; (*b*) at the lower uterine segment.

(*a.*) *At the placental edge* there is an evident naked-eye division into a compact and a spongy layer. The thickness of the entire decidua is about a quarter of an inch, the compact layer about a twelfth, the spongy layer a sixth. The surface is covered with a single layer of columnar epithelium (see Plate V. fig. 11). The cells show no trace of cilia, and have the appearance of being somewhat degenerated, the intracellular network is swollen, giving the protoplasm a very granular appearance, while the nuclei, though here and there normal, are often irregular and angular in outline, and stain faintly with hæmatoxylin. The compact layer consists mainly of a felted mass of large decidual cells, whose diameter is generally from 18 to 30 μ, but which vary within even wider limits. Their nuclei are large, and are of a connective tissue type. Scattered among these are a certain number of leucocytes (not very many), and traversing the layer are numerous thin-walled blood-vessels, and the generally compressed ducts of the glands. The spongy layer is seen to be due to the persistence and dilatation of the uterine glands. The spaces formed in this way are very large (Plate III. fig. 1), and take up most of the layer, the trabeculæ of decidual tissue between being comparatively narrow. The epithelium lining these gland-spaces varies considerably in character; that lining the ducts and the spaces nearest to the compact layer is generally somewhat degenerated and flattened, the epithelium of the deeper spaces is cubical and more normal in appearance; while the epithelium of the gland-spaces close to the muscular coat is cylindrical, and is not distinguishable from that of the deep glands of the normal non-pregnant uterus. The spaces generally contain granular débris, degenerated epithelial cells, and leucocytes. In the interglandular tissue the large decidual cells are not so numerous as in the compact layer, and there are proportionately more leucocytes.

(*b.*) *At the lower uterine segment* the decidua is of about the same thickness, but the compact layer is relatively much thicker, and contains fewer ducts, while the spongy layer is not nearly so well defined, nor are the glands so much

dilated nor so numerous as at the edge of the placenta. The surface is covered by epithelium having the same characters as that at the placental edge.

Decidua Reflexa.—At its origin where, including the chorionic villi imbedded in it, the membrane is about a third of an inch in thickness, this has the same structure as the adjoining vera; it looks indeed as if the compact layer of a part of the decidua vera had been separated from the spongy layer below, and folded back so that the surface epithelium of the reflexa came in contact with that of the vera. Indeed, glands can be seen opening on the outer surface of the reflexa whose deeper expansions are to be found in the vera; the ducts are folded round at the junction just as the surface epithelium is. There are other glands opening on the outer surface of the reflexa, though not very many, whose fundi do not pass out of the reflexa; but these glands are never very long, and there is no trace of a spongy layer anywhere in the reflexa, nor do any glands open on the inner or fœtal surface of the reflexa. This surface is of course occupied by the chorionic villi at this stage, and the part of the decidua in contact with them has the structure of the compact layer, and presents appearances like that of the serotina at the point where the villi are pushing forward into it,—appearances which will presently be described.

The decidua reflexa retains this character for some distance, perhaps half an inch or so from its origin, but as it thins out over the ovum its structure alters. The surface epithelium is lost, all traces of glands disappear, the decidual cells become more and more degenerated and are replaced ultimately by a fibrinous layer which contains immense numbers of leucocytes, most of which are also degenerated. Scattered through this layer are degenerated villi, denuded of epithelium and surrounded by a layer of fibrin. The villi close to the chorion are healthy much further up the decidua than the outlying ones are; but, at the very top, the reflexa consists only of a thin chorion of degenerated fœtal connective tissue, with no epithelial covering, and external to this a few strands of fibrinous looking material with numbers of leucocytes.

Placenta.—For its examination sections were made from

amnion to muscular coat, and in these there are to be seen from within out, amnion, chorion, chorionic villi, maternal portion of placenta, and muscular coat.

The *amnion* is from 30 to 60 μ in thickness, and made up of flattened epithelium with flattened nuclei on a basis of connective tissue.

The *chorion*, 0·1 to 0·2 mm. thick, is slightly separated from the amnion, but it is difficult to say whether this separation may not be partly artificial, as there seem here and there to be connective-tissue fibres running between the two. The connective tissue of the chorion is of the usual type. The epithelium covering its outer surface varies from place to place along the main chorion. It is perhaps most usually a single layer of low cubical cells, but here and there are to be found two layers, when the appearances are the same as those about to be described in the terminal villi.

The *chorionic villi* are formed of ordinary fœtal connective tissue with blood-vessels running through it. The latter are not nearly so wide nor so numerous as they become towards the end of pregnancy. The special point of interest in regard to these villi is, however, their covering, which varies somewhat from place to place. Over the main villus-stems, as over the main chorion, there is often a single layer of cells, but in some places on these larger stems, and almost uniformly over the smaller villi, the epithelium consists of two, sometimes even of three, layers of cells (Plate IV. figs. 2 and 5). The inner of these layers consists of cubical cells, with a large nucleus and relatively clear protoplasm; the outlines of the individual cells can usually be made out. The outer layer consists of cells more or less degenerated, the protoplasm is granular, and stains more deeply with eosin than that of the inner layer of cells, the outline of the cells can seldom be made out, the nuclei are smaller than those of the inner layer, stain deeply, and are often flattened or angular; there is, in short, every reason to regard this layer as one derived from proliferation of the inner layer. The ectoderm of the fœtus itself in this pregnancy has two layers, and presents appearances almost identical with that of the epithelium covering its villi. The villi of all parts of the placenta which were examined, and the undegenerated villi imbedded in the

decidua reflexa, all had this structure (except those villi which were imbedded in a fibrinous mass, which will be described shortly), and in *none* of the dozens of sections systematically examined was there *any appearance which could give rise to the suspicion that the maternal epithelium had any part in forming the covering of the villi, or that there was anywhere an endothelial covering external to the epithelium.*

The *intervillous spaces* do not seem to contain blood in this specimen; near the chorion they seem indeed to be empty, while near the maternal part their only contents seem to be degenerated débris, apparently the remains of part of the decidua serotina. Here and there, in the part of the fœtal placenta next the maternal portion, are islets of this degenerated decidual tissue, in some of which villi are imbedded, and these villi, as well as those which are here and there imbedded in the surface of the decidua serotina and reflexa, are sometimes without any epithelial covering. The connective-tissue part of the villus is generally surrounded by a ring of fibrinous-looking material, probably the same as that whose origin from the epithelium Minot discusses at length.

There are also, in relation to many of the terminal villi, peculiar masses of cells, which will, however, be more appropriately described after the decidua serotina has been discussed.

Decidua Serotina.—The portion of this layer which remains beneath the rapidly advancing fœtal placenta is only about half the thickness of the decidua vera, and, like it, can be divided into a compact and a spongy layer, with this difference, however, that whilst in the vera the spongy layer is twice as thick as the compact layer, in the serotina the compact layer is at least twice the thickness of the spongy layer, and contains hardly any glands or ducts; these are almost entirely confined to the spongy layer. The compact layer presents other differences from that of the vera; there are many large blood-vessels, apparently veins, in it, with more or less degenerated walls. In some cases the endothelium lining these degenerated vessels has begun to proliferate (Plate V. fig. 12), and in some of these thrombosed vessels the lumen is entirely taken up by young connective-tissue cells—a con-

dition hitherto supposed to come on only after the eighth month of pregnancy (Friedländer, Leopold). The decidual cells present different characters in different parts of the serotina. Next the fœtal placenta they are like those of the decidua vera, but are almost always degenerated, *i.e.* their nuclei stain faintly, the outline of the cells is more or less blurred, and their protoplasm is often converted into a fibrinous-looking mass staining a bright pink with eosin. Rather deeper in the serotina the decidual cells are normal, and in still deeper parts, especially between the glands of the spongy layer and just above this layer, the development of the ordinary connective-tissue corpuscles into decidual cells is very beautifully shown. The change consists in a progressive enlargement both of nucleus and cell-body, both of which stain more deeply than usual in the intermediate stage. The above arrangement of the different forms of decidual cells seems to be the typical one, but sometimes irregularities occur, *e.g.* the intervillous spaces are sometimes bounded by cells still in the young stage. This is probably due to irregularity in the growth of the fœtal part of the placenta.

The impression produced by a study of these and of many other preparations is that, as the villi grow, the decidua serotina disappears before them. It is an obvious and well-known fact that the maternal part of the placenta at the end of pregnancy is exceedingly small as compared with the fœtal part, and very much smaller than it is in the earlier months, but the cause of this decrease is not so obvious. It must, of course, be evident from what has been said that the degenerating decidua is absorbed, but, Is it absorbed by mother or by fœtus? It is difficult to believe that the absorption is carried on by the maternal tissues, for in the first place there are not many lymphatic vessels to be found in the decidua; and in the second place, though leucocytes, the usual removers of dead material, are present in considerable numbers in the decidua, they are to be found rather in the active parts of it than in those already degenerated, and they do not seem sufficiently numerous for the task of absorbing what is relatively such a large mass of tissue. Can the fœtal tissues be the absorbing agents? We are inclined to think that they are, in part at

least, and would point in support of this to the analogy of the rabbit's placenta, where the fœtal epithelium certainly must absorb or cause absorption of the degenerated epithelium and connective tissue of what one may call the serotina there, as we have already pointed out. A further support to this theory is to be found in the existence of a very peculiar set of cells in this placenta, which do not seem to have been described elsewhere. We have already pointed out that the villi tend to have a thicker epithelium towards their extremities, and at the very tips of the villi, where they come in contact with the surface of the degenerating decidua, we find the cells in question, epithelial in character, as figs. 7 and 9 on Plate V. show, and apparently resulting from a proliferation of the epithelium at the extremities of the villi. They are rapidly growing, as the occurrence of numerous mitotic figures among them sufficiently demonstrates, and they have all the characters of embryonic epithelial cells,—a round, deeply staining nucleus, a clear cell protoplasm, and sharply-marked cell outlines. They remind one in fact most forcibly of the cells of the "ectoplacenta" in the rabbit, the epiblastic epithelium which destroys the degenerated uterine epithelium, and is the forerunner of the true placenta. These masses of cells, which are directly continuous with the epithelium covering the villi, form, in sections, irregularly-shaped projections, often ten or a dozen cells deep, whose surface towards the serotina is usually flattened and rests directly upon the degenerated tissues there, or sometimes even upon young decidual cells. When this occurs, the difference between the two sets of cells is at once apparent. It seems possible that these cells may have to do with the absorption of the degenerated decidua, and that they may even utilise the material obtained from the disintegrating cells for their own nutrition, and at the same time indirectly favour the nutrition of the fœtus by hastening the removal of temporary tissues, and furthering the formation of the true placenta. Probably this epithelium early fulfils its function and itself disappears, as it is not found, at least in the form here described, in any of the later placentæ we have examined, nor does it seem to have been noticed by other authors. In the placenta of a four and a half months' uterus, which we owe to the kindness

of Dr. William Russell, we found, however, a set of cells at the points where the villi impinge upon the serotina, which apparently represent a later stage of this "trophoblastic" epiblast. One of these points is represented in Plate V. fig. 8, and the cells in question are seen to form a double or treble row of large embryonic-looking cells continuous with the epithelium covering the rest of the villus, which consists at this point of two layers. The portion of the serotina touched by these cells is extremely degenerated. It will be noticed that the connective tissue of the villus is condensed to form a sort of basement membrane below the trophoblastic cells at this stage, which does not occur in the six weeks pregnancy.

Other Human Pregnancies.

These resolve themselves into two classes—the early abortions, and the later uteri with placentæ *in situ*. The former are not usually suited for the study of the minute relations of parts, as the whole deciduæ and embryo very seldom come away at once, and even when this does exceptionally happen, the relations are almost invariably disturbed by blood extravasations, old or recent. The latter class of preparations in our hands forms an extremely valuable series, but at present we propose only to utilise them to explain the further history of the villi, with special relation to their epithelial covering.

The Early Abortions.—We possess several, of dates from one to three months, and the villi in those parts which are least disturbed present appearances identical with those of the six weeks' pregnancy described at length. All the early specimens indeed show similar appearances, and it is not till we reach the specimen (6, p. 19) that we find any marked change, though the epithelium becomes flatter in the latter specimens.

Four months' Uterus and Placenta (see Plate IV. fig. 3).—The villi are covered by a single layer of epithelium, which consists of flattened, deeply-stained nuclei, imbedded in a thin protoplasmic layer, in which the cell outlines can no longer be distinguished. Towards the tips of the villi there are sometimes two layers, and at the very extremities there seem sometimes to be several layers; but as our sections of this

specimen were not cut in series it is impossible to be certain on this point. At some points on the villi there are patches of that deeply staining substance derived from degenerated epithelium to which Langhans, Minot, and others have given the name of "canalised fibrin." The villi which are actually imbedded in the degenerated superficial decidua have no epithelial covering.

Four and a half months' and six months' Uteri.—The appearances here are practically identical with those of the four-months' uterus.

Full time Uteri and shed Placentæ (see Plate IV. fig. 4).—In all of these there is only one layer of epithelium covering the villi, and it is flatter even than in the four months' uterus. The nuclei are almost all degenerated, and the protoplasm in which they are imbedded is small in amount. The deeply-stained masses mentioned in the description of the four months' uterus, which have the appearance of being agglomerations of degenerated nuclei, are here much more numerous. The free villi at the deeper part of the placenta do not differ, as far as their covering goes, from those of the more superficial parts; there is no thickening of the epithelium. In the uteri with placentæ still attached there is a relatively large number of villi imbedded in what is left of the decidua serotina. These villi have no epithelial covering, and the superficial layer of the decidua in which they lie consists of a degenerated homogeneous-looking connective tissue, in which the remains of decidual cells can here and there be distinguished.

It will be seen from these descriptions that we can fully confirm Minot's dictum (*l.c.*, p. 395) that "the chorionic epithelium advances in its differentiation to a stage equivalent to the two-layered stage of the epidermis, and there stops; whatever further change occurs is degenerative."

The only other important points in which the villi alter histologically are in regard to the connective tissue and blood-vessels. As pregnancy advances the connective tissue becomes more fibrous and generally more fully organised, and the blood-vessels become more numerous, wider, and have more fully differentiated walls.

We have now to consider some questions as to the

structure of the human placenta, restricting ourselves to three points:—

1. *The nature of the covering of the villi, and the alleged rôle, in the formation of the placenta, of the surface epithelium.*
2. *The probable nature of the decidua reflexa.*
3. *The probable reason why the human ovum grafts itself, as a rule, within a certain area of the genital tract.*

1. *The nature of the covering of the villi, and the alleged rôle, in the formation of the placenta, of the surface epithelium of the serotina.*

In this country no paper has dominated research on these points so much as the classical one of Goodsir, "On the Structure of the Human Placenta," followed up as it has been by the well-known work of Ercolani and Turner.

Goodsir described a double epithelial covering of the villi, and held the outer to be maternal and the inner fœtal. He also figured a distinct space between these, bounded by a limiting membrane, and also an outer limiting membrane to the maternal epithelium. He speaks of part of the decidua serotina being shut off from the main portion by the maternal sinus system, the cells of the two being continuous by the lumen of the threads "which passed in great numbers from the vascular edges of the venous openings, and from the walls of the cavity of the placenta on to the extremities and sides of the villi and tufts of the placenta." He then goes on to say, "This observation led me at once to perceive the real signification of the external cells of the placental tufts. I saw that the great system of cells was a portion of the decidua, all but cut off from the principal mass by the enormous development of the decidual vascular network, but still connected with it by the minute files of cells which fill the cavities of the placental threads. This system of cells, the external cells of the villus, with the external membrane, belong to the organism of the mother."

Turner in his paper, "Some General Observations on the Placenta, with special reference to the Theory of Evolution," represents the maternal epithelium as a fully-developed layer over the villus, stating at the same time that "the layer of fœtal epithelium cannot be seen on the villi of the fully

formed placenta" (p. 37, text of fig. 7). He also figures Goodsir's threads as connective-tissue strands joining serotina and villus. From a consideration of our specimens, we believe that the covering of the villi is in the early placenta made up of a multiple layer of epithelium, and that it is epiblastic, *i.e.* entirely fœtal. It is impossible to look at our specimens, and to come to any other conclusion. We hold that Goodsir's investigation by no means proves that the maternal epithelium is represented on the villus. The recent work on the early relations of the villi and maternal tissue in the bat, rat, and ruminants, has shown that shortly after ovum-contact the maternal epithelium disappears, *i.e.* the villi come into immediate relation with the connective tissue. In the paper of Turner's already quoted, the diagrams should, in our opinion, be modified by the obliteration of the maternal epithelium, as this plays no essential part in the formation of the placenta.

The important question has now to be considered as to what condition the serotina is in when the villi graft themselves. The early pregnancy specimen shows *the decidua vera fully completed and covered with columnar epithelium, while the reflexa is also covered in great part with columnar cells.* This tends to show that the ovum has not grafted itself on a fully-formed decidual portion, with its surface epithelium formed, but on the decidua while forming. This point, however, comes up more clearly in our next section (2).

2. *The probable nature of the decidua reflexa.*

William Hunter first pointed out that the human ovum had a decidua arched over it, and he applied the term "reflexa" to this portion. In no human ovum has this been found incomplete, although the general text-book diagram represents the decidua serotina sending folds up to coalesce over the ovum—a purely literary description based on no observation. That there is a decidua reflexa admits of no doubt. Its method of formation has, however, been disputed. Goodsir speaks of it as a cellular decidua formed "of a non-vascular cellular substance, the product of the uterine follicles." Goodsir evidently felt the difficulty of explaining the decidua reflexa from a completed serotina

with its surface epithelium fully formed, and clothing the external surface of the villi. Hence his hypothesis, which is just John Hunter's, without the "cellular."

The whole difficulty as to the reflexa disappears if we accept the hypothesis our specimens so strongly indicate. The villi, with their epithelial covering, purely epiblastic and fœtal in its origin, graft themselves on the decidua serotina, *while this serotina is forming, prior to its completion, and thus the serotina completes itself over the ovum as it were; the ovum becomes imbedded in the serotina, and the reflexa is merely the superficial portion of the serotina. The serotina proper is the deep portion.*

We consider the human ovum to be an imbedded one, not attached to the serotinal epithelial surface, and with the epithelial folds of the serotina arching over it to form the so-called reflexa, but one actually growing in the substance of the serotina. This idea of an imbedded ovum is of great interest in relation to the development of the placenta in other mammals, but we defer consideration of this point.

3. *The probable reason why the human ovum grafts itself, as a rule, within a certain area of the genital tract.*

It is a remarkable fact that the human ovum grafts itself normally in a definite and limited area. This area is the triangular surface of the mucous membrane of the body of the uterus, and is bounded below by the os internum, above by the inner openings of the Fallopian tubes. The ovum never grafts below the os internum and very rarely in the Fallopian tubes. It is also noteworthy that the ovum normally grafts itself only within the limits of that part of the mucous membrane of the uterus denuded of its superficial layer by the menstrual flow, and only rarely in the tubes which do not participate in menstruation so far as providing the menstrual discharge is concerned.

The hypothesis we now advance completely explains all the facts both as to normal and abnormal implantation that are at present at our command. It is briefly this. Suppose the human ovum cannot graft on an epithelial surface but only on connective tissue. We say suppose; but there is strong if not absolute proof for the supposition.

1. In many mammals with a bicornuous uterus it has


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been clearly demonstrated that the first result of the touch of the villi on the uterine mucous membrane is to cause the disappearance of the epithelial covering, *i.e.* the villi develop in connective tissue.

2. In the human ovum the villi have never been seen in contact with the surface epithelium of the serotina, although of course pregnant uteri in the very earliest stages have not yet been obtained.

3. The villi of the human ovum have always, in the earliest stages as yet obtained, been seen developing in connective tissue.

Under our hypothesis we understand at once—

1. That menstruation denudes the surface epithelium in the special area for safe-grafting of the ovum.

2. That the ovum, even if fertilised in the Fallopian tube, cannot graft itself there, as the epithelium is intact.

3. That it may graft itself in the Fallopian tube, if the epithelium has been removed by disease and the connective tissue laid bare.

4. The decidua reflexa is at once explained.

In the six weeks' pregnant human uterus, and also in a five months' one, we found at the tips of the villi active phagocytic cells, analogous to those in the villi of the hedgehog, rabbit, and rat, credited with the power of active absorption of epithelial and connective tissue.

It is therefore possible that, as Hubrecht supposes, we get a process in the early stages of human pregnancy analogous to the hedgehog, *i.e.* the early epiblastic covering of the ovum grafts itself on a fully formed serotina, destroys the epithelium, embeds itself in the serotina, which closes over it, thus forming the reflexa; and that the villi and intervillous spaces form as in the hedgehog. There are, however, additional facts in regard to human pregnancy, considered as that of the pregnancy in the highest mammal, which must be taken into account in forming a hypothesis. These are—(1) the occurrence of menstruation, which denudes a certain area of the genital tracts of its epithelium monthly; (2) the great danger of Fallopian tube pregnancy; (3) the non-occurrence of pregnancy during suckling when no menstruation goes on.

We have therefore put forward, as a mere working theory, the hypothesis that the human ovum can only graft on connective tissue, a view that can be added as it were to Hubrecht's speculation.

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For additional literature, see Minot.

DESCRIPTION OF PLATES III., IV., AND V.

The following letters are used in all the figures with the same meaning :—

ep. = epithelium.
c.t.c. = connective-tissue corpuscle.
c.t.f. = connective-tissue fibre.
m. = mitotic figure.
b.v. = blood-vessel.
l. = leucocyte.
r.b.c. = red blood corpuscle.
deg. dec. = degenerated parts of decidua.

Fig. 1.—Six weeks' pregnancy, human ; a section at the point where the decidua reflexa joins the decidua vera and decidua serotina.
a. = amnion ; *ch.* = chorion ; *ch.v.* = chorionic villi, with intervillous space ; *v.* = villus ; *d.r.* = decidua reflexa ; *d.v.* = decidua vera ; *com.l.* = compact layer ; *sp.l.* = spongy layer ; *mus.* = uterine muscle ; *gl.* = gland ; *dil. gl.* = dilated glands of spongy layer.

Fig. 2.—Transverse section of a villus from placenta of human six weeks' pregnancy. Obj. Zeiss. DD. Oc. 4.

Fig. 3.—Part of a villus from placenta of human four months' pregnancy. Obj. etc. as in fig. 2.

Fig. 4.—Part of a villus from human full-time placenta ; *d.n.* = mass formed of degenerated epithelial nuclei. Obj. etc. as in fig. 2.

Fig. 5.—The two layers of epithelium clothing the villi of human six weeks' pregnancy. Obj. Zeiss. Apoc. 2·0 mm. hom. imm. Comp. Oc. 8.

Fig. 6.—Ectoplacenta ("trophoblast") of eight days' pregnancy (rabbit), in its relation to the uterine epithelium ; *d.m.ep.* = degenerated maternal epithelium ; *ect.* = ectoplacenta, at *a.* passing down to become continuous with the rest of the epiblast. Obj. Zeiss. Apoc. 2·0 mm. Comp. Oc. 4.

Fig. 7.—Trophoblastic (?) epithelium at the extremity of villus in six weeks' pregnancy (human). *y.d.c.* = young decidual cells ; *d.b.v.* = blood-vessel with degenerated walls ; *d.c.* = degenerated decidual cells ; *o.l.* = degenerated outer layer of fœtal epithelium. Obj. etc. as in fig. 6.

Fig. 8.—The same, from four and a half months' pregnancy. *b.m.* = basement membrane. Other letters, Obj. etc. as in fig. 7.

Fig. 9.—Part of the trophoblastic epithelium from a section similar to that represented in fig. 7. Obj. Zeiss. Apoc. 2·0 mm. Comp. Oc. 8.

Fig. 10.—Epithelium from a uterine gland in the serotina immediately underlying the villus drawn in fig. 9, under the same power, for comparison. *cil.* = remains of cilia.

Fig. 11.—Epithelium covering the decidua vera in six weeks' pregnancy. *d.c.* = decidual cells. Obj. etc. as in fig. 6.

Fig. 12.—Thrombosed vessel from serotina of same case, surrounded by forming decidual tissue. *fib.* = fibro-blasts ; *deg. w.* = degenerating vessel wall. Obj. Pillischer ¼. Oc. 2.