The Ætiology of Eclampsia and Albuminuria and their Relation to Accidental Hæmorrhage.

(An Anatomical and Experimental Investigation.)[1]

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THE study of eclampsia (and the albuminuria of pregnancy) can be carried out from two points of view, the *clinical* and *anatomical*, which concerns itself with a description and interpretation of the symptoms and the morbid changes present, and the *experimental*, in which an attempt is made to reproduce these symptoms and morbid changes in the lower animals. The investigations here recorded were, to begin with, carried out along clinico-anatomical lines. From these preliminary studies there soon emerged an experimental line of inquiry. As a matter of fact, this was entered upon as a necessary test of the validity of the conclusions to which the preliminary investigations had led.

Within recent years most of the investigations into the cause of eclampsia have issued from the belief that the placenta is the most likely source of a poison, which all are convinced is the cause of the disease. There can be no doubt that pregnancy is the cause of eclampsia and that the poison is, at any rate, in its ultimate origin to be traced to the child or to the placenta. That it is not the child is proved by its occurring in cases of hydatid mole, where there is no fœtus. This leads inevitably to the conclusion that the direct or indirect source of the poison resides in the chorionic elements. That the relationship between the uterine contents and the toxæmic states is a very direct one is shown by their frequent immediate cessation after the emptying of the uterus, or after the intra-uterine death of the fœtus. On the other hand, even when the child dies *in utero*, the toxæmia may persist until the child and placenta are delivered. It would in such cases seem clear that the death of the child (the macerated state of which at delivery testifies to the time when this death occurred) must, by the consequent thrombosis of the vessels, prevent any poison which might have been produced in it from being conveyed to the placenta. The placenta, therefore, in such a case, must be the source of the poison; and to my mind, the only

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interpretation legitimate under such circumstances is that, although the placenta usually becomes detached from the uterine wall when the child dies, it may in some cases remain fixed. When this is so, it will continue to pour into the blood-stream the toxic materials and thus perpetuate the condition which killed the infant. We thus see that an analysis of apparently irregular and irreconcilable data leads to a simple explanation.

It is impossible to gainsay the fact that there is an intimate and perfectly direct association between the uterine contents and the toxæmia. One fact, however, apparently inconsistent with such a view, is *post-partum* eclampsia. In about 20 per cent. of cases eclampsia occurs after labour. The great majority occur on the first day, and probably within a few hours after labour. No matter how we would explain these cases, we must inevitably start by admitting that something of a chemical nature has been left behind after the birth of the child and the placenta. We thus see that any experimental investigation into the cause of eclampsia must concern itself primarily with the attempt to isolate from the placenta (not from the child) some chemical substance that can reproduce the changes in animals.

Relation between Albuminuria and Eclampsia and Placental Disease.

It has for long been recognized that there exists a definite association between the toxæmic states and placental disease. On the other hand, infarcts of the placenta are not infrequent in cases where there is no sign of toxæmia. They are more likely to be present in the last two months of pregnancy, and Eden has suggested, with great reason, that they are to be looked upon as signs of senility in a short-lived organ. Their relative frequency has been differently stated by different authors. Meyer found them in 2 per cent. of 1,124 placentæ, Rossier in 17½ per cent. of 1,174, whilst Whitridge Williams found white infarcts, measuring 1 cm. or more in diameter, in 63 per cent. of 500 placentæ. Such figures, though exhibiting a wide margin of difference, leave no doubt regarding the relatively high frequency of the condition. On the other hand, there can be equally little doubt that these changes are associated in some special manner with the toxæmias, albuminuria and eclampsia. In Rossier's figures given above 54 of the women suffered from albuminuria, and, in these, infarcts were three times more common than where the urine was healthy. In Meyer's patients, where albumin and

casts were present, infarcts were four times more frequent than where there was a normal urine. Fehling found them in 50 out of 91 albuminuric patients. "It is accordingly apparent," says Whitridge Williams, after stating these figures, "that the majority of investigators, who have busied themselves with the subject, believe that a marked relation exists between albuminuria on the part of the mother and infarct formation in the placenta." The infarcts, which are of greatest importance in this respect, are those of the recent or red variety. It is with them that albuminuria is especially associated. White infarcts, as such, seem to possess little clinical importance. Out of 7 cases of eclamptic placentæ examined by myself, there were massive red or purple infarcts in 5, whilst out of 6 cases of severe albuminuria, there were similar structures in 3. That is, in 13 toxæmic placentæ there was recent placental disease, evident to the naked eye, in 8—i.e., roughly 60 per cent.

"What is the meaning of this obvious association between placental infarction and the toxæmias?" is a question that has often been asked. Most workers admit that it is impossible to explain this relationship satisfactorily, or they attribute it to the action of the general toxæmia, of which the albuminuria is an evidence. For example, Eardley Holland, whilst admitting that infarcts are more frequent in albuminuria and eclampsia, says that "they may be looked upon as the result of a chronic toxæmia; as to their connexion with eclampsia, they are merely accompaniments, not consequences. The presence of these chronic degenerative changes in eclamptic placentæ has been investigated by Brindeau and Nattan-Larrier, who give them no special significance." Whitridge Williams, in a summary of the position, in so far as he could interpret it, said "marked infarct formation is not infrequently observed, and often results in the death or imperfect development of the fœtus. It is usually associated with albuminuria on the part of the mother, though at present we cannot account satisfactorily for the relation between them."

Placental disease of this kind has been usually looked upon merely as an accompaniment or as the result of the toxæmic state. So far as I know, no serious attempt has been made to regard the placental disease as the cause of the toxæmia, and this in spite of the fact that there is, in all the evidence which has accumulated through the years, not one single item which is logically inconsistent with such an interpretation.

It *is* true, then, that placental infarction may be present without any evident toxæmia. It is also true that there may be a severe toxic condition, and no evident change in the placenta. It is the very readiness

with which the truth of these statements can be proved that has, in my belief, obscured the real nature of the relationship. To complete the statement of this relationship, where there is massive recent infarction there is always a toxæmia.

The meaning of this apparent paradox will become apparent when I say that, after I had been working at the subject for some time, studying the placentæ in their clinical relationships, I discovered that, *if there is an acute toxæmia ending rapidly in labour, the placenta may present evidence of disease, or it may look perfectly normal to the naked eye. If, on the other hand, the acute attack passes off and labour only supervenes, say ten or fourteen days after, we find extensive recent necrosis. Plate I, fig. 2, is a good example of such a case. This important finding at once suggested that it is the recent autolytic changes in the affected organ that generate the poison.* As I shall show, this conclusion from anatomical data is completely supported by the experimental results. It is this that explains why, in an albuminuria which becomes established gradually and persists for some time, one is more likely to find marked placental disease. *It is just the comparatively slow involvement of the placenta that allows of the continuance of the pregnancy and the evolution of the infarcted regions. Where there is a sudden and extensive involvement of the placenta, the toxæmia is so fulminant that the pregnancy ends before any naked-eye changes in the placenta are produced.* The import of these statements will emerge in a clearer light later when the experimental work is entered upon.

It should be remembered that the placental organ is unique in the sense that, if a part of its substance undergoes necrotic changes, the degenerating patch is a massive poison focus bathed all round by circulating maternal blood. A ready access into the systemic circulation of any toxic material is thus allowed. There is no other region in the body where such a condition of affairs could obtain.

It is easy to understand that a comparatively small placental disease may occur without any untoward effect. Under these circumstances the absorption of toxic products from the dying patches is so gradual, and, at any one time, so small in amount that it is tolerated. Where, however, this normal and limited change becomes excessive there is a pouring into the maternal circulation of more poison than the system can safely deal with. Such an explanation accounts at once for the presence of the toxæmia, where the placental disease is marked. I contend that it is a much more logical one than to suppose that the toxæmia develops independently and acts upon the placenta by

hurrying up and exaggerating a process that is so common in a smaller degree as to be almost normal. The one view is an explanation of a relationship, the other is meaningless, except as the statement of an extraordinary coincidence.

Mild degrees of albuminuria are common in pregnancy, and may well be due to those cases of comparatively small placental involvement. An explanation, on the lines I have laid down, accounts likewise for the chief time incidence of the toxæmic states we are considering being in the last two months of pregnancy, just the time when the senile changes in the placenta are most likely to be in evidence. It accounts also for the very frequent cessation of the symptoms with the intra-uterine death of the child and the detachment of the placenta. This circumstance is due to the fact that the separation of the placenta withdraws the poison-laden foci from the maternal blood-stream, and the protective mechanism thus initiated is continued by the blocking of the open mouths of the maternal vessels by the thrombosis that quickly occurs.

The Cause of Placental Infarction.

(*I*) *General Anatomical Considerations.*

The placenta is a temporary structure, and is so constructed that it can come away readily during labour. It is only so closely incorporated with the uterine wall that shearing on this wall is prevented. As a matter of fact, naked-eye examination shows that all that serves to bind placenta to uterus are a number of thin films of decidua. As I have shown in another place, there are, in the uterine mucosa, none, or practically none, of the supporting elements, such as muscle, elastic tissue, &c., which are found in other regions. Derived as it is from the mucosa the same applies to the decidua. The vessels lose these supporting coats as soon as, or nearly as soon as, they enter the placenta. This fact must also be considered in relation to the loose connexion which is necessarily present between placenta and uterine wall.

If we examine the placenta still attached to the uterine wall, it is found that the thin decidual films, which attach the placenta, bridge across large venous channels. In point of fact, the placenta seems to rest almost entirely on a greatly expanded blood lake, broken up into individual spaces by the bridging sheets. Even to the naked eye one can see these spaces opening on the one side through the placental surface into the intervillous space, and, on the other side, becoming

continuous with the sinuses in the muscular wall of the uterus. On the placental side the blood spaces are lined by a thin layer of compact decidua. As we know, from microscopic examination, this thin layer is complete practically all over the placental surface. Where the vessels perforate the placenta it is absent, and, in addition, here and there, comparatively large tracts on the surface may be seen where the villi dip straight into the blood spaces. It is through such openings that Veit believes there may be a wholesale "deportation" of villi into the maternal blood-stream. The separation of the placenta is rendered easier by an interesting change which occurs in the decidua. This consists of an œdematous loosening of the tissues, and is often seen in separated placentæ just under the compact layer (fig. 1), as also in the decidual plugs that extend from this layer into the substance of the placenta.

This arrangement between placenta and uterus is ideal from the point of view of ease of separation, but it obviously also means a ready tendency to vascular disturbance. There is a very loose organic binding, and to all intents and purposes the placenta merely rests against the uterine wall. When the child is expelled the retracting uterus grasps and expels the placenta, the soft decidual fixing strands offering practically no obstacle. During pregnancy there is nothing to disturb the placental fixation. It is known that the uterus contracts intermittently, but this can do nothing but empty the placenta of its blood. The liquor amnii will disseminate the tension equally over the uterine and placental surfaces, and it is likely that the constantly recurring intermittent uterine contraction, by expressing the placenta at definite intervals, leads to a heart-like, pumping action. The placental blood space is, in a sense, a greatly expanded maternal vessel. When a decidual vessel pours its blood into this a great diminution in velocity and force must take place, just as occurs when a river pours its waters into a lake. This circulating speed will become less and less as the small stream issuing from the vessel passes further and further into the placental blood lake and becomes wider and wider. The flowing force, therefore, in this space, derived from the *vis a tergo* of the general circulation, must be extremely low, and for an efficient passage of the maternal blood throughout and away from the placenta other factors must come into play. The recurring systole and diastole of the uterine muscle must, by exercising respectively a compression and a suction action, play an important part. We can imaginatively recognize the necessary existence of other factors. Thus, the villi are

FIG. 1.—Placenta from Case of Albuminuria. Shows recent retro-placental clot subtended accurately by a recent infarction, which is marked off from the surrounding placenta by its darker colour and solid appearance. There is a suggestion of a "capsule." This really means a commencing disappearance of the hæmoglobin in the blood-cells, a change which, in one part, has occurred to such an extent as to produce a pale infarct.

FIG. 2.—Placenta in Case of Eclampsia. In one part a large purple or recent infarct is seen, with no naked-eye indication of how it has been formed. At another region a retro-placental clot is seen surmounted by an older infarct: the colour is becoming paler, the solution of hæmoglobin being most marked at the periphery. This gives the appearance of a "capsule." This fig., therefore, shows two stages in the infarction process. By the time the pale stage, and perhaps even the purple stage are reached, the toxic products of necrosis have diffused into the blood circulating freely round about in the healthy placenta.

PLATE I.


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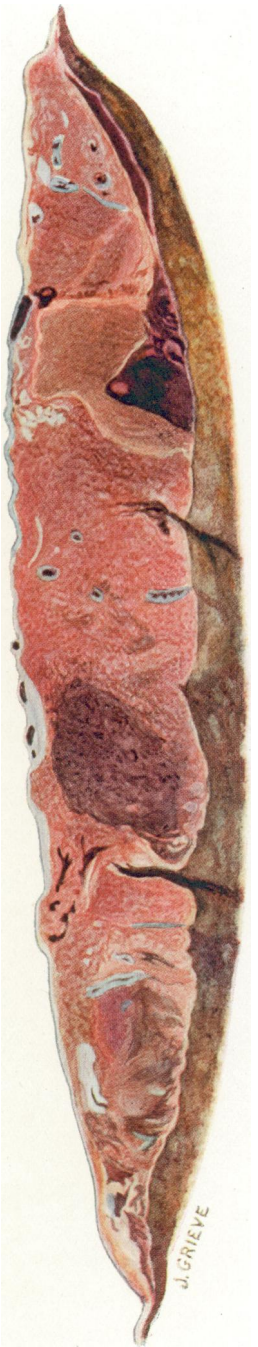
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greedily absorbing fluid from the circumambient blood, and this must entail a continual mass movement of the blood in the space. Then, the taking up of oxygen and the other ingredients in solution in the blood, and the giving out of waste products, must mean a constant chemical alteration in the blood with constant diffusion currents backwards and forwards of the respective chemical ingredients in an effort to readjust the equilibrium.

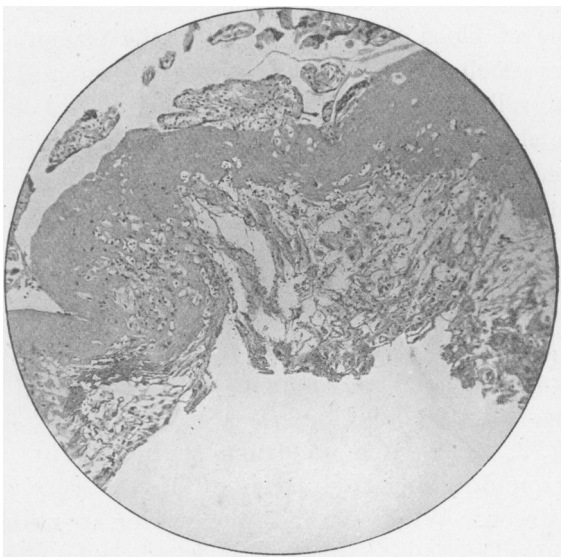


FIG. 1.

Decidual surface of placenta. Villi are seen above, then the thin compact decidua, and under this the loose decidua at the line of cleavage.

(*II*) *Changes Present in Localized Placental Death.*

Every person who has studied even a small number of placentæ is familiar with the so-called white and red infarcts. These consist of cubical, wedge-shaped, or irregular, sometimes sprawling, areas of yellowish or reddish tissue, which have lost the normal spongy appearance. They are firm in consistence. In the great majority of cases they lie with their base against the decidual surface. Sometimes an infarct may, at first sight, seem to lack this relation to the decidua, and to be embedded in the centre of the placenta or even to lie up against the chorion. In the majority of cases, however, on tracing the sections of the infarct, it is found to strike the decidua at a broad base. The

oblique position of the infarcted region is what led to the erroneous first impression. In my experience, this decidual relation is so constant that it clearly must be considered as of great value and importance in any attempt to throw light on the causation of the condition. Many infarcts of the red or purple variety are difficult or impossible to recognize in the fresh placenta. When the placenta is put into fixing solution the blood quickly oozes from it, because in the healthy intervillous spaces it does not clot. (This it is which explains how rarely we find the villi embedded in blood in microscopic sections of placenta.) With the escape of blood the cut surface of the placenta, where it is healthy, becomes much paler. The diseased areas remain dark, and are thus thrown into relief against the paler background.

One fact which has emerged clearly from my investigations is that the various appearances included under the term "infarct" are different stages in one and the same process and not, as is often stated in the text-books, independent pathological states.

(1) In the earliest stage recognizable to the naked eye the patch is deep red, purple, or even black. *It may not be visible till thrown into relief against the surrounding paler placenta, which has lain for some days in the fixing solution, into which the unclotted blood in the intervillous spaces has oozed.* This stage is seen in Plate I, figs. 1 and 2, and Plate II, fig. 2. The patch stands out distinctly, and is sharply cut off from the surrounding, healthy placenta. In the very earliest stage this is all that is seen. When less recent, however, it is edged all round by a kind of capsule, seen on section as a thin whitish or yellowish streak (Plate I, fig. 1). Throughout the patch, black points and rounded spots are often visible, corresponding to blood in engorged villous vessels. In this stage the spongy character, though partly lost, has not quite gone.

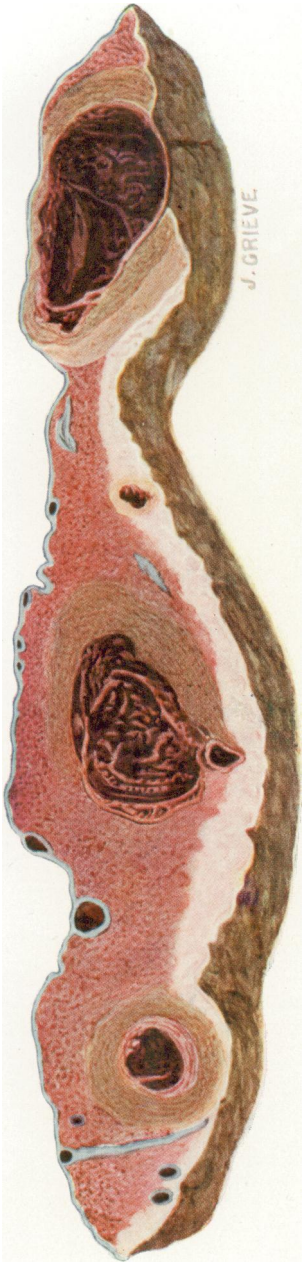
(2) In this stage the colour becomes lighter. The dark red or purple becomes dusky brown, chocolate-coloured or brick-red. The spongy character of normal placental tissue has disappeared, and the patch cuts solid, the section showing a smooth surface all over (Plate II, fig. 1).

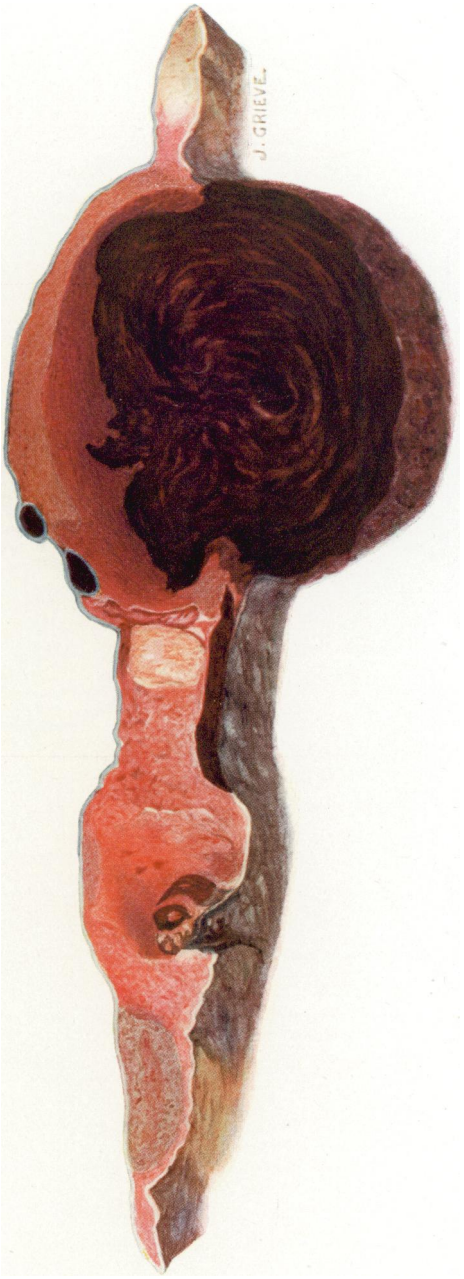
(3) In the older infarcts the colour becomes progressively lighter. The dark brown of the preceding stage becomes light brown, yellow, and then sometimes almost pure white.

That such a description of infarcts is the true one is proved by the fact that one can find, often in the same placenta, all the various stages between the earliest, purple, and the latest, white, stages. In Plate I, fig. 1, is shown a large infarct surmounting a large clot. That it is not quite recent is shown by the yellow "capsule," and by the fact that one

FIG. 1.—Placenta from Case of Severe Albuminuria. Hæmorrhages partly retro- and partly intra-placental, surrounded by areas of necrosis imbedded in and surrounded by healthy placenta. Note how accurately the infarcts are related to the clots, an appearance which indicates that the necrosis is due to the interference with the maternal blood supply consequent on the hæmorrhage. The infarcts are fairly recent, corresponding to the intermediate stage. Towards the periphery of one infarct, however, the colour is becoming paler, due to the solution of the hæmoglobin. On one side of the central clot the placenta is healthy, the nourishment here being maintained.

FIG. 2.—Placenta from Case of Acute Toxæmia. Large retro-placental clot (accidental hæmorrhage) is seen, subtended accurately by a deep red or recent infarct. This is clearly formed as the result of the interference with the maternal blood supply in this part. To one side a smaller old infarct, and further along an infarct of recent formation, though beginning to become pale, are seen.





YOUNG: Ætiology of Eclampsia and Albuminuria. Plate II.

part has passed into the pale stage. No doubt if it had been left the whole infarct would soon have become similar in appearance.

What is the explanation of these changing colours? Why is the later stage pale whilst the early is dark? The first explanation that suggests itself is that it is associated with an alteration in the blood contained within the affected portion. That such is the case is proved by a microscopic examination of the various phases. To begin with, the villi are engorged throughout, the thin-walled capillaries in the small villi and the thicker vessels in the large villi are greatly expanded and are tightly packed with blood cells. In the small villi the vessel expansion may be so extreme that the stroma has become displaced to the periphery and there intervenes between the blood in the villi and that in the intervillous space only a very thin sheet of tissue (figs. 2 and 3). The purple colour of the fresh infarct is therefore due to the villi being turgid with poorly oxygenated blood. The whole appearance in this stage closely simulates the vascular hyperæmia and stagnation which occurs in other tissues when there is any local lowering in vitality, such as might result, for example, from injury. To my mind the engorgement, which is present in the early infarction, is of a smaller origin. It is an evidence of local reaction, which precedes the local death, that is inevitable when the blood supply of the part is cut off. In the later stages the blood within the villi, and any blood present in the intervillous regions, becomes paler and paler. The blood cells absorb the staining matter less and less. The hæmoglobin becomes completely removed and nothing but the shadowy outlines of the corpuscles are seen; or there may be a crumbling process, which results in a kind of granular debris—all that is left of the original blood cells. These stages correspond to the later stages of the infarction, and demonstrate readily the meaning of the phases presented by the changing nodule. It would thus seem that one of the chemical alterations occurring in the blood pent up in the vessels consists in a change in or solution of the hæmoglobin. Müller has shown that a similar change occurs during autolysis in the lung, and Mathes has reproduced the same change in the placenta by autolysis. In my experiments on placental autolysis, which I will record later, I have noticed the same result.

In association with these changes in the vessels and stroma there are other important structural alterations in the infarcted placenta. These have been carefully described by other investigators. One of the most frequent is a somewhat remarkable one. It consists of a *close packing*

of the villi together throughout the whole or part of the infarct. In many cases the spaces between the villi are occupied, sometimes tightly, with blood cells. There may be at the same time a deposit of fibrin. This blood undergoes disintegrating changes similar to those already referred to in the villous blood. In the condition, however, which we are considering, the intervillous space is empty or nearly so, and the villi, instead of being separated from one another by comparatively wide intervals, as in the normal regions round about, have come close together. They may simply lie opposed to one another, or there may

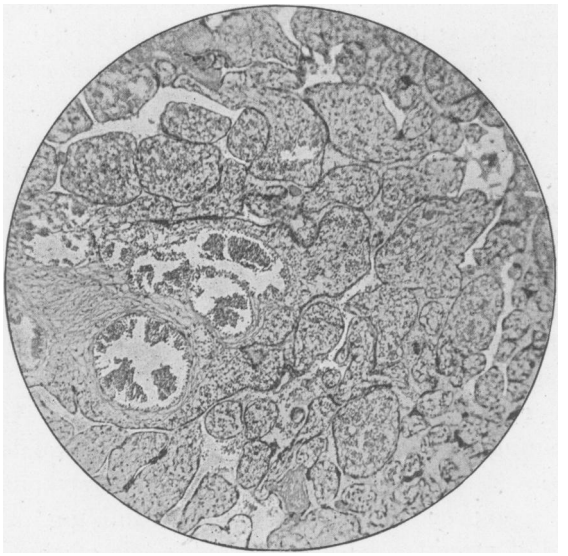


FIG. 2.

Recent (red) infarct. Villi packed together. Note the engorgement of the vessels. Case of accidental hæmorrhage without albuminuria.

be an actual cohesion or fusion of the epithelial surfaces (figs. 2, 3 and 4). In such cases the vessels are usually, as in other infarcts, greatly expanded, but not necessarily so, and the condition cannot be attributed to a general increase in the size of the villi, caused in this way, with a corresponding crowding of them together. Eden, so far as I know, first specially pointed out this rather remarkable condition, and explained it as due to a "progressive diminution of blood supply to a part of a cotyledon, by obliteration of a maternal artery [which] would cause the villi to become crowded together because

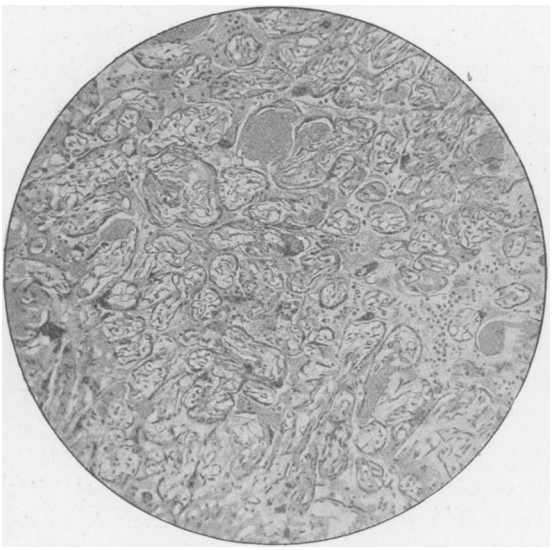


FIG. 3.

Old (white) infarct. Villi packed together. They are degenerated and poorly staining. The expanded vessels are well seen. The blood cells in these cases are pale, due to a disappearance of the hæmoglobin. Case of albuminuria.

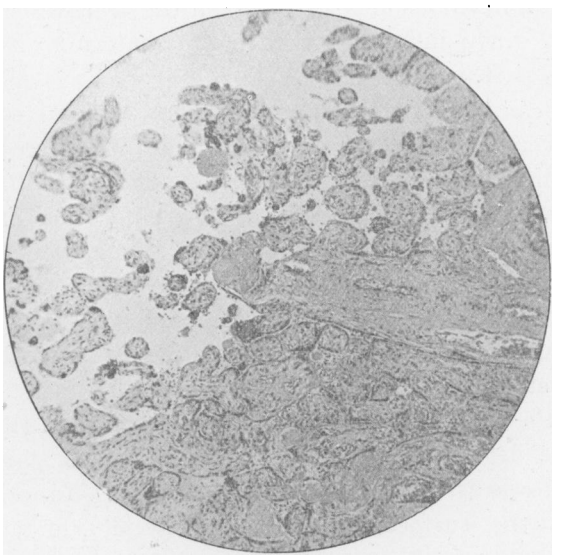


FIG. 4.

Edge of recent (red) infarct. To the right the densely packed villi are seen, to the left the healthy placenta. Case of albuminuria.

there would not be sufficient blood in the part to maintain them at their normal distance from one another." The pressure exerted by the rest of the placenta "would drive the villi together into a closely crowded, consolidated mass." This I believe to be the real explanation of the process. In other words, it must be looked upon as one of the possible changes where the local blood supply is disturbed. It will occur where the venous channels remain patent, or where the surrounding placental pressure can squeeze out the blood after obliteration of the afferent supply has taken place.

Clotting in the Intervillous Blood Space.—As I have already stated, one never finds any trace of coagulation in the intervillous space in the healthy placenta. In infarction a noteworthy appearance is the formation of fibrin, in the meshes of which red blood corpuscles are often entangled. *That this fibrinous deposit is not necessarily secondary to the changes in the villi is shown by the fact that we can often find it in conditions in which we definitely know there has been a stagnation of the maternal blood, and where the villi are healthy—e.g., accidental hæmorrhage.* As I shall show later the coagulation is primary; the necrosis, which later on occurs in such cases, being secondary. As the result of the examination of a large number of placentæ, healthy and diseased, I have convinced myself of the truth of this statement. When we find a fibrinous deposit between the villi we can be sure that there is some grave interference with the maternal circulation in the corresponding part.

The *other changes* in the infarcted regions, which result in a gradual disintegration and softening, have been fully referred to by other writers, and need not be detailed here. The epithelial layers soon show changes. In the earliest stages a proliferation of the syncytial nuclei, forming masses of darkly staining tissue, would seem to be a sign found specially and characteristically in this condition. Later on both layers of the epithelium become pale and eventually crumble away. Similar changes attack the stroma and the cells of the vessel walls. In the later stages the autolytic process results in a solution of the tissues, with the result that cavities may be formed in the centre of the infarcts. The degenerative changes often seem to start and progress most rapidly towards the centre of the nodules. In other cases they commence at the surface, as in the left-hand side of the infarct in Plate II, fig. 1, or in an eccentric position, as is shown in Plate I, fig. 1.

(III) Factors responsible for Infarction.

Whilst an understanding of the exact origin of localized placental death is not essential to my interpretation of the toxic process, I believe that the ultimate explanation of albuminuria and eclampsia must remain hidden until light is thrown on these changes. There have, in the past, been two opposing ideas regarding the origin of placental infarction :—

(1) Eden, Whitridge Williams, and others believe that it is due to a change commencing primarily in the villi themselves. Their blood supply is interfered with as the result of an obliterating change in the vessels. This leads to a degeneration of the epithelium and stroma of the villi, and secondarily to a coagulation of the maternal blood.

(2) Other investigators, such as Hofmeier, believe that the degeneration is due to an interference in some way with the maternal blood supply.

The first, and, in this country, the most commonly accepted idea naturally assumes that the villi are dependent for their nourishment upon the fœtal blood supply, and that once this is obstructed they must undergo progressive necrosis. If one could show definitely that the villous structures are independent of the fœtal blood, and, moreover, can live and proliferate when this is removed, so long as the maternal supply remains intact, it would render this explanation of the infarction process untenable. This is not difficult to do. There are several considerations which show it :—

(1) The time when the chorionic elements are most active and proliferate most rapidly is during the early stages of the development of the ovum, where there are, as yet, no fœtal vessels formed, and where the trophoblast and its villi obviously live directly upon the mother's blood.

(2) In hydatid mole the chorionic villi live, and, as we know, actively proliferate, when there is not a trace of a fœtal vessel, and when the entire nourishment is derived from the blood of the mother. The same is true of chorionepithelioma.

(3) In tubal pregnancy one can sometimes recognize the independence of the villi of the fœtal blood in a diagrammatic manner. Where there has been a considerable hæmorrhage into the extra-chorionic space great masses of villi become strangled in blood-clot. I have seen one such case where all the trunks in the neighbourhood of the chorion had undergone fibrinous necrosis, but near the tube wall, where, in parts,

the maternal circulation was unimpaired, the tips of the necrotic villi remained healthy (fig. 5).

These facts demonstrate beyond doubt that the villi, even after the fœtal blood supply is removed, can live, so long as the maternal supply remains uninvolved.

That the localized patches of dead tissue in the placenta are dependent upon an interference with the maternal blood supply is indicated by other findings of a positive nature:—

(1) As I have pointed out, in by far the largest number of cases, the infarcted areas lie in relation to the decidual surface. Moreover, in every such case one can detect degeneration, often necrosis, of the decidua. It is obvious that were infarction due to maternal causes, this is the disposition that would obtain.

(2) In large infarcts, resting upon the decidua, one sometimes can see, even with the naked eye, small nodules of healthy placenta on the outer or decidual aspect, which are obviously cut off entirely from the main part of the healthy placenta. Tracing in sections cut by the knife is sufficient to show this in such cases. This complete isolation of a healthy patch in a dead mass of tissue can mean one thing only, that whereas the remainder of the infarcted portion has lost its nourishment, the healthy nodule has retained its maternal supply. It is obvious that such a finding must be one of rare occurrence, but I have seen it twice, and in each case the healthy piece has rested against the decidua and into it healthy maternal vessels could be seen opening.

(3) *Retroplacental or Intraplacental Hæmorrhage as a Cause of Infarction.*—A consideration of the changes associated with placental hæmorrhage provides one of the most convincing proofs of the maternal origin of infarcts. Where there has been a hæmorrhage in the decidua serotina or into the placenta itself, there will be apt to be a local deprivation of the corresponding part of the placenta. The discovery of necrotic changes in these regions would be strong confirmatory evidence of the thesis I am trying to prove. As a matter of fact, it was the almost accidental discovery of this evidence that first convinced me of the fallacy of the usual explanation. One of the most surprising features of this investigation has been the great ease with which such evidence, and that of an unequivocal nature, has been obtained when it was looked for.

Where a retroplacental hæmorrhage is not quite recent one invariably finds the adjoining placenta diseased. The extent to which the necrotic process has gone depends upon the time during which the

circulation has been cut off. Over old clots we see old, yellow, or white infarcts, whereas over young clots the infarction process is only in an early stage. Over clots of recent formation it may only be recognized on careful examination with the unaided eye, or it may not be evident without microscopic examination. In the earliest stages recognizable to the naked eye it consists of a deeply stained purple or dark brown patch, often difficult to recognize until the blood has been allowed to diffuse from the adjacent healthy placenta. In Plate I, fig. 1, this appearance

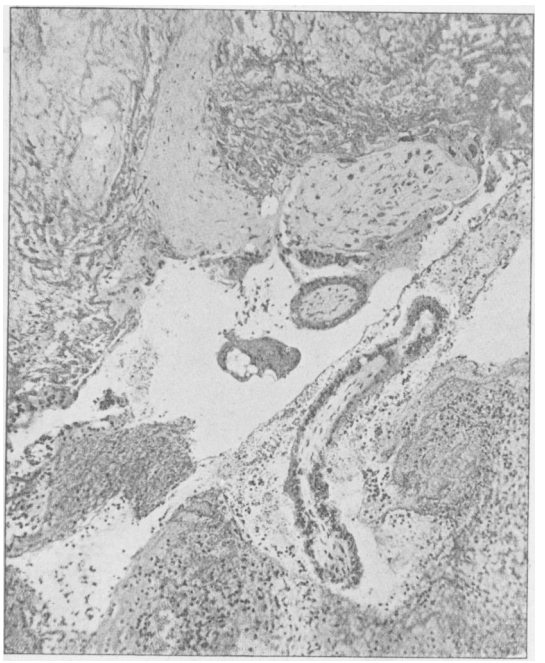


FIG. 5.

Tubal pregnancy. Above, the necrotic villous trunks are seen strangled in blood-clot. Below, the tips of the same villi are seen to be healthy where they lie in spaces in which the maternal circulation is maintained.

is shown. The necrotic area was at first difficult to recognize. It is seen to be not quite recent, because it is sharply outlined by a pale yellowish margin. Figs. 6, 7 and 9 show infarcts subtending retro-placental clots (*see* also Plate II, figs. 1 and 2).

In view of what I have said there can be little doubt that we are here brought face to face with an infarct in the making. The objection

that might be urged, that the hæmorrhage is secondary to the necrosis, is disposed of by the appearance, a common one, seen in Plate II, fig. 1. Here the solid infarcted portions are seen closely and accurately nestling round the clot. If the necrosis had been primarily developed it is obvious that any bleeding into the placenta would not have chosen to so displace the solidified tissue. It would have found much less resistance in the loose retroplacental decidua.

As is well known, hæmorrhage in the placenta is commonly associated with toxæmic states. Not infrequently, in fact almost always, one finds masses of blood-clot of varying age adherent to the maternal surface. The possible ætiological importance of these clots, to which formerly little attention has been paid, will be evident from the statements just made, and this ætiological significance will be seen to force itself upon us even more clearly when we study the conditions that obtain in accidental hæmorrhage. The bleeding, in the cases we are dealing with, is most frequently retroplacental. Over the blood there is a thin layer of compact decidua, which is invariably necrotic, when the condition has been present for a sufficient time. In other cases the bleeding may be within the substance of the placenta. Here again such clots are often surrounded by a necrotic layer of placenta (Plate II, fig. 1).

Whilst the observations I have just recorded are amenable to one interpretation only and supply us with evidence proving that, in these cases, the necrotic placenta is dependent upon an involved maternal circulation, in many cases, in fact the majority, we do not find this unmistakable evidence. It is true that the majority of infarcts are related to the decidual surface, but in many it is impossible on naked-eye or microscopic examination to be sure of their exact mode of origin. The decidua is usually diseased and the vessels are thrombosed, but these changes might quite well be, considered in themselves, secondary, and have usually been so considered. A little thought, however, will show that a very likely explanation of the hæmorrhage in the decidua, to which I have called attention, would be blockage of the decidual veins or the veins in the muscular wall—e.g., by thrombosis. This, in the presence of a free arterial supply, would tend to a backward pressure in the thin venous channels and would readily account for a hæmorrhagic escape, situated as they are in a soft unsupported decidua. Such an explanation has been actually advanced by Veit as the cause of the retroplacental bleeding in accidental hæmorrhage, though he has attributed it to a blockage of the veins by masses of deported villi and

not to thrombosis. Be this as it may, I believe that the almost certain factor operating in these cases is a blockage in the veins, and the frequency with which thrombosis is found in the decidual vessels and veins of the muscular coat suggests rather that the responsible agent is an excessive occurrence of this change, which is so frequent during the later months that it may almost be considered normal (Friedländer). Where the vein also is blocked hæmorrhage will be the result. But this will only be one way in which the vascular changes will manifest themselves. *If there is a blockage of the artery, anæmia of the corresponding part of the placenta will occur* and this will be the only sign of the vascular involvement. That such is a very common factor in infarct formation is shown by the fact that a majority of the infarcts in my specimens show a close packing together of the villi into solid masses containing no blood in the intervillous space, *as if a kind of collapse has occurred subsequent to a cutting off of the entering blood*, just as collapse of the lung follows obstruction of a bronchus (figs. 6, 7, 8 and 9).

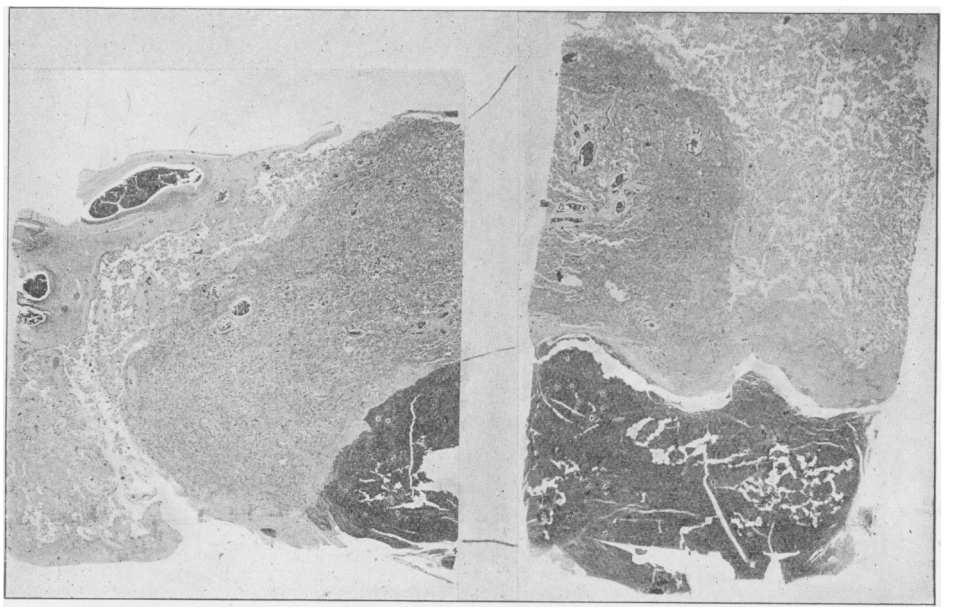


FIG. 6.

Recent (red) infarct accurately subtending retroplacental hæmorrhage. Shows dense packing of villi. The naked-eye appearance of this infarct is shown in Plate I, fig. 1. Case of albuminuria.

We may now summarize in a few words our conclusions regarding the origin of infarcts. In the first place, there can be no doubt that the chorionic elements are dependent immediately and directly upon the maternal blood for their nourishment, and can live and flourish where the fœtal blood is absent. This fact renders untenable the belief that infarction is due to an obliterating change in the vessels of the villi. A recognition of this fact leads inevitably to the conclusion that

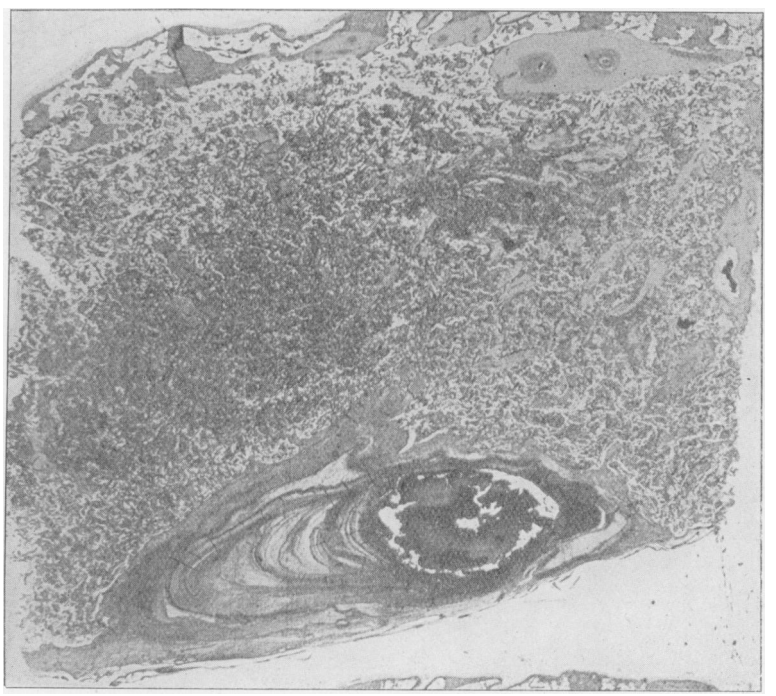


FIG. 7.

Recent infarct (invisible to naked eye in fresh placenta). The early stage of the consolidation process is seen in a region where the blood supply is cut off by thrombosis in the underlying vessel. Case of eclampsia.

necrosis in the placenta will occur if the maternal blood supply is interfered with. I have shown that we can often find direct and undoubted evidence of such necrosis occurring in regions where there has been an arrest in the corresponding maternal supply of blood. Where there is an obstruction in the vein or veins hæmorrhage will be more likely to occur and will act as a signal post indicating the presence

of the obstruction. Where the artery or arteries are involved, alone or in conjunction with the veins, anæmia of the part of the placenta concerned will occur, followed again by necrosis. In such cases it may be difficult to find absolute anatomical proof of this mode of origin, but we may glean hints of its occurrence by a careful examination of the changes.

Remarks on the Maternal Circulation in the Placenta.

The observations I have just recorded indicate the fallacy of the usual idea regarding the circulation in the placenta. This is usually considered to be so free throughout, that any interference in one part is

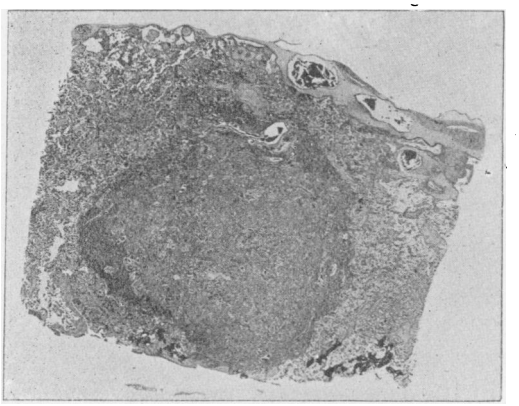


FIG. 8.

Recent (red) infarct. Shows consolidation process well advanced. In this there is no sign indicating how the maternal blood supply has been cut off. This information is often absent. Case of eclampsia.

quickly made good by an inflow from the adjacent regions. The placenta is not to be looked upon as a loose sponge in which there is a kind of irregular mingling of the maternal blood. So far is this from the truth that I believe it more likely that, just as in other tissues, each portion is supplied by certain maternal vessels and relies on them entirely for the nourishment. By injecting some colouring matter into the centre of an isolated lobule one can easily satisfy oneself of its isolation from the adjacent placenta, so far as its blood supply is concerned, for only with great force can we drive the fluid beyond it into the other parts. We can easily understand that this must be so, when we

remember that, in the natural state, the fissures between the cotyledons are occupied by solid columns or partitions of decidua, which often run up throughout the entire thickness of the placenta. During separation these septa are left attached to the uterine wall. The separation is rendered easy in these regions by the œdematous loosening of the decidua immediately under the compact layer, which occurs in the later weeks of pregnancy, and to which I have already alluded. Not only are the cotyledons independent of one another so far as their vascular supply is concerned, but differing parts of the same cotyledon are dependent on different vessels for their nourishment. In each of these areas there is a complete circulation, though, at the boundaries of such circulatory systems, it is probable that there is a mingling of the bloods.

Relation between Accidental Hæmorrhage and the Toxæmias.

Accidental hæmorrhage is a subject of great importance in connexion with the thesis I am attempting to establish. The evidence which it provides is pertinent to the discussion and is even more convincing and less confusing than that to which attention has been directed on the preceding pages. In accidental hæmorrhage we have a retroplacental bleeding, which occurs with greater or less rapidity and leads to a corresponding amount of placental detachment. It must be considered as merely an exaggeration of the hæmorrhage in a similar site, which is fairly common in the last weeks of pregnancy. There are all grades between the smaller hæmorrhages (Plate I, fig. 1), through the comparatively large bleeding shown in Plate II, fig. 2, up to the condition we are considering, where there is an excessive loss of blood. The special interest which this condition possesses for us resides in its close relationship to the toxæmias, albuminuria and eclampsia. Its affinity with albuminuria has been recognized since it was pointed out many years ago by Winter. Its relation to eclampsia was referred to by Essen-Möller in a contribution to the recent International Congress in London. Essen-Möller reported two cases from his own clinic which were associated with eclampsia. Seitz has recorded two, Winter one, Harry one, and Hartmann two. Moreover, Bar and Kervily have found in one case, where there were no fits, degenerative lesions in the liver similar to those present in eclampsia. (I quote these references to the literature from Berggren's paper.) Whilst this is so, one thing emerges clearly from the investigations on this relationship and is expressed by several

of the authors—namely, that *it is impossible to look upon the toxæmia as the cause of the bleeding. For, in a large number of the cases, there is no trace of a toxic state.* For instance, in eight cases collated by Berggren, albuminuria was present only in four; in Zweifel's twenty-one cases there were thirteen cases without albuminuria. Essen-Möller brings out this same fact in a striking way. In 7,000 accouchements at the University of Lund, albuminuria was observed in 11 per cent., whilst accidental hæmorrhage was observed in only 0·45 per cent. He therefore says that "if albuminuria is a cause of retroplacental hæmorrhage, it is a cause of no great activity. But it is equally necessary to consider it from an opposite point of view. Out of my twenty-nine cases eleven showed albuminuria, and this figure rises to seventeen if we include cases with a trace only. So that whilst albuminuria is seen in only 11 per cent. of confinements, it is seen in 37 to 50 per cent. of cases of accidental hæmorrhage. It therefore seems to me that we can draw from these facts a second conclusion—namely, that the frequency of albuminuria in retroplacental hæmorrhage suggests something more than the idea of a coincidence pure and simple."

Such a condition of affairs, otherwise an admitted mystery, is readily explained in terms of the interpretation of the toxic states which I have already advanced. In accidental hæmorrhage we obviously have a corresponding part of the placenta cut off from its blood supply. If the hæmorrhage develops and extends so rapidly that it quickly kills the patient or determines a complete separation of the placenta, either naturally or by the interference necessitated in the patient's interests, there will be no opportunity for the necrotic changes to develop and there will be no toxæmia. The nature of the condition is such that termination in one or other of these ways must be common, and readily accounts for the fact that in about 50 per cent. of such cases there is no toxæmia. But, if the placenta remains attached at one part for some hours or days, the circulation there will remain undisturbed, and there will be an opportunity for the discharging into the maternal blood of the toxic ingredients, quickly elaborated by the disintegration of the separated portion. Only in such cases will an albuminuria or an eclampsia develop. As in the retroplacental hæmorrhages of smaller amount, so here it is easy, in cases where the blood-clot is not quite recent, to demonstrate the infarction changes in the severed portion or portions. The degree to which the change is manifest depends on the time that has elapsed since the bleeding occurred. I have had an opportunity in my specimens of recognizing only the earliest stages.

When present they are, however, distinct. On some occasions they have been found only after microscopic examination in a placenta that looked quite healthy to the naked eye. The discovery of these changes must be looked upon as strong confirmatory evidence in support of the truth of the reasoning which had foretold their existence. I shall refer, later on, to the question of the ætiology of accidental hæmorrhage, in so far as we have facts that permit of such an investigation.

I regret that a complete clinical history, so far as albuminuria is concerned, was obtained in none of my specimens. Whilst this would have given added interest to the discussion it is, however, not essential. For the study of the anatomical changes in accidental hæmorrhage I have had one complete uterus, to which the placenta is still attached, and eight placentæ, as well as pieces removed from the uterine wall from four cases of fatal accidental hæmorrhage.

Changes in the Placenta.

The alteration in the placentæ varies with the age of the clot and the amount of separation that has occurred. In one case, in which there was not much hæmorrhage, there was no albuminuria. The labour ended soon after the first onset of the bleeding. In it an interesting appearance was found. The blood-clot was quite fresh. The placenta was examined soon after removal, and it was noted that the part of the placenta (about a quarter of the whole) that had been severed from the uterine wall was deeply congested as seen from the amniotic surface, the remainder being quite pale. This appearance corresponds to the earliest stage of the degenerative process, which is characterized by an expansion of the vessels in the villi. It would seem to be analogous to the congestion that occurs round an infarct in other parts of the body. The unaffected vessels undergo a rapid engorgement after the cutting off of the blood to the affected part. In the placenta the vessels of the villi, in which the circulation is primarily uninvolved, undergo a similar engorgement. For the rest, the degenerative changes in the placenta are similar to those which I have already described under the heading of infarction in general. In this condition, of course, they are more extensive, as large masses of the placenta, or even the whole placenta, are apt to be deprived of their blood supply. The changes may be equally developed in the affected parts or, where differing regions have been detached at different times, the changes may be more marked in some places than in others. One

of the first changes to develop is a *fibrinous deposit in the intervillous space*. As I have already pointed out, this is to be looked upon as a certain sign of severe vascular involvement. It may be present before any visible changes have occurred in the chorionic elements. In the majority of cases, however, where it is found there has occurred a congestion of the villous vessels (fig. 2).

In fig. 9 is seen another typical appearance found in these cases. A small recent clot is adherent to the decidual surface. Subtending this clot there is a region of definite consolidation in the placenta; in

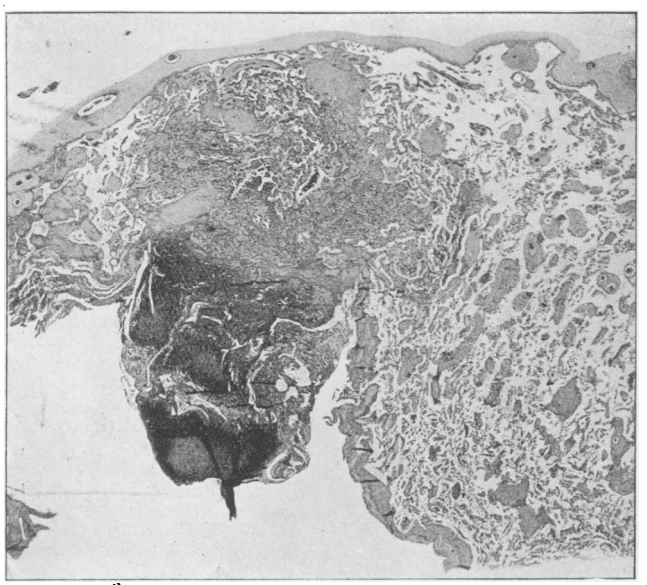


FIG. 9.

Recent (red) infarct subtending retroplacental clot. This infarct was invisible to the naked eye. Case of severe accidental hæmorrhage without albuminuria.

other words, a commencing infarct. It is localized to the region of the clot, and, even on naked-eye examination of the section, *the villi can be seen to be densely packed together*, the looser placental tissue all round being seen. Under higher magnification fibrinous threads are seen between the villi, and the vessels in the villi are greatly expanded. The epithelial covering of the villi is not obviously diseased. This section is taken from a placenta near a huge clot which had severed practically half of its surface from the uterine wall. As the result

of the accumulating blood the placenta had been so compressed that its thickness was reduced by one-half, and in some places by two-thirds. Throughout this enormous piece of placenta changes similar to those just described were found—i.e., there had taken place a huge early infarction.

At first sight it might seem possible to explain the degeneration in these cases as due to the compression of the blood-clot, and no doubt this must play a part in the devitalizing process. That it is not the necessary factor, however, is shown conclusively by the occurrence of the changes in placentæ, in which a ready detachment has occurred without any obvious compression having taken place. This is, as a matter of fact, the usual condition of affairs. In these cases we find the intervillous coagulation and the congestion of the villi in the earlier stages, and the necrotic changes in the villi in the later stages. As I have said, a packing of the villi into solid masses, suggesting a collapse of the placental substance, is present in the majority of such cases. It is doubtless due to the anæmia of the part attendant on the interference with the blood entering, and, although the veins are almost certainly involved, and a leakage away along the normal channels is thus rendered impossible, the forcing of the blood out of the intervillous spaces into the surrounding, less involved, intervillous regions is probably a matter of comparative ease. Especially is this likely in view of the fact that, at the confines of the individual circulatory systems in the placenta there is probably under ordinary circumstances a certain mingling of the bloods. *In any case, the appearances leave no doubt of the fact that when the blood supply of any part of the placenta is interfered with, collapse and solidification is likely to occur.*

The appearances in the one case of accidental hæmorrhage in which I have been able to make a complete study of the placenta in situ are interesting. The placenta was completely separated by a huge blood-clot except at one edge. The hæmorrhage is completely retroplacental, a fine layer of compact decidua covering the outer surface of the placenta. There were, throughout the separated part, changes such as I have referred to. The placenta is pale throughout, except at its attached edge, where the most recent disintegrative change is seen, in the shape of a large purple patch. It is clear that this is just the region where the most recent evidence of a degenerative process will be evident. It is the last part to be separated. As I have indicated on a preceding page, the purple colour soon gives place to a paler hue as the autolytic process leads to a solution of the hæmoglobin. This

is the condition of the remaining part of the placenta. After an examination of such a specimen one can be left in no doubt whatever that the disease in the placenta is secondary to the deprivation of the maternal blood supply.

Changes in the Uterine Muscle, Decidua, and Vessels in Accidental Hæmorrhage.

The chief subject for this study has been the complete uterus, to which I have just referred. For this specimen I am indebted to Professor Kynoch, of Dundee. I have, in addition, been able to study sections cut from four complete uteri from fatal cases of accidental hæmorrhage. These are in the Museum of the University of Liverpool, and, naturally, the chance of anything like a complete investigation of them was impossible. For them I am indebted to Professor Briggs. My remarks will be chiefly directed to the specimen of Professor Kynoch. In it a thorough examination was made. The other specimens served to provide confirmatory evidence of much that it demonstrated. The complete specimen consists of the uterus removed after death. The specimen was shown to the Edinburgh Obstetrical Society last year by Professor Kynoch, and I need not refer to the clinical history. The uterus is occupied by an immense blood-clot. The placenta has been detached by this, except along one edge, where it is still adherent to the uterus. There are marked and important changes in the muscular wall and in the decidua.

Changes in the Decidua.—These were discovered purely by accident as the result of the way in which the specimen was cut. The decidua vera is deeply congested. In the sections the *vera* is marked by a deep red line, and is obviously the seat of diffuse hæmorrhage or of vascular congestion. Microscopically the appearance was found to be due almost entirely to an enormous expansion of the decidual vessels into thin-walled sinuses. Here and there areas of hæmorrhage are present (fig. 10). In the adjoining muscular wall the vessels are in a state of congestion, and surrounding them there may be scattered hæmorrhages, but the changes here are nothing like so evident as in the decidua. The congested vera can be traced directly (even by the naked eye) into the serotina under the placenta, where the same vascular changes are present in an even more marked degree. In the *serotina* the vascular expansion is excessive, and there is an extensive blood leakage into the surrounding tissues. It is obvious that it is to

the congestion and hæmorrhage here present that the enormous blood escape into the retroplacental space is due.

Changes in the Muscular Coat.—In no place is there any evidence of degeneration of the muscular tissue. In many places there is an expansion of the vessels, and an œdematous escape. In the muscular coat underlying the placental site (and also, but to a less extent, in that under the congested vera) the vascular changes are most evident, and here a hæmorrhagic leakage through the vessel walls has occurred. These appearances Essen-Möller and others have previously described. In one of my other specimens there was an extensive hæmorrhage into

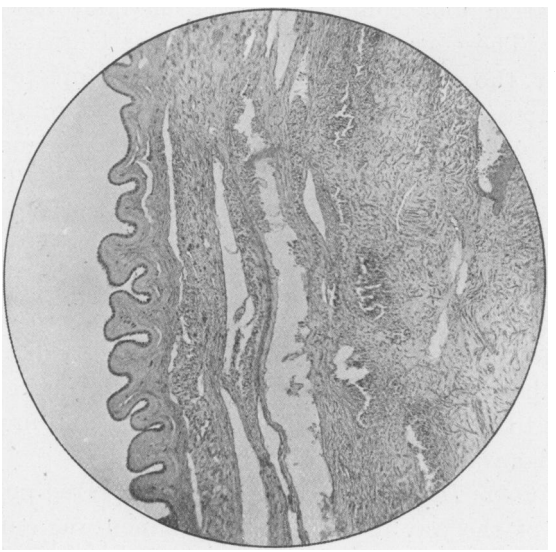


FIG. 10.

Accidental hæmorrhage (Professor Kynoch's case). Piece of uterine wall beyond the placenta. To the left the amnion and chorion are seen, then the decidua vera showing greatly expanded vessels and hæmorrhage. To the right the muscular wall beset with small hæmorrhages. (It is therefore a case of "diffuse utero-placental apoplexy.")

the muscular coat, which was visible as a deep purple patch under the peritoneum over the greater part of the anterior surface of the uterus.

It is evident, from a study of these changes, that the vascular disturbances present in accidental hæmorrhage are widespread, and in any attempt to account for them one must recognize that they are found throughout the uterus, and are not confined to the placental region. It has been amply proven that a toxæmic state cannot be considered

as an ætiological factor, for in 50 per cent., if not more, there is no albuminuria. In discussing the causation of the milder degrees of retro-placental bleeding it was pointed out that a blockage in the veins of the decidua or adjacent muscle might quite well explain the condition. As a matter of fact, this explanation has been advanced by Veit to account for accidental hæmorrhage, his belief being that a mass of deported villi may plug the vein. In my belief this is an unlikely explanation, for it is difficult to see how a mass of villi sufficiently large could be severed from the placenta, though from Veit's sections which I have had the opportunity of examining, it is evident that there may occur a very luxuriant growth of villi along the veins adjacent to the placenta. To my mind a thrombosis in the veins is a more likely explanation. It is well known that thrombosis of the veins of the decidua and uterine muscle is so common that it may be looked upon as a normal change in the later weeks. It is also known that during pregnancy there is a very special tendency to the excessive formation of thrombi in the veins throughout the body. A blockage of the small veins near the placenta may quite well account for the smaller degrees of hæmorrhage in the retroplacental site. For the vascular changes present throughout the uterus in cases of accidental hæmorrhage are so widespread that it is evident that, if blockage of the veins is the cause, it must be a blockage that is far back in one of the main venous trunks in the uterus or even in the broad ligament.

As I have said, I had only one specimen in which a complete examination of the changes was possible. In it I decided to investigate the main ovarian and uterine branches, and, to my surprise, without the least difficulty a massive, extensive, and fairly old-standing thrombosis was found in the ovarian vessels on each side, especially in the left. The uterine vessels seemed to be healthy. *It is therefore probable that accidental hæmorrhage is due to a thrombosis in a main venous trunk in the uterine wall, or even in the pelvis. The thrombosis probably occurs slowly, and may be present without any untoward signs, so long as it is not sufficient to obstruct the lumen of the vein completely. Let the obstruction become complete, especially let this occur suddenly, and the great venous pressure thrown back throughout the affected regions of the uterus will at once lead to the changes described.*

The main purpose of this investigation was not a discussion of the ætiology of placental infarction, or even of the ætiology of accidental hæmorrhage. I have devoted considerable space to their consideration, because I believe that the usual interpretation which

is placed upon them has blocked the way for an enlightened effort to fathom the exact relationship existing between the toxæmic states (albuminuria and eclampsia) and placental disease. Hitherto this relationship has been considered as, in many respects, a mystery. This attitude, as I have tried to show, was due solely to the failure to recognize that placental disease must be considered as due to a cutting off of the maternal blood supply. *Whatever be the cause of the vascular interference, it is certainly not due to a toxæmic state. The study of the anatomy of placental infarction showed this, and the investigation of the conditions present in accidental hæmorrhage have proved it. It is clear, then, that if placental disease is especially prone to exhibit itself in association with a toxæmic state, and if it can be shown to be neither due to this toxæmic state nor to any condition accompanying this toxæmic state, the only solution of the riddle is that the necrotic placenta is the source of the poison.*

There is no method of evading this conclusion. I pointed out early in this research that the clinical evidence in ordinary cases of albuminuria and eclampsia, taken in conjunction with the anatomical, strongly suggested that this was the true explanation of the relationship. An exactly parallel study carried out in regard to accidental hæmorrhage leads to the same conclusion.

Experimental Reproduction of Eclampsia in Lower Animals.

The anatomical investigations recorded in the preceding pages indicated that the poison or poisons responsible for albuminuria and eclampsia are elaborated in a dying placenta. They, moreover, led to so precise a knowledge of the exact manner in which this process occurred that it seemed likely that an imitation of it *in vitro* should enable us to isolate the toxic material for experimental purposes.

One fact issued clearly from these investigations—namely, that the poison must be elaborated early in the course of the disintegrative change of the placenta; for there may be a fulminant toxæmia with an apparently healthy placenta. In severe toxæmias, however, if several days elapse before the birth of the placenta, massive, recently necrotic areas are visible. The time during which the placenta has been retained has allowed of the evolution of the devitalized patches into visible dark red or purple nodules of solidified tissue. In my earlier experiments this fact was not grasped. The placenta was autolysed for eight days or longer, and, although a suggestion of success was every now and

then obtained, the results were, on the whole, disappointing. With a clearer understanding of the exact process the results were positive all along the line. To begin with, a definite standard, by which the results were to be gauged, was formulated. Such a standard was not difficult to obtain, as the clinical and morbid picture in eclampsia is so precise. An attempt was to be made to reproduce this in lower animals in its totality. The main objects to be aimed at were: (1) The production of severe convulsions; (2) the reproduction of the liver changes, which, it is well known, are especially characteristic of eclampsia; and (3) the reproduction of the degenerative changes in the kidney.

Convulsions.—This, the main symptom in eclampsia, I had expected, when beginning my experiments, to find developing only some time after the animal had been brought under the influence of the extract of the autolysed placenta; for it has been usually believed that the convulsive seizures are due to the accumulation in the system of some product of faulty metabolism, and are secondary to the liver or kidney involvement. When the proper method of preparing the placenta was discovered, one of the most immediate results of the injection (sometimes developing within twenty or thirty seconds) were severe and prolonged muscular spasms. In many cases the condition was an accurate reproduction of an eclamptic seizure.

Liver Changes.—These are so characteristic, as found in eclampsia, that I decided to make them the chief touchstone by which to test my results. Workers who have specially devoted their attention to these changes almost unanimously testify to their special association with eclampsia. They consist in a diffuse involvement of the organ. On naked-eye examination whitish areas are found scattered irregularly throughout its substance. In most cases small, they may in unusual cases form large white patches. Microscopically, they are seen to consist of "focal necrosis," which, in the case of the younger and smaller patches, are especially distributed towards the periphery of the lobules. In addition, there is thrombosis in the vessels, especially towards the periphery of the lobules, and, in many cases, there are scattered hæmorrhages. So characteristic are these changes that Konstantinowitsch says that a diagnosis can be made from an examination of the liver alone. The specially characteristic feature is the localization of the early changes to the outer parts of the lobules. In this respect, also, my results have been positive. The subcutaneous injection of extracts made from autolysed placenta have given liver changes identical in every respect to those just referred to. I have

been able to reproduce the focal necrosis, in the earlier stages especially, located in the periphery of the lobules (figs. 11 and 12). In other cases, large, sprawling masses of necrosis have been found, and, in one animal, necrosis of a great part of one lobe of the liver was produced. Moreover, thrombosis in the vessels at the lobule periphery would seem to be the cause of the necrotic changes. Throughout the liver in these cases a diffuse fatty degeneration of liver cells is often present, as also scattered areas of hæmorrhage.

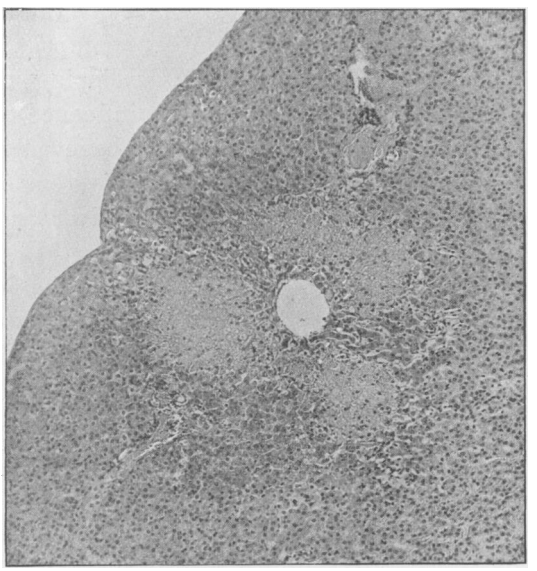


FIG. 11.

Liver of guinea-pig injected subcutaneously with extract of autolysed human placenta. Shows "focal necrosis" similar to that found in the human liver in eclampsia.

Kidneys.—The changes in the kidney, though usually found in eclampsia, are neither so consistent nor so characteristic as the liver changes. In many cases they are slight. In marked cases there may be patches of necrosis scattered throughout the organ. The part specially affected is the epithelium of the convoluted tubules, which shows a cloudy swelling, a fatty degeneration, or coagulation necrosis (Schmorl). In my experiments I have been able to reproduce these changes exactly, and it is especially important to note that the special region, which the toxic material that I have isolated affects, is the epithelium of the convoluted tubules (fig. 13).

Technique and General Method of Experiments.

The animals used were almost entirely guinea-pigs, and number forty-seven in all. For the extract fresh normal human placentæ were used.

Method of Preparation of Placenta.

To begin with, this caused considerable anxiety and trouble. As I soon discovered, it is well-nigh impossible to obtain a placenta in

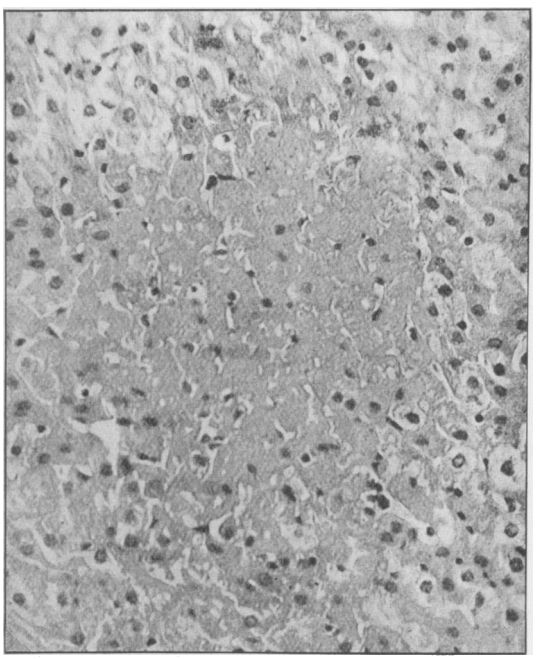


FIG. 12

Liver of guinea-pig injected subcutaneously with extract of autolysed human placenta. Focal necrotic patch similar to that found in eclampsia.

an absolutely sterile state. Some method had, therefore, to be discovered of preventing the growth of organisms, whilst allowing the natural ferments of the placenta to act. I first used thymol, adding a small piece of this to the saline solution in which the placenta was immersed. This method I employed when I was allowing the autolysis to continue for seven or eight days. I invariably found that there was

a copious development of *Staphylococcus albus* by that time. I next turned my attention to chloroform. This is admirable as an antiseptic, but I suspect that it must inhibit the action of the ferments. In some cases, however, I got a suggestion of positive results with this method. After the autolysis was completed the chloroform was extracted by evaporation *in vacuo*, and the juices were extracted by means of Büchner's press. The methods which I am at present using are three in number :—

(1) Once it was recognized that only a short period of autolysis was required it was thought that, by drying small pieces of placenta in the incubator, the drying process, whilst allowing a short autolysis, would take place so quickly that the risk of infection would be so meagre that it need not be allowed to enter into one's calculations. For this reason small pieces of placenta are washed freely in sterile water, spread out flat on sterile dishes, and placed in the incubator. In twelve or sixteen hours they are quite dry and can be powdered in a sterile mortar. The fibrous structure that remains at the end unpowdered can be easily removed by straining the whole through a fine wire sieve, previously passed through the flame. In this way we obtain a reddish-brown, fine powder that can be injected subcutaneously, suspended in saline solution.

(2) As the results obtained with this powder were so strikingly positive, it was decided to employ some other method of autolysing the placenta, which would not be open to even the shred of suspicion, so far as infection is concerned, to which this powder may be held liable. For this reason pieces of placenta, about $\frac{1}{2}$ in. square, were washed free of blood as before, and placed in glycerine and incubated in it. When ready, two or three pieces are placed in a sterile mortar and pounded with 10 c.c. of saline solution.

(3) Recently I have been placing the placenta in saline solution, on the surface of which a film of toluol is placed. The proportions by weight of placenta to saline are two to one. If the whole is thoroughly shaken up before being placed in the incubator, enough of the toluol remains in solution to prevent any organismal growth. This method I began to use when it became apparent that the toxic material or materials liberated by the autolysing placenta were extremely soluble. It was thought that by simply employing the supernatant solution into which the toxic substance had dissolved the same results should be obtainable.

Record of Experiments.

There are several points which require further investigation before a complete publication is possible. For example, I have obtained evidence, during the course of my work, that there are two distinct chemical substances responsible for the eclamptic attack. With the employment of the dry powder marked convulsive seizures are usually obtained, as also the liver changes. With the employment of the glycerine extract, whilst muscular spasms are often present, there are never convulsions, though the liver and kidney changes are obtained in a marked degree. These facts suggest that whilst the powder contains both of the toxic substances the glycerine extract contains chiefly that which has a special tendency to produce thrombosis. For these reasons I will record only those aspects of the results which are more or less final in their demonstration, and which are necessary to substantiate the belief that we have isolated the toxic material responsible for eclampsia.

Control Experiments.—A rigorous control was carried out. For this purpose twenty guinea-pigs (which were injected, sometimes over a long period, with extracts of the ovary or corpus luteum) were employed. These experiments were carried on coincidently with mine, and the animals were obtained from the same stock. For the opportunity of examining these control animals I am indebted to Dr. A. C. McMaster. In every case the liver and kidneys were examined. In none of them were convulsions, or other immediate signs of poisoning, ever produced. This disposed of the possibility that the spasms obtained in my experiments were merely due to the injection of foreign proteid, &c. In none of the controls were the liver and kidney changes discovered which are characteristic of eclampsia, and which I obtained with the placental injection. I think the absence of the typical liver lesions in such a large number of control animals may be considered as convincing proof of their specificity as found in my experiments.

Details of Experiments.

The injections were invariably made subcutaneously into the loose tissues of the back. By employing this method one had in view the avoidance of a rapidly fatal result, such as is apt to happen with intravenous injection. As other experimenters have shown (Weichardt, Pilz, Freund, &c.), the intravenous introduction of placental extract is

quickly followed by death, due to a widespread intravascular thrombosis. Even though the right toxic substance had been isolated in their experiments, a proper test of its effect, as regards the morbid changes produced, was rendered impossible. Another objection, that of Lichtenstein, was overcome by the subcutaneous method of injection. This worker has shown that the intravenous injection of mineral matter in small particles—e.g., sand—may cause results exactly similar to those obtained by Weichardt, Pilz, and Freund, and he believes that these were due, not to any toxic action on the part of the placenta, but merely to the introduction of free cellular elements into the circulation.

Injection of Fresh Placental Extract.—Five animals were injected with the juice expressed from the placenta by means of Büchner's press. This is definitely toxic, if employed in large quantities, doubtless due to the action of a foreign proteid. In two animals 2 c.c., 3 c.c., and 10 c.c. were injected respectively on three successive days. The last dose killed within twelve hours. Three animals were injected with 10 c.c. of this extract at one time and two lived. In none were convulsions produced, and, in those that died, no specific liver or kidney changes were observed.

Extract of Placenta autolysed for Seven to Nine Days in Chloroform.—Thirteen animals were used: 5 to 8 c.c. of the extracted juice were injected once or twice daily till the animals died. In some this occurred after three to four injections, in others not till twelve or fourteen had been given. In one definite and marked convulsions were obtained; in most of the others general muscular spasms. Immediately after the injection the animals always became stupid and dull within a few minutes. In none were the liver and kidney changes produced.

Placental Powder.—It was the use of this that gave the first definitely positive results. Fifteen animals employed: 0·4 or 0·5 grm. of the powder was suspended in 6 or 8 c.c. of saline solution, and injected subcutaneously, usually night and morning. Three or four injections are sufficient to kill. In twelve, convulsive seizures were produced, varying from extremely marked tonic and clonic spasms of the whole body, lasting from ten minutes to an hour or longer, to general twitchings of the muscles of the head, trunk, and limbs. Other immediate signs of a toxic action were giddiness and a tendency to fall to the side, drowsiness with, in many cases, a complete absence of response on touching the eyes. To anyone acquainted with guinea-pigs these signs will at once assume suggestive proportions. In all, *degenerative lesions in the liver* were obtained, in six typical focal peripheral necrosis,

whilst in two large, irregular sprawling masses of necrotic liver tissue were found. These appearances are shown in figs. 11 and 12. Degenerative lesions in the kidney, especially involving the convoluted tubules, were found, but these were neither so evident nor so constant as the liver changes (fig. 13).

Saline Solution in which Placenta was autolysed for varying Short Periods of Time.—Six animals were used for this. Quantities varying from 5 to 10 c.c. of the supernatant fluid were removed after periods of

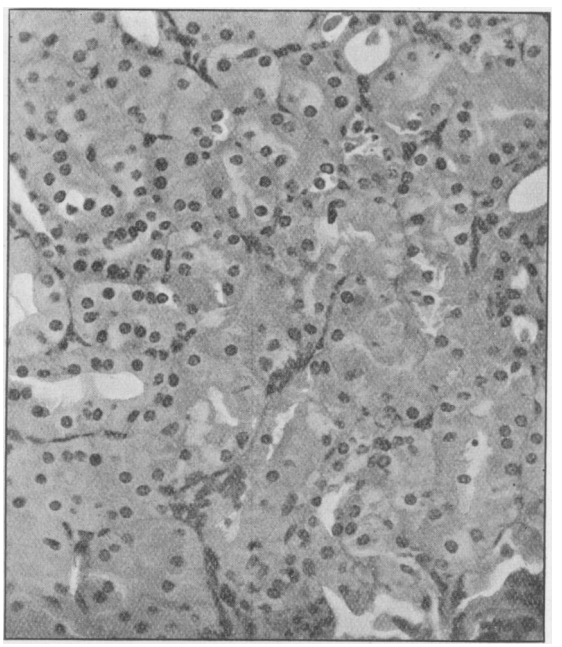


FIG. 13.

Kidney of guinea-pig injected subcutaneously with extract of autolysed human placenta. Convoluted tubules showing evident degenerative changes.

autolysis varying from one and a half hours to sixty hours. These experiments were primarily carried out for the purpose of determining whether the toxic material passed readily into solution. For this purpose the presence of convulsive spasms was taken as a test. The results in this respect were positive, and showed that even as short a period of autolysis as one and a half hours was sufficient to liberate, at any rate, the element that provokes convulsions. The spasms are short-lived. Whereas, with the powder, the spasms may last for twenty

minutes or longer, with this solution, even in markedly positive cases, the spasms rarely last for more than twenty or thirty seconds. So far, an investigation into the liver and kidney changes in such cases has not been carried out.

Placenta autolysed for Short Periods in Glycerine.—Eight animals were employed. The autolysis was allowed to continue for periods varying from ten to thirty-six hours. It soon became evident that the extract thus prepared is extremely toxic. Almost immediately after the injection, even of the extract of the short autolysis, the animals become dull and stupid, and often giddy. There may be general muscular spasms, but this is rare, a fact which shows that the specially toxic ingredient must differ from that present in the dried placental powder. Whereas with the powder the animals usually have recovered to a very large extent six or eight hours after the first dose, with this extract they never regain their usual vitality and remain till the end in a toxic state.

In this connexion it is interesting to note that the necrotic changes in the liver and kidney are especially marked with the glycerine extract. They were obtained in all the animals. In one animal the greater part of one lobe of the liver was found necrotic at the post-mortem examination. The presence of well-marked kidney changes is important, in so far as they were not specially developed in the animals injected with placental powder. It is well known that, in eclampsia, the severity of the kidney lesions varies greatly in different cases. Even in fulminant cases they may be slightly marked. These considerations suggest that there are two different toxic agents operating in eclampsia and albuminuria, and that the exact clinical picture, presented in an individual case, depends upon the relative proportions of these two materials present. The one material has a special affinity for the cerebrospinal tissues, and may be called the convulsive agent. The other has a special tendency to produce necrosis in liver and degeneration in kidney, perhaps, as has been suggested by many workers, because of a hæmagglutinative element.

Clinically, it is known that there are two different types of eclampsia. In one the chief symptom is convulsions, though it is usually associated with specially marked liver lesions and often presents kidney changes. In the other, there may be no convulsions. In these cases there would seem to be a special tendency for severe necrotic changes to occur in the liver and, especially, in the kidney. Under the latter category would come these cases of "symmetrical necrosis of the cortex of the

kidneys," which Jardine, Teacher, and Kennedy, of Glasgow, and others have reported. These two different clinical types would correspond to the two different toxic bodies liberated by a dying placenta.

General Summary.

That eclampsia and the albuminuria of pregnancy are due to the liberation of the products of early autolysis of the placenta has been established by the following considerations :—

(1) The toxæmias are especially associated with recent infarction of the placenta. In severe cases, ending rapidly in labour, there may be no evidence, visible to the naked eye, of placental disease. If, however, the placenta is born several days after the attack, massive necrosis, obviously of recent origin, is seen. It requires some time for the necrosis to evolve into visible form.

(2) Placental infarction is due to an interference with the maternal blood supply of the part. It can be shown conclusively that the chorionic elements are dependent, immediately and directly, upon the maternal blood supply, and, so long as this is retained, can live, even when there is no fœtal supply.

(3) The interference with the blood supply, which is responsible for the infarction, is not dependent upon a toxic state and, in point of fact, may occur in the most extreme form, where there is no evidence of a toxæmia—e.g., accidental hæmorrhage. An examination of the placenta, wherever there is definite evidence of an involvement of the maternal supply, invariably shows disease corresponding exactly to the area of this involvement. This disease will be evident to the naked eye unless the involvement is quite recent. The study of accidental hæmorrhage was shown to be specially important in this connexion.

(4) The placenta is so constructed that, if a part of it die, the products liberated from the dying patch can pass directly into the blood-stream. The organ is unique in this respect. It thus arises that for the occurrence of a toxæmia a circulation of blood round the poison-generating foci is necessary. An understanding of this fact at once dispels many of the difficulties associated with this study. It explains, for example, the cessation of symptoms after the death of the child (and separation of the placenta), and it explains the absence of a toxæmia in cases of accidental hæmorrhage (50 per cent. of the whole) in which the placenta is completely detached by the blood-clot, or by other means. The cases of accidental hæmorrhage associated with a

toxæmia are those in which part of the placenta remains attached for some time after the separation of the adjacent part by a retro-placental bleeding. The necrosis of this part liberates the toxic materials.

(5) Where the placental disease is gradual in its onset there is more chance of the evolution of the infarcted patches. This explains why, in long-standing albuminurias, there may be more visible placental disease than in an acute eclampsia. It is just the gradual development of the toxæmia that allows of the pregnancy continuing.

(6) These facts all suggest that the toxæmias are due to the autolytic products liberated in the early stages of the placental death. By imitating the process, which occurs *in utero*, it has been possible to isolate from the healthy placenta a material or materials of a soluble kind which reproduce the clinical features and morbid changes, which all agree are especially characteristic of eclampsia. These are (*a*) convulsions, (*b*) peripheral focal necrosis in the liver, and (*c*) degenerative lesions in the kidney, especially located in the convoluted tubules.

In conclusion, I would say that, whilst *post-partum* eclampsia constitutes the only difficulty which I know of in the way of absolute proof of my thesis, I think the evidence I have advanced is sufficiently cogent to necessitate a thorough exploration of the uterus in all such cases for a small piece of retained placenta; for a comparatively small piece may suffice to liberate fatal poisons.

I have to thank Sir Halliday Croom and Dr. Haultain for their kindness in allowing me to obtain the specimens of placenta from the Maternity Hospital during their period of office there.

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DISCUSSION.

The PRESIDENT (Dr. W. S. A. Griffith) said that all members of the Section would recognize the importance of Dr. Young's views on the ætiology of eclampsia if they were established by further investigation. If his theory as to the cause could not apply to every case it might be correct for a group, but it was difficult to see how it could apply to cases occurring after delivery was completed. If it were shown that in all the delayed cases a portion of the placenta was retained it would be necessary to explain how it was that in common cases where retention of portions of the placenta occurred (sometimes large portions, of which the President gave an instance) no symptoms of toxæmia developed. Dr. Young submitted his views and invited thorough criticism. The President hoped that so important a subject, so ably investigated, would receive this criticism from the members of the Section.

Dr. OLIPHANT NICHOLSON had listened to Dr. Young's paper with great interest. It was generally agreed, he thought, that eclampsia was caused by a toxin circulating in the blood-stream, and many things pointed to the placenta being intimately concerned, directly or indirectly, with the elaboration of the toxin. The toxin of the eclampsia acted on the circulation like adrenalin, and caused a great rise in blood-pressure, due to its intense and widespread action in contracting the arteries and arterioles. The cutting off of the arterial blood supply to kidneys, liver and lungs produced great venous congestion in these organs; as regards the kidney, the main clinical symptom of the disease—suppression of urine—was thus brought about; while in the lungs great œdema might occur. Clinically, in impending eclampsia, the circulatory features could not fail to attract attention. When Dixon and Taylor, in 1907,[1] asserted that human placental juice contained a substance which contracted the arterioles, and raised the blood-pressure even more strikingly than adrenalin, one began to think that the source of the eclamptic poison had been discovered. In 1909, however, Rosenstein stated that *fresh* human placenta did not contain any blood-pressure-raising principle, and that the autolytic enzymes of the placenta could not produce pressor substances without the help of micro-organisms. So it seemed to be settled, once and for all, that the pressor substance

[1] *Proceedings*, 1908, i, p. 11.

described by Dixon and Taylor was really the result of initial putrefaction in the placenta. Now Dr. Young seems disposed to think that this conclusion has been too hastily accepted. He has isolated a substance from the placenta which is capable of causing, in animals, not only violent convulsions, but also changes in the liver quite similar to those found in eclampsia. In *dead* placenta, as in putrid meat, a powerful pressor substance is formed—very like adrenalin in its chemical formula. Was Dr. Young's toxin similar to this? It was interesting to recall that some eleven years ago H. Müller and W. Albert wrote papers in which they hinted that the toxin of eclampsia was the product of putrefactive changes occurring within the uterine cavity. They regarded eclampsia as an intoxication which was caused by the action of bacteria within the decidua —a latent microbic endometritis. The association of high temperature with many cases of eclampsia might suggest this kind of origin, and *post-partum* eclampsia would be more easily explained. In their view the toxin originated from death and putrefaction occurring in part of the uterine contents, and the Dixon and Taylor vaso-constrictor was elaborated in a similar manner. So was Dr. Young's toxin, in his opinion, and it might really be the toxin of eclampsia. But some vaso-constricting substance was certainly present in the blood at the very commencement of pregnancy, and long before any autolytic changes in the placenta would be likely to occur. Clinically, the changes in the maternal heart and circulation in pregnancy—dilatation of the right side of the heart, tendency to œdema of the lungs, overfilling of the veins of the legs, and venous pulsation in the neck—pointed most conclusively to the presence in the blood of some principle which caused constriction of the arterioles. It seemed impossible to admit that some autolysis of the placenta occurred in every pregnancy as a matter of course, and it was more in accordance with physiological reasoning to regard the placenta as a new metabolic gland, temporarily grafted into the maternal organism, and producing a more or less profound hormonal upheaval. It was this metabolic upset which, in his view, was responsible for the appearance in the blood of a vaso-constricting substance as soon as gestation commenced. That constituted the so-called "toxæmia of pregnancy," and it might be trifling or exceedingly grave, according, he believed, to the personal factor present. When this toxæmia steadily advanced, the arterial blood supply to the various glandular organs was so greatly shut off that portions *did* sometimes undergo necrosis. That actually did happen in the case of the kidney and liver, and why should not portions of the placenta die too, and undergo autolysis? Then the manufacture of a toxic pressor substance, such as Dixon and Taylor had described, or such as Dr. Young had isolated, would be explained—a substance capable of causing convulsions and coma. It would be interesting and important to get the opinion of a competent chemist on the nature of the toxic body which Dr. Young had separated from the necrosed areas of placenta—whether or not it was the result of putrefactive changes and allied, perhaps, to tyramine. He thought that Dr. Young had shed an instructive side-light on the most fascinating and puzzling riddle in obstetric medicine.

Dr. MCMASTER referred to work he had been doing recently that involved the injecting subcutaneously of emulsions of animal tissues and of watery extracts of animal tissues. In some instances the emulsions had become infected, and had caused the death of the animals injected. The livers of these animals had been examined, and in no cases had changes similar to those Dr. Young had shown been produced. A fatty degeneration had been found, and evidence of degenerative changes in liver cells, also scattered inflammatory foci, but in no instance had necrosis been observed. He found that guinea-pigs always twitched after subcutaneous injections, probably as a result of the pain caused, but in the case of Dr. Young's animals the twitchings were much more violent than in his own cases and amounted to fits; the animals became stupid, and lost their conjunctival reflex.

Dr. T. W. EDEN said that he wished to congratulate Dr. Young on the elaborate piece of work he had done, which, he felt sure, had interested the Section very much. If he might select one or two points for criticism he would refer, in the first place, to the view expressed by Dr. Young that red and white infarcts were stages of the same process. He (Dr. Eden) had been interested in the subject of placental infarcts, and the observations which he made some years ago led him to the conclusion that the primary change in white infarcts was an obliterative endarteritis of the chorionic vessels. He hoped Dr. Young would publish the histological evidence in support of the view he had advanced that night. With regard to Dr. Young's main thesis, it appeared to him to prove too much. If the detachment of a placental cotyledon by accidental hæmorrhage a day or two before labour was all that was required to produce an acute toxæmia, that condition might be expected to be very common instead of very rare. Cases of accidental hæmorrhage of placenta prævia were comparatively frequent, but were very rarely accompanied by toxæmic conditions comparable to eclampsia. Further, the process of formation of a blood mole ought, on Dr. Young's hypothesis, to lead to acute toxæmia, but we learn that this was certainly not the case.

Dr. JAMES YOUNG thanked the Section for the way in which they had received his paper, and for the kindly and helpful criticism they had offered. Dr. Griffith made the most serious objection to any placental explanation of eclampsia when he asked how *post-partum* eclampsia was to be accounted for. There could be no doubt that the origin of the poison was the child or placenta, therefore in such cases there must be something left behind. The retention of pieces of placenta was a common thing, whereas eclampsia was comparatively rare. Such a piece remained attached, doubtless, because at that region the placenta was especially adherent, a fact that explained why one often found after curettage, carried out some time after for hæmorrhage, that the villi had remained well nourished. The vascular attachment had remained good. Even a small part dying might account for a severe *post-partum* toxæmia. Then as regards the absence of a toxæmia in cases where the fœtus and placenta were delivered in a stinking state, Dr. Young had seen such cases. The remarkable

thing was there was not the slightest rise in temperature, though the staphylococcus was obtained. The only explanation of such a fact was that soon after the detachment of the placenta the blocking of the vessels by thrombosis prevented absorption of the infective products. The same explanation, doubtless, accounted for the absence of eclampsia in similar cases. Eclampsia had been reported in such cases, and was quite explained by an incomplete placental separation. It was well recognized that a toxæmia often ceased immediately with intra-uterine death, whereas in other cases it did not. These facts meant only one thing, that where placental separation was complete absorption was prevented, but it continued where a part remained attached. Dr. Williamson said that convulsions were produced by many things in animals. Surely Dr. Williamson must be thinking of twitchings, which were common with any foreign matter. In his controls Dr. Young had never found true convulsions. Glycerine had been used in one of the methods of preparing the extract, but the results completely discounted what Dr. Williamson said, because, with this extract, convulsions were not obtained. The importance of this finding was referred to in the paper. Then Dr. Williamson enumerated a list of materials that can cause liver changes exactly similar to those found in eclampsia. A careful study of the literature showed that these changes were found only rarely, if ever, in other conditions. In the experiments the only possible causes of the liver changes were, firstly, sepsis; secondly, foreign animal matter; and, finally, a material specifically obtained in the way the placenta was prepared. Sepsis was excluded by cultural tests and by the controls; foreign proteid was excluded by the controls, leaving the only interpretation that which had been advanced. Dr. Young thanked Dr. Oliphant Nicholson and Dr. McMaster for coming from Edinburgh to take part in the discussion. The latter he thanked especially for permission to mention his experiments as controls. Dr. Eden asked if eclamptic placenta was used. The answer was in the negative, because the demonstration of positive results with it might, by some, be held to mean simply that some of the toxin was held up in the placenta without being elaborated there. In answer to another question, Dr. Young said that it was easy to show that the red and white infarcts were merely different stages in the same process. There were all grades between them, the white was more necrotic, and the hæmoglobin was dissolved out by the autolytic process.