THE PATHOGENESIS OF POST-PARTUM NECROSIS OF THE ANTERIOR LOBE OF THE PITUITARY GLAND

By
H. L. Sheehan and J. P. Stanfield

ABSTRACT

From a histological study of the lesions which develop in the vessels of the human pituitary gland during the first two days after the onset of post-partum necrosis of the anterior lobe, it is concluded that the primary vascular disturbance is a spasm involving the arteries which supply the anterior lobe and the stalk. This arrests the portal blood supply and also the direct arterial blood supply to the lobe, but permits a slight circulation to continue in the stalk. If the spasm is relieved within about an hour the parenchyma suffers only a transient functional damage. If it continues for several hours all the tissues in the anterior lobe are killed and, when blood finally attempts to flow into the dead vessels, stasis and thrombosis occurs. This thrombosis is a secondary phenomenon and is not the cause of the necrosis. Variations in the extent and the duration of the spasm account for the variations in the size of the necrosis; in about half the cases the lesion involves 97 to 99 per cent of the anterior lobe, but the pars tuberalis and a small amount of the pars interlobaris always survive. The arterial spasm is certainly related to a severe general circulatory collapse at the time of delivery, but the reason for its very specific localisation to the anterior lobe of the pituitary gland remains obscure.

In previous papers (Sheehan 1937, 1948) accounts have been given of the morphological changes which are seen in post-partum necrosis of the anterior lobe of the pituitary gland during the first two weeks after its onset. The relevant literature was reviewed in those papers, but several further reports have been published since then (Louw 1947; Destro 1953; McKay et al. 1953; Baker et al. 1953; Pliss 1955; Vandervort et al. 1955; Bárdos & Pontuch 1956; Frangenheim 1956; Liebegott 1957; Mariuzzi 1958; Dyson 1959; Pascoe & McGuiness 1959; Tisne et al. 1959; Wells et al. 1960). The present paper is concerned essentially with the local vascular disturbances which give rise to the ischaemic necrosis, but as a necessary introduction two basic subjects will be considered first: the
blood supply of the normal pituitary gland, and the significance of the parenchymal changes that are seen in the necrotic areas.

THE BLOOD VESSELS OF THE NORMAL PITUITARY GLAND

The blood supply to the human pituitary gland has been described elsewhere (Stanfield 1960); a discussion of the relevant literature was given in that paper, and will not be repeated here. It may however be pointed out that two descriptions given recently (Badellino et al. 1959; Duvernoy & Koritké 1960) are, in our view, very inaccurate.

The present short resumé of the anatomy of these blood vessels is intended only to provide a basis for the understanding of the vascular disturbances. This account is based on numerous normal human pituitary glands studied by injection methods and by serial sections, and also on serial sections of 10 glands with necrosis of the anterior lobe of 1 to 4 days duration. These necrosed glands are of particular value in the study of the blood supply, because, though many of the vessels are collapsed and inconspicuous, certain individual vessels are distended by thrombus and can thus be followed easily along their entire course. Furthermore, in these glands with anterior lobe necrosis, the survival of certain areas in relation to particular vessels also provides evidence about the local circulatory pattern.

The blood supply of the pituitary gland comes from two main sources: – the inferior hypophyseal arteries and the superior hypophyseal arteries (Fig. 1).

The inferior hypophyseal arteries arise from the internal carotid arteries soon after they enter the cavernous sinus. They run to the groove between the anterior and posterior lobes, and divide there into ascending and descending branches which anastomose with their opposite fellows to form an arterial circle around the groove. This arterial circle gives the blood supply to the posterior lobe. In addition it gives off an »interlobar artery« on each side which runs in the pars intermedia to the genual septum, i.e. the fibrovascular septum in front of the intraglandular genu of the stalk. Each of these interlobar arteries gives off two important branches which provide anastomoses to the superior hypophyseal system; these will be mentioned later.

The superior hypophyseal arteries originate from the internal carotid artery just as it emerges into the cranial cavity. They run backwards to form a plexus in the subarachnoid space around the base of the pituitary stalk. This plexus gives off a big »lateral artery« (McConnell 1953) on each side. These vessels pass down free in the subarachnoid space, about 2 mm in front of the stalk and 2 mm lateral to it, and enter the upper part of the anterior lobe. At this point they turn posteriorly in its substance and travel back to reach the genual
septum, where each of them divides into three »long stalk arteries« which course upwards in the tuberalis septum of the stalk. These form anastomoses with the »genual branches« of the interlobar arteries.

A number of smaller arteries run directly from the plexus into the neural part of the stalk and the tuber cinereum, and are referred to as the »short stalk arteries«. These have a variable number of anastomoses with the long stalk arteries.

These two series of arteries (the terminal branches of the loral arteries, and the direct arteries from the plexus) pass into the neural stalk and the tuber cinereum, and terminate there as the central arteries of peculiar vascular structures which Fumagalli (1941) has called »gomitoli« (Fig. 2). A gomitolo is about $\frac{1}{2}$ to 1 mm long and about 100 $\mu$ in diameter; the total number has not been counted, but is probably in the neighbourhood of a hundred. Each gomitolo consists of a straight central artery surrounded by a sheath of coiling sinusoidal capillaries (Fig. 3). At intervals, the central artery gives off very short arterioles which empty directly into the sinusoidal capillaries, and in this way it has usually become completely distributed by the time it reaches the end of the gomitolo. The short arterioles have a very thick media but no internal elastic lamina; they appear to be little more than sphincters which control the flow of blood from the central artery.
Figs. 2–3.

2. Normal stalk injected with indian ink and cut in longitudinal section, showing gomitoli and their outflow to the capillary network of the stalk. X 21.
3. Transverse section of a normal gomitolo, showing an unusually wide central artery and slightly congested sinusoidal capillaries. H. E. X 300.

The sinusoidal capillaries of the gomitoli drain into the network of capillaries which extends throughout the straight part of the neural stalk. In the genu the capillary network is replaced by numerous »parallel vessels« (McConnell 1953) which run transversely across the genu, and are presumably related to some special function of this part of the stalk.

The capillary network in the neural stalk drains in turn into larger sinusoids, which run up to the surface of the neural stalk and join together to form the portal venous sinuses. These sinuses pass down along the surface of the stalk in two distinct groups (Fig. 4). On the posterior surface of the stalk there are about 6 large »posterior portal sinuses«, lying directly under the pia. In front there are 20 or 30 smaller »anterior portal sinuses«, which run down in the tuberalis septum. These portal sinuses have a certain amount of muscle and elastic tissue in their walls, and appear capable of exerting some control of the flow of blood along their lumen.

The posterior portal sinuses run down the posterior surface of the stalk to near its lower end, and then slant forwards to the side of the stalk. Here they enter the upper surface of the anterior lobe and turn sharply outwards to be distributed fanwise in the upper half of the lateral part of the anterior lobe. The anterior portal sinuses run straight down to the point where the stalk enters
the anterior lobe. Here most of them turn forwards in the "pars interloralis" beneath the upper surface of the anterior lobe and are distributed at intervals downwards into the gland. A few of them run vertically down in the "fibrous core" and are distributed partly along its course but mainly from its lower end. Thus the general pattern is that most of the portal blood enters the upper part of the anterior lobe, and has to run downwards through the capillary meshwork of the gland to supply the lower part.

Though a great deal of the blood supply is by way of these portal sinuses, there is, without any doubt at all, a significant direct arterial supply to the anterior lobe. Daniel et al. (1959) maintain that there is no direct arterial supply to the anterior lobe, but their views on this particular point can not be accepted. The direct arterial supply comes from three main sources. The first is the important "artery of the fibrous core" which originates on each side from the lower aspect of the loral artery in the substance of the anterior lobe and runs down in the fibrous core. At the lower end of the fibrous core this artery is distributed by numerous small branches which pass out in all directions into the upper half of the anterior lobe. These branches are little more than large capillaries, but they have a delicate internal elastic lamina and thus can easily be followed in serial sections. The second source of the arterial supply comes from the interlobar branches of the inferior hypophyseal circle. On each side the interlobar artery gives off a vessel which is called the "communicating artery". This runs forward into the upper half of the anterior lobe, and
anastomoses either with the upper end of the artery of the fibrous core, or with the main trunk of the loral artery. The third and smallest source of direct arterial blood supply to the anterior lobe is also bilateral, from branches of the inferior capsular artery which enter the lower surface of the lateral pole. Occasionally there is an anastomosis of almost capillary dimensions between this artery and the lower end of the artery of the fibrous core. Apart from this source from the inferior capsular artery, the direct arterial supply to the anterior lobe is entirely into the upper half of the gland. Thus both the arterial and the portal blood supply to the lower half of the lobe appears to be almost only by way of the capillary meshwork, but this is so large as to allow a free circulation to all parts of the lobe.

In most cases the interlobar artery has a transverse anastomosis with its fellow by an artery crossing the mid-line on the front of the posterior lobe. Sometimes there is a transverse anastomosis between the arteries of the fibrous core, and less commonly between the communicating arteries. In the present series no transverse anastomoses have been found between the loral arteries or between the long stalk arteries.

The venous drainage of the pituitary gland has been described recently by Green (1957). The venous outflow from the stalk is entirely by the portal veins down to the anterior lobe; there seems to be no outflow by any other channel. The venous blood from the anterior lobe passes out by a series of veins which penetrate the capsule all over the surface of the gland and empty into large sinuses around it. These, in turn, empty into the cavernous sinuses. The most important group in the present connection is the postero-medial group of superior hypophyseal veins. These drain blood from the pars interloralis (i.e. that part of the anterior lobe which lies just in front of the stalk) and thus provide a possible outlet for blood from the lower end of the anterior portal sinuses when the anterior lobe is almost completely necrosed.

Comments

The anastomoses between the superior and inferior hypophyseal arterial systems vary considerably from case to case. Furthermore, certain individuals have an unusual pattern of the main arteries, even to the entire absence of the loral arteries and their replacement by a very large system of long stalk arteries which originate high up in the stalk from the superior hypophyseal plexus. These variations account for the wide range of size of the areas of ischaemia produced by cutting the pituitary stalk. In ordinary transection of the stalk, either surgical or traumatic, the loral arteries and the portal vessels are divided. Thus the anterior lobe receives blood only by the direct arterial supply along the interlobar arteries and the inferior capsular arteries. This keeps a variable amount of the lobe alive, though there is always extensive necrosis (Russell 1956; Daniel et al. 1958; Ehni & Eckles 1959; Le Beau & Foncin 1960). A very
instructive case has been described (Daniel et al. 1959) where the stalk was torn across right at its attachment to the hypothalamus, leaving the superior hypophyseal vessels intact and in connection with the stalk and the anterior lobe. The anterior lobe thus had a continuing arterial and portal circulation, and survived almost undamaged. It would be of great interest to know the effect of transecting the lower part of the stalk of the human pituitary gland, but leaving the loral arteries intact in their whole course through the arachnoid space and into the anterior lobe.

THE PATHOLOGY OF THE NECROSIS OF THE ANTERIOR LOBE

The material analysed in the remainder of this paper consists of the ten pituitary glands with post-partum necrosis of 1 to 4 days duration which were used for the study of the vascular supply, and also of a further five pituitary glands with post-partum necrosis of 1 to 4 days duration which have been examined in step serial sections with detailed study only of one section every 200 µ. 10 of the pituitary glands showed very gross necrosis leaving not more than 2 to 8 mm³ of tissue alive; the other 5 showed smaller necroses ranging from those destroying about three-quarters of the gland down to those which involved only about 5 or 10 per cent of the gland.

THE EXTENT AND DISTRIBUTION OF THE NECROSIS

In cases of post-partum necrosis, the size of the lesion varies; sometimes only a few small areas of parenchyma are affected, but in about half the cases the anterior lobe is almost totally destroyed. Even in these extensive necroses there is always some surviving parenchyma; usually about 2 to 8 mm³, which is about 1 to 3 per cent. of the anterior lobe. The actual volumes of the necrosed and surviving parts of the lobe can be ascertained by making projection drawings of step-serial sections of the entire gland, followed by weighing or planimeter measurements. Visual assessments of the extent of the damage are much less reliable; this is particularly the case when the assessments are based on a single mid-line sagittal section of the gland, because the largest mass of surviving tissue is usually situated just in front of the stalk and thus occupies a relatively large area of a mid-line section.

When the necrosis is very extensive, the small areas of surviving parenchyma are restricted to certain standard sites.

(a) The pars tuberalis and its continuation into the adjacent part of the pars interloralis. In this latter site the live tissue forms a narrow shallow wedge extending forwards for a short distance in the mid-line. This is the region where the anterior portal sinuses enter the gland.
(b) The genual septum, and the thin layer of parenchyma and cysts which lies immediately in front of the posterior lobe and corresponds to the pars intermedia of other species.

(c) A very thin layer of parenchyma directly under the capsule over most of the lobe. This surviving layer is rarely more than one or two cells deep; in a few places it may be an entire acinus or more in thickness, but in other places it is completely absent.

When the necrosis is not so extensive, these three surviving areas are larger, and in addition certain other parts of the anterior lobe remain alive.

(d) A subcapsular area in the antero-superior surface of the gland around the point of entry of the loral artery. From this, a thin cuff of live parenchyma may accompany the loral artery into the gland for some distance, even so far as to extend down around the fibrous core.

(e) A subcapsular area just behind the lateral pole, where small twigs from the inferior capsular artery enter the gland.

(f) A vertical column beneath the capsule at the lateral edge of the pars intermedia just in front of the interlobar groove. This appears to be related to tiny twigs from the inferior hypophyseal arterial circle in the groove.

When the necrosis is still less extensive, the surviving areas are centred on the same sites but they are much larger and coalesce with each other. The live region of the anterior lobe in front of the pars intermedia is quite deep, and continues above into a large mass of surviving tissue below the pars interloralis.

Finally, when the damage is of only trivial degree, the necrosis is confined only to a patch on each side in the substance of the gland, usually sited anterolateral to the fibrous core and relatively near the surface.

The posterior lobe is usually undamaged, but very occasionally there is an extension of the necrosis from the anterior lobe back into the substance of the posterior lobe, recognisable as patches of loosening and disorganisation of the structure. These must be evaluated very critically; artefacts produced during the removal of the gland give appearances of this kind and are often seen in presumably normal pituitary glands obtained at routine autopsies.

The neural stalk survives in almost every case, though it usually shows important vascular lesions and sometimes haemorrhages or small areas of softening. Here again it is important not to misinterpret artefacts; unsatisfactory autopsy technique can stretch or bend the stalk.

THE EARLY STAGES OF THE NECROSIS

It is well known from general pathology that, when any tissue dies as a result of ischaemia, some hours must pass before the necrosis-changes are sufficiently advanced to be identifiable on routine histological examination. The time required for the lesion to become recognisable in this way depends on various
factors: the type of tissue, the degree of re-establishment of blood-flow, the amount of diffusion from neighbouring live tissue, and so on. In the particular case of the pituitary gland, when the greater part of the anterior lobe has died, the necrosis-changes proceed rather slowly and the lesion is not really obvious until after about 12 to 15 hours.

The question arises whether the very early stages of the morphological change can be identified in obstetric patients who die during the first 12 to 15 hours after very severe circulatory collapse at about the time of delivery. It is a reasonable inference that in a considerable proportion of these patients the anterior pituitary gland has been dead for several hours before the patient died, and thus that it might be expected to show incipient necrosis-changes. In fact, the study of a series of about 50 pituitary glands from early deaths of this type does not show any abnormality in the anterior lobe when the patient has died within 6 hours after delivery, but shows various grades of a characteristic change in about one-third of the patients who have died at 6 to 12 hours after delivery. This change, which could easily be passed over on cursory examination, consists of a separation of the acinar cells en masse from the basement membrane, without any dissociation of the cells from each other. The appearance is analogous to the «sleeve-separation» of tubules which occurs in the early stages of renal cortical necrosis, and may be interpreted as probably the first stage of histological necrosis. It is not due to post-mortem autolysis, as it has been found in several pituitary glands put into fixative within an hour after the death of the patient. In the cases which show this «sleeve-separation» of acinar cells, there is usually also a vascular lesion indicative of ischaemia of the anterior lobe. This vascular lesion will be discussed later; it consists of marked congestion and sometimes of fibrin thrombus in a number of large sinuses in the pars interlaterialis and in others lateral to the genual septum.

This account of the early histological stages relates to cases where there has probably been death of almost the whole anterior lobe. We do not happen to have observed the early stages of small necroses, or if we have, we have failed to recognise them.

THE DEVELOPED STAGE OF THE NECROSIS

At about 12 to 15 hours the dead tissue begins to be recognisably necrotic by ordinary histological standards, and during the next day or two this becomes quite obvious. The course of events is similar to that in infarcts in other parts of the body; the following account is concerned only with special features related to the pituitary gland or to points on which there has been misinterpretation in the literature. The terminology in this section will be that used in previous accounts of infarction of the kidney (Sheehan & Moore 1952; Sheehan &
Davis 1958), since the general pathology of the pituitary gland infarction is very similar.

On general grounds, it may be presumed that the outer part of the ischaemic area consists of a »live margin zone«, in which the circulation is arrested but there is sufficient diffusion from outside to maintain the life of the parenchyma as well as of the endothelium. However, in the pituitary gland, the parenchyma cells have an equal and moderate sensitivity to ischaemia, and there are no tissue components which are specially vulnerable so that they could act as markers of the zone (as in the kidney). Thus in the places where the ischaemic area is contiguous with healthy parenchyma no histological evidence of a live margin zone can be seen.

The periphery of the obviously necrotic tissue consists of the »partial survival zone«, where the endothelium survives but the parenchyma cells are all dead and undergo fairly rapid necrosis-changes. The red corpuscles here may remain unchanged for two or three days. The outer edge of the partial survival zone is remarkably straight and often runs across the centre of an acinus. It shows no irregularities corresponding to the capillary pattern, and may therefore be interpreted as the inner limit of diffusion which is sufficient to maintain the life of the parenchyma. This implies that, external to the partial survival zone, there is a live margin zone with no circulation.

The inner margin of the partial survival zone represents the inner limit of diffusion sufficient to maintain the life of the relatively resistant endothelium. This zone encloses the main mass of the infarct which is beyond the range of significant diffusion. Here the necrosis-changes are very slow; the dead nuclei retain their staining reactions for several days, but the red corpuscles become dehaemoglobinised in about 12 to 15 hours and disappear completely within 24 hours.

The »polymorphonuclear zone« appears in the outer part of this mass at 36 to 48 hours, and divides the infarct into a »peripheral dead zone« lying external to the polymorph zone, and a »central dead area« lying internal to it, as in any infarct elsewhere in the body. In the absence of infection, the polymorph zone fades away by the end of the first week.

The pituitary gland provides an excellent illustration of the fact that the development of the margin zones of an infarct depends on the amount of diffusion from the neighbouring live tissues. Where the necrosis extends up to the surface of the anterior lobe in a part where the capsule is in contact with the relatively avascular bony wall of the sella (e.g. over the anterior and lower surfaces of the gland), there is a thin subcapsular live margin zone. The other margin zones are shallow and lie close to the edge, and little or no polymorph zone may be formed. On the other hand, where the necrosis abuts on vascular soft tissues (e.g. at the upper and lateral surfaces of the lobe), or on a fairly large mass of live parenchyma which has a continuing blood supply (e.g. just
in front of the stalk), the margin zones are thicker and deeper and are well
developed. When an artery survives and carries a cuff of live tissue around it
into the main area of the necrosis, this cuff is surrounded by margin zones,
whose depth appears to be related to the amount of blood-flow along the
artery.

The rate of the necrosis-change, being also dependent on diffusion, is directly
related to the development of the margin zones. Certain authors have observed
that the nuclei have disappeared from one part of the necrosed area but not
from another, and have concluded that this represents lesions of two different
ages. This view seems to have arisen from a misinterpretation of the different
rates of necrosis-change between the margin zones and the central dead area.
An ordinary post-partum necrosis results from one single ischaemic episode;
we have never observed in the otherwise uncomplicated cases of our series a
necrosis which seems to have extended locally a day or two later, nor two
separate necroses of different ages. Thus it is not possible to accept the hypo-
thesis that the arterial supply may be arrested secondarily many hours after the
arrest of the portal supply.

As in any infarct, the appearances depend on the size. The above description
is that of a large lesion. If the necrosis is of only moderate size, the central
part consists only of peripheral dead zone and this is surrounded by a partial
survival zone; in such a case there is of course no development of a polymorph

Fig. 5.
Partial survival zone at 3 days post partum, showing necrosis of parenchymal cells but
survival of endothelium. H. E. × 320.
zone. If the necrosis is less than about 200 μ in diameter, it is exposed to excellent diffusion from the large surrounding mass of live tissue. Thus it consists only of partial survival zones meeting from opposite sides; all the parenchyma cells die and undergo rapid necrosis-changes, but the endothelium of the capillaries and sinusoids remains quite healthy (Fig. 5). To continue the interpretation into a theoretical field, a very small area of ischaemia would be made up entirely of live margin zone, and thus would show no histological changes subsequently.

THE VASCULAR LESIONS

The necrosis of the parenchyma is clearly due to an episode of ischaemia, and it is therefore necessary to consider in detail the histological changes which are observed in the blood vessels. Are these vascular lesions the primary cause of the ischaemia, or are they merely secondary to it? Do the lesions indicate the site of the primary disturbance in the vessels? In order to answer these questions, the condition of each part of the vascular system of the pituitary gland must be analysed separately.

LESIONS IN VESSELS AT THE MARGIN OF THE NECROSIS

The present section is concerned only with the branches of the lower ends of the portal sinuses and with the capillaries at the sites where these vessels pass through the margin zone into the infarct. Consideration of the lesions in the arteries which pass through the margin zone will be deferred to a separate section.

During the first few hours after the delivery, there are no recognisable changes in any of the vessels. Lesions are first seen at about 6 to 12 hours, and they are always well marked from about 12 hours onwards. They are quite specific, and are never seen in normal pituitary glands.

In the case of an extensive necrosis, the large branches of the lower ends of the portal sinuses always show a characteristic change. At the point where they pass through the partial survival zone into the necrosed area, they are widely ballooned, and their lumen is filled with a mass of packed red corpuscles without any intermingling of fibrin. This distension of the vessels by packed corpuscles continues into the central dead area for a variable distance, often about 200 μ but sometimes for nearly one millimetre. It is to be noted that the passage of the large branches of the portal sinuses through the margin zone does not produce any indentation of the general line of the edge of the infarct; i.e. there is never an apparently surviving portal sinus projecting into the dead tissue and carrying in a cuff of live tissue around it.

At about 15 hours the corpuscles in those parts of the sinuses which lie in the central dead area undergo the ordinary process of dehaemoglobinisation.
and at about 24 hours they disintegrate and disappear, leaving the sinus empty but still quite dilated. The corpuscles in the partial survival zone retain their haemoglobin and their normal structure for several days.

The capillaries in the partial survival zone do not usually show any very striking distension with blood at any time, though they may have some degree of stasis-dilatation in the neighbourhood of the lateral pole. Occasionally they contain small solid fibrin thrombi in the centre of the lumen, but this is rare.

When the necrosis is of only moderate size, the lower branches of the portal sinuses which run into the necrosed area are relatively small. Where they pass through the partial survival zone they are commonly dilated by packed corpuscles, but sometimes they contain a loose fibrin thrombus instead, which is adherent to the endothelium and often occludes the lumen. The subsequent changes are similar to those described for a large necrosis.

When the area of necrosis is only a small one, the vessels passing through the margin zone are mainly capillaries, though there may be a few small sinusoids. These vessels do not become so dilated by corpuscles, but fibrin thrombi are formed in very occasional capillaries in the partial survival zone. These thrombi have a rather firm solid texture; they usually lie in the centre of the lumen, and do not appear to be occlusive.

When the necrosis is a very small one and has endothelium surviving in the capillaries throughout it, there are no recognisable vascular changes. In particular, thrombosis does not occur in these live capillaries.

Comments

In an earlier paper (Sheehan 1937) the tentative conclusion was drawn that the thrombosis in the portal sinuses and the capillaries gave rise to the necrosis, there being no other obvious histological cause. In the light of further experience, we wish to retract that inference unreservedly. From what is known about the experimental production of infarction in other organs, it must be accepted that the vascular lesions in the margin zone of the pituitary necrosis are purely secondary phenomena. They indicate that there has been a local circulatory disturbance in two stages: an initial period of total ischaemia, followed by an attempted re-establishment of circulation in the area.

The duration of the initial period of ischaemia is presumably at least 2 hours and may be 6 or 8 hours in some cases. During this period the greater part of the anterior lobe has been deprived of its blood supply, and dies. In particular, all the vessels in the area die. At this stage the dead vessels do not show any thrombosis or other histological change, and there are no important necrosis-changes in the dead parenchyma. This indicates that there has been no blood-flow into the area, either along the portal sinuses or along the capillaries from the neighbouring live tissue. The evidence is to a great extent negative, and the inferences about the condition of the vessels in the margin of the incipient
infarct are mainly based on the subsequent course of events. However, the fact that in the later stages none of the portal sinuses carry a cuff of live tissue projecting into the main mass of the necrosed tissue is strong evidence that no blood circulates along any of these vessels during the period of ischaemia.

The second step of the interpretation is that, at the end of the period of ischaemia, blood attempts to flow into the area but that it fails to re-establish a circulation. This inflow of blood comes principally by way of the large terminal branches of the main portal vessels. It penetrates along these branches for some distance into the area which has been killed by the ischaemia. These vessels are dead, and, even with the slight pressure of the reflow, they become widely distended. The plasma escapes through their walls, and the red corpuscles remain as a packed mass filling the lumen. The absence of any similar dilatation and stasis in the capillaries of the partial survival zone indicates that there is no significant inflow along the capillaries from the neighbouring live parenchyma, and thus that even then the circulation in that parenchyma must be poor.

This general account applies to the course of events in the severest cases where there is a large pituitary necrosis. The changes in the vessels may however be modified; the two main controlling factors being the size of the area involved, and the duration of the initial period of ischaemia. These factors operate in the same direction, and are probably associated; it is extremely difficult to disentangle them on histological grounds.

The size of the area of ischaemia

When the area of ischaemia has been above a certain critical size, so that it is destined to contain a central dead area as well as the full series of margin zones, the vessels in the partial survival zone are severely damaged, and the vessels internal to this zone are quite dead. The attempted re-establishment of a circulation thus leads to stasis and dilatation of the sinuses.

When the area of ischaemia has been of only moderate size, some of the sinuses may permit a sluggish reflow of blood through them for a short time, probably to be measured only in minutes. This implies that there are small channels of outflow for the blood. The corpuscles are therefore able to pass on, but fibrin is laid down rapidly from the very slowly circulating blood, producing a coarse meshwork which is adherent to the damaged walls and soon closes the lumen completely.

When the area of ischaemia has been smaller, some re-establishment of the circulation is possible. The vessels do not become distended with blood but, owing to the damage to their walls and the slow circulation through them, a solid fibrin thrombus is laid down. This does not occlude the lumen, and a circulation of blood continues permanently through the vessels. As a result, the dead parenchyma undergoes fairly rapid necrosis-changes.

Small areas of ischaemia have had sufficient diffusion to allow the capil-
laries to survive, and thus a good circulation can be re-established through
them without any thrombosis occurring. Plaut (1952) examined a series of small
necroses of the pituitary gland in non-obstetric cases and noted that, though the
parenchyma was dead, the capillaries survived and there was no thrombosis.
He concluded that the necrosis was not due to mechanical obstruction of vessels.
His findings were obviously quite consistent with the present interpretation.

The last and mildest condition is a hypothetical one. If the area of arrest
of blood-flow has been very small (e.g. about 50 µ in diameter), diffusion
from the margin zone has been sufficient to keep the parenchyma as well as the
capillaries alive throughout the entire area during the period of ischaemia.
Thus, when blood attempts to flow through the area again, there is no impedim¬
ent to the re-establishment of a good circulation, and no subsequent histo¬
logical lesions occur either in the vessels or in the parenchyma.

*The duration of the ischaemia*

When the period of ischaemia has lasted long enough to kill the walls of all
the sinuses and capillaries, the vascular changes are those which have already
been described.

If the period of ischaemia has been of lesser duration, so that the parenchyma
has been killed but the endothelium of the sinuses and the capillaries has only
been damaged, a re-establishment of circulation through the area is possible.
The morphological changes will depend on the severity of the damage to the
endothelium. With severe damage and a slow blood-flow, a loose fibrin throm¬
bus will be formed, occluding the lumen and rapidly arresting the flow; with
less damage and a better blood-flow, a solid fibrin thrombus will be laid down
in the lumen and the flow will continue; with minimal or no endothelial
damage, there will be a full re-establishment of blood-flow without any throm¬
bosis.

The mildest grade is again a hypothetical one, but is a necessary assumption
in the series; it concerns the case where the period of ischaemia has not lasted
long enough to kill any of the tissues in the area. The time may be very tenta¬
tively assessed as in the region of about ½ to 1 hour. At the end of this period
a circulation of blood can be re-established throughout the area, and all the
tissues will retain their normal histological appearances. However, it is possible
that the function of the parenchyma may be impaired for a few days. This is
suggested by the clinical course of some patients who have a period of general
circulatory collapse at delivery but are revived by transfusion within an hour
or two. These patients do not seem to have a pituitary necrosis, at any rate of
clinically significant size, because they do not develop any signs or symptoms
of chronic hypopituitarism in the months and years subsequently. Nevertheless,
during the first few days after the delivery they may have a complete absence
of mammary activity, similar to that which occurs in patients who do develop
subsequent hypopituitarism. It may reasonably be inferred that in these cases
the pituitary gland has been subjected to a fairly generalised but short period of ischaemia, which has produced no important structural lesion but has caused a functional disturbance during the first few days of the puerperium.

Other factors

The vascular changes at the margin can also be influenced considerably by the force and volume of the attempted reflow of blood into the area. The flow down the portal vessels is the most important factor in this connection, but consideration of this point will be deferred to a later section. The flow along the capillaries into the margin of the infarct is less significant, but its effects can sometimes be identified in the field of supply of the inferior capsular artery or in the vicinity of large areas of surviving parenchyma. At these sites the capillaries at the margin may be distended by packed red corpuscles.

LESIONS IN THE PORTAL SINUSES IN THE STALK

The walls of the portal sinuses remain alive along their whole course down the stalk. However, various types of thrombosis are very common. These will be given separate descriptions here, but intermediate grades do of course occur.

The most severe lesion is a distension of the portal sinus along its entire length by a mass of packed red corpuscles. At the lower end of the sinus this continues directly into the mass of packed corpuscles in the branches of the vessel at the margin zone of the necrosis (as described in the previous section). This stasis lesion is more common in the main trunks of the posterior portal sinuses (Fig. 6), but occasionally affects some of the anterior ones (Fig. 7).

In less severe types, occlusive thrombi of loose fibrin are found in the lower ends of the portal sinuses, but the main branches further down contain thrombus made up of a mixture of fibrin and red corpuscles. As the branches of the sinuses pass into the partial survival zone, the fibrin component gradually diminishes and disappears so that the vessel contains only packed red corpuscles. Proximally the fibrin thrombus may build up in the main trunk of the sinus as a thin core in the centre of the lumen for a variable distance; this is sometimes only about 100 μ long but in other cases it extends for 2 or 3 mm up the stalk. In histological sections, the upper part of the sinus may contain some blood or appear empty.

In the least severe type the portal sinus contains no thrombus right down to the point where its branches pass into the margin of the infarct. Here the lumen becomes occluded by a short thrombus consisting of a meshwork of fibrin with red corpuscles entangled in it.

Comments

The survival of the walls of the portal sinuses in the stalk does not give any indication as to whether these vessels have carried a blood-flow during the
Figs. 6–9.


7. Stasis-congestion of anterior portal sinuses at the point where they enter the pars interloralis. 1¼ days post partum. H. E. × 26.

8. Gomitoli in stalk, showing gross stasis-congestion and some thrombosis. 1¼ days post partum. H. E. × 300.

9. Capillary network of stalk, showing widespread thrombosis. 2 days post partum. H. E. × 190.
period of ischaemia of the anterior lobe. The anterior sinuses run in the tuberalis septum, where, as will be described later, they are exposed to diffusion from the continuing circulation in this part of the stalk. The posterior sinuses lie on the surface of the stalk, where they are also exposed to diffusion from the cerebrospinal fluid. Thus, even if the portal sinuses carry no blood-flow at all, their walls remain alive.

There are two clues to the circulatory condition in the portal sinuses during the period of ischaemia of the anterior lobe. The survival of the stalk indicates that throughout this time the blood in its capillary network must have some outflow, though quite a small outflow would be sufficient to prevent infarction of the stalk. The route could be either via the parallel vessels and thus to the posterior lobe, or via one or more of the portal sinuses. There is evidence in support of the latter route. The survival of the pars tuberalis and a portion of the pars interloralis, even in the most severe cases, suggests that throughout the period of ischaemia of the anterior lobe there is a trickle of blood from the stalk down a few of the anterior portal sinuses, and escaping from the upper surface of the pars interloralis by the postero-medial group of superior hypophyseal veins. This trivial blood-flow down the anterior portal sinuses is insufficient to provide any blood supply to the main mass of the anterior lobe.

When the period of ischaemia ends, and an attempt is made to re-establish a circulation, the first event is that blood flows down the portal sinuses and into the branches which pass into the area of incipient infarction. As has been explained earlier, this leads to ballooning of the dead vessels in the margin zone by packed corpuscles, and further circulation through these vessels is impossible.

When the lower end of a portal sinus has all the branches at its lower end occluded in this way, there is no venous outlet for the blood. The whole sinus thus becomes filled by stationary blood, the plasma escapes through the walls, a slight refilling occurs, and so on, until within about a minute or so the lumen is packed with corpuscles along its entire length. This produces the condition described above as the most severe lesion.

If there are some small channels for the escape of blood from the lower end of the portal sinus, a slight flow may continue down the sinus. This flow permits the gradual but fairly rapid deposition of a loose fibrin thrombus on the proximal end of the mass of packed corpuscles which has just been formed in the dead sinuses at the margin zone in the anterior lobe. In cases where the flow is very sluggish, the fibrin thrombus may build up backwards for some distance along the lumen. Apart from this, the blood circulating through the sinus remains fluid; thus it can escape from the vessel after death, giving the histological picture of an empty lumen.

The least severe disturbance, with only minimal fibrin thrombus at the lower end of the sinus, appears to indicate a relatively good outflow. This applies
particularly to the anterior portal sinuses; the venous drainage from the pars interlateralis seems usually not to be interrupted.

The other factor of importance is the rate of flow into the upper ends of the portal sinuses. This is very poor when there are severe lesions in the vessels inside the stalk, as will be explained in the following section. Under these circumstances extensive thrombosis or stasis is common in the portal sinuses, and may extend up along their whole length. An impaired inflow to the upper end of the portal sinus is presumably almost invariably associated with an impaired outflow from its lower end, and it is scarcely possible to differentiate between the two effects.

LESIONS IN THE GOMITOLI AND THE CAPILLARY NETWORK OF THE STALK

There are no histologically recognisable changes in the gomitoli and capillaries of the stalk until several hours after the delivery. The changes which develop in them at that time, and the number of gomitoli involved, are closely related to the size of the early infarct of the anterior lobe.

When the necrosis of the anterior lobe is a large one, many or most of the gomitoli show characteristic lesions. Their sinusoidal capillaries are very widely distended by packed corpuscles, or by coarse fibrin thrombi attached to the wall and often occluding the lumen (Fig. 8). The central artery is not easy to find among the ballooned sinusoidal capillaries; in some gomitoli it can be identified and appears normal, but in others it is probably unrecognisable because it is so dilated and thrombosed. In the gomitoli whose sinusoidal capillaries are distended with corpuscles or thrombus, the short arterioles can not be recognised.

When the necrosis of the anterior lobe is rather less extensive, most of the gomitoli are normal but some of them have solid fibrin thrombi in the centre of the lumen of a few of their sinusoidal capillaries. These thrombi must not be confused with the smaller hyaline bodies which are sometimes found lying free in the lumen of the stalk capillaries of normal pituitary glands.

When the pituitary necrosis is only a small one, there are no recognisable lesions in the gomitoli.

The capillary network of the stalk is always less affected than the gomitoli. When the necrosis of the anterior lobe is a very large one and the majority of the gomitoli show lesions, parts of the capillary network show stasis or fibrin thrombosis (Fig. 9), and this thrombosis may extend right along to the larger sinusoids which form the origin of the main portal sinuses (Fig. 10). Most of the gomitoli in these patches are severely damaged, and their ballooned sinusoidal capillaries have sometimes ruptured, giving rise to petechial haemorrhages. The neural stalk may show small patches of necrotic softening.
These cases have a very striking naked-eye appearance at autopsy. The stasis in these small vessels makes the entire stalk and tuber cinereum bright red, with a sharp line of delimitation from the normal white hypothalamic tissue above the tuber. The posterior portal sinuses are usually very prominent and bright red because of their distension by red corpuscles.

In the cases where the pituitary necrosis is small, there are only minor lesions of the gomitoli, the capillary network is not thrombosed, and the tissues of the stalk appear normal.

The parallel vessels across the genu only rarely show any thrombosis or stasis.

Comments

The initial problem concerns the survival of the stalk. This structure is too thick to be kept alive only by diffusion from the cerebrospinal fluid, and must therefore have some continuing blood-flow through its capillary network during the period when the anterior lobe is ischaemic.

This blood-flow comes either by way of those gomitoli which are still open during the period of ischaemia, or as a direct arterial supply by the short stalk arteries. The amount of the circulation varies from case to case. When there is a good flow, the blood permeates throughout the whole capillary network, and the resultant diffusion keeps all the tissues of the stalk alive, including the gomitoli. When the capillary circulation is less satisfactory, some of the gomitoli may suffer partial damage during this period. When the circulation is reduced still further, gross lesions occur in groups of gomitoli and in the capillary network related to them, and these areas of the stalk may be severely damaged or even killed.

Though some circulation seems to continue in the capillary network of the stalk, it is probably very slight, as was explained in the previous section. Thus it may be inferred that in the severe cases there is a great reduction or an arrest of blood-flow through the majority of the gomitoli at this stage, and thus that many of these structures are damaged.

At the end of the initial period of ischaemia, blood begins to flow through the gomitoli again. Their short arterioles are probably temporarily paralysed and thus may allow blood to pass at high pressure from the central artery into the sinusoidal capillaries. The subsequent course will depend on the degree of damage that the gomitoli have suffered during the period of ischaemia. If they have been badly damaged, the sinusoidal capillaries become ballooned by packed corpuscles, and the flow ceases at once. With slightly less damage there may be some poor circulation for a minute or two, allowing the formation of a loose fibrin thrombus which rapidly stops the flow. Minor damage will permit a better circulation, and the only effect on the sinusoidal capillaries is that a thin solid fibrin thrombus is formed in the centre of the lumen. With less damage still, the gomitoli will show no lesions.
It will be clear that there is no histological method of determining whether a gomitolo has survived because some blood has continued to flow through it during the period of ischaemia of the anterior lobe, or because it has been in the diffusion area of the circulation in the capillary network. The distinction is not of practical importance, as in either case the gomitolo will be capable of normal function when the period of ischaemia passes off, but the theoretical implications are significant in regard to the discussion in the next section.

The lesions in the capillary network are explicable on lines similar to those which apply to the gomitoli. They are most marked in the areas of partial necrosis of the stalk, where there has presumably been no blood-flow during the initial period.

It is sometimes suggested that the stasis in the sinusoidal capillaries of the gomitoli is due to an obstruction of their outflow as a result of the arrest of the circulation down the portal sinuses. This is not a valid explanation; lesions can be found in gomitoli when the related capillary network shows no distension by corpuscles.

**LESIONS IN THE ARTERIES SUPPLYING THE GOMITOLI**

This part of the arterial system falls into three anatomical subdivisions.

1. The vessels which run in the arachnoid space before they reach the pituitary gland or its stalk. These consist of the superior hypophyseal arteries, the arterial plexus around the upper end of the stalk, and the loral arteries in their course from that plexus down to the upper surface of the anterior lobe. No lesions are seen in any of these vessels.

2. The loral arteries in their course through the anterior lobe to the genual septum. Important lesions occur here; they will be detailed below.

3. The long stalk arteries which are the terminal branches of the loral artery and ascend the stalk, and the short stalk arteries which pass directly into the stalk from the arterial plexus. Nearly all of these arteries subdivide and finally terminate as the central arteries of the gomitoli. Apart from the rather uncertain lesions in the central arteries themselves, which have been described in the previous section, there are no histological changes in this part of the arterial system.

The problem of particular importance concerns the loral artery in its course through the pituitary gland. Its condition here depends on the extent of the necrosis in the anterior lobe.

When the infarct is a very large one, the loral artery becomes necrosed as soon as it enters the margin zone. The passage of the artery into the infarct does not indent the straight line of the edge of the necrosed area. The artery is widely distended, and during the first day it is filled with red corpuscles along its whole course through the infarcted tissue. Within about a day, there
Figs. 10–13.

10. Thrombosis and stasis-congestion of capillary network of stalk near point of origin of posterior portal sinuses. 2 days post partum. H. E. × 100.


12. Live segment of loral artery projecting into main area of infarction with a thin cuff of live parenchyma. 1½ days post partum. H. E. × 52.

13. Survival of fibrous core artery and of a shallow cuff of parenchyma around it. The longitudinal segment of loral artery is also alive. 2 days post partum. H. E. × 28.
is lysis of the corpuscles in the segment of the artery which traverses the central dead area, and the lumen then appears empty. Necrosis-changes are obvious in the media where the artery passes through the peripheral dead zone. When the polymorph zone appears, some of these leucocytes accumulate under the endothelium and disintegrate there, giving the characteristic appearance of a »basophil intimitis«.

When the infarct is less extensive, the loral artery appears normal as it passes through the surviving part of the anterior lobe (Fig. 11). When it reaches the infarct it may continue alive for some distance beyond the general outline of this area, and carry in a narrow cuff of live parenchyma around it, about one or two alveoli deep (Fig. 12). Further in, the cuff of live tissue becomes very thin and finally disappears, and the vessel passes through the indented line of the peripheral dead zone. At this point the arterial wall suddenly becomes necrotic and an occlusive fibrin thrombus usually fills the lumen. Sometimes this extends a little proximally as a mural thrombus along the segment which carries the cuff of live tissue. Occasionally the thrombus continues distally as a dense meshwork of fibrin along the endothelial surface of the artery for some distance into the central dead area. A different type of lesion is sometimes seen at the point where the artery passes into the peripheral dead zone and becomes necrotic; red corpuscles may erupt into the wall, giving the lesion known as »haematomedia«, and very occasionally this blood may extend out a little into the adventitia. Otherwise the changes in the artery in the central dead area are as described earlier; it is dilated and filled with corpuscles which disappear at about 18 to 24 hours.

In the cases where the necrosis of the anterior lobe is of only small size, the loral artery passes entirely through healthy tissue and shows no lesions.

Comments
The general pathological principles on which the lesions are interpreted are as follows. Ischaemic lesions in an artery depend on two factors: the flow of blood down its lumen, and the circulatory condition in the tissue around it.

If the surrounding tissues have a continuing circulation, this provides adequate diffusion to keep the walls of the artery alive, whether or not blood continues to flow down the lumen. Thus no histological changes will develop in the artery. It is impossible to decide from the histological appearances of the segment of an artery traversing live tissue whether or not there has been a circulation through the vessel; conclusions on this matter can only be reached by inference from the condition of the other segments of the artery.

A very different condition obtains when the artery passes through an area of tissue which has been deprived of all other blood supply, so that there can be no diffusion from outside to keep the artery wall alive. If during the first few hours there is no flow down the lumen, the artery dies in that part of its
course which traverses the area of general tissue ischaemia, and, when subsequently some blood-flow begins in the vessel, a thrombus will be formed in the lumen at the point of junction between the live and the dead segments. On the other hand if during the first few hours there is even a slight flow of blood through the lumen of the artery, this flow of blood will provide sufficient diffusion to keep the wall of the artery alive and also to maintain a cuff of surviving tissue around it through the area where all the other tissue is dead. The width of this cuff depends upon the efficiency of the blood-flow through the artery. A special version of this circulatory condition is sometimes seen in the outer part of an infarct; it is possible for blood to flow into an artery for a short distance, even though the vessel is occluded near the centre of the infarct so that the flow has no peripheral outlet. The blood in this segment of the artery is presumably only moving to-and-fro in relation to the pulse wave, but it remains fluid temporarily and can keep the wall of the segment alive and even maintain a narrow cuff of live parenchyma around it. After a day or so a solid occlusive thrombus is formed in the lumen at this point.

The condition of the arteries in the pituitary gland is readily explained in accordance with the above general principles.

(1) All the arteries of the first part of the system lie in the subarachnoid space, where they are bathed in cerebrospinal fluid and thus receive adequate diffusion from outside. This is quite sufficient to account for their normal histological appearances, and no conclusions can be drawn about the blood-flow through them during the period of ischaemia of the anterior lobe.

(2) The segment of the loral artery which lies in the infarcted part of the anterior lobe and is necrosed can have had no blood-flow during the period of ischaemia. The real problem concerns the blood-flow in the segment proximal to the infarct.

When the artery passes into the infarct without indenting the general line of the margin, it is very probable that there has been no blood-flow along the live segment of the artery for some distance before it reaches the margin zone, and that this proximal segment has survived purely as a result of diffusion from outside.

On the other hand, when the first part of the loral artery survives and carries a cuff of live tissue around it into the outer part of the main area of the infarct, there must have been some movement of blood in this segment, and therefore there must have been a blood-flow in the more proximal part of the artery where it runs through the live tissue before it reaches the infarct.

When the loral artery passes through healthy anterior lobe tissue along its entire length, it has presumably carried a blood-flow, but the evidence is equivocal. Some of the survival of the tissue might be due to diffusion from the lumen of the artery, but the live area is usually so extensive that it is almost certainly receiving a fairly good portal blood supply. It should be pointed
out that the loral artery never passes across the area of a small necrosis.

(3) Considerable interest attaches to the survival of the long stalk arteries. They have lost their main source of blood because their parent vessels, the loral arteries, are necosed and occluded in their course through the infarcted anterior lobe. Nevertheless this does not prove that the long stalk arteries carry no blood-flow during the period of ischaemia; they have a possible supply by other channels: viz. anastomoses low down in the stalk with the genual branches of the interlobar arteries, and also anastomoses high up in the stalk with the short stalk arteries which come from the superior hypophyseal plexus. Furthermore, the long stalk arteries could certainly survive because of diffusion from the continuing capillary circulation in the stalk. As has been previously explained, the capillary network of the stalk is not entirely supplied by the long stalk arteries; some of the gomitoli derive their arterial supply from the short stalk arteries.

LESIONS IN THE ARTERIES TO THE ANTERIOR LOBE

(1) The artery of the fibrous core is the largest of the vessels which give a direct arterial supply to the anterior lobe.

In all large infarcts, the loral artery is necosed before it gives off the artery of the fibrous core, and this latter vessel is therefore involved in the general necrosis. When the infarct is not quite so large, the loral artery may remain alive beyond the point where it gives off the artery of the fibrous core. This artery then survives and carries a cuff of live tissue around it down to near the lower end of the fibrous core but usually no further (Fig. 13). In small necroses the loral artery and the artery of the fibrous core are normal, and there is survival of all the tissue from in front of the fibrous core back to the posterior lobe.

(2) The communicating artery, which originates from the interlobar artery and unites with either the loral artery or the upper end of the artery of the fibrous core, is usually nearly as large as the latter vessel.

In the case of a large infarct, the communicating artery dies as it passes through the margin zone at the back of the necrosed area. When the infarct is less extensive, the artery may continue alive for some distance into the necrosed area, carrying a cuff of live tissue around it. Small infarcts do not involve the region of the communicating artery.

(3) The inferior capsular artery gives capillary twigs into the lateral pole, but does not itself enter the gland as an artery. No lesions have been identified in this vessel in the capsule.

Comments

From the vascular anatomy of the pituitary gland it is clear that an extensive necrosis of the anterior lobe can not be produced by an arrest of the portal
circulation alone; the direct arterial supply must also be affected during the initial period of ischaemia.

The histological findings indicate that in all the large necroses there has been in fact no blood-flow along the artery of the fibrous core or along the communicating artery. When the necrosis is smaller these arteries remain alive, but it is impossible to determine whether this survival is due to a good blood-flow down their lumen, or to diffusion from a good portal circulation in the area.

Evidence of a more definite character about one part of the direct arterial supply can be obtained from the condition of the lateral pole of the anterior lobe. In the normal gland, this region receives its direct arterial supply from the inferior capsular artery and from a thin branch of the artery of the fibrous core; it receives its portal blood supply mainly from the posterior but also from the anterior portal sinuses. The relevant evidence may be considered in regard to two different conditions.

(a) The potential efficacy of the direct supply by the inferior capsular artery alone can be assessed from the findings after a transfrontal surgical hypophysectomy uncomplicated by cauterisation of the sella. In such an operation part of one lateral pole of the gland is usually left in situ. This tissue can obtain its blood supply only from the inferior capsular artery, since the superior and inferior hypophyscal arterial systems and the portal vessels have been removed with the rest of the gland and the lower half of the stalk. The amount of tissue which survives at the lateral pole is often quite large; it ranges from 30 to 60 mm³, as measured by serial sections in seven cases dying at a few days to a few weeks after surgical hypophysectomy. This volume may be taken as an index of the blood supply by the normal inferior capsular artery.

(b) In the case of a large post-partum necrosis the lateral pole has a similar limitation of its possible source of blood supply. This blood can come only from the inferior capsular artery; the alternative blood supplies by the portal vessels and by the artery of the fibrous core are cut off by thrombosis, and no capillary seepage is possible because the anterior lobe has undergone massive necrosis. Nevertheless, in this particular condition there is either no surviving tissue at the lateral pole, or a small islet whose volume is only about 2 mm³. This great difference from the condition following hypophysectomy indicates that, during the ischaemic episode which causes a post-partum necrosis, the direct arterial supply by the inferior capsular artery must be completely arrested or at any rate reduced to a minute trickle.

**LESIONS IN OTHER VESSELS**

In a few cases where there is a large necrosis of the anterior lobe, there may be an extension of the necrosis into the posterior lobe or into the genu of the
stalk, associated with thrombosis of small vessels in the posterior lobe or even in the parallel vessels. This is presumably due to a vascular disturbance similar to that which occurs in the blood supply of the anterior lobe; it may possibly be related to an anomalous distribution of vessels in the gland. The lesion is of clinical importance because it may give rise to the diabetes insipidus which occasionally follows a post-partum necrosis; the literature on this subject has been reviewed recently (Evans 1960).

LESIONS IN THE PITUITARY VEINS

Sometimes a small thrombus is found in the veins running from a necrosed area of the anterior lobe into the cavernous sinus. This appears to be secondary to the necrosis.

The subject is however of some importance in other conditions. Non-infected thrombosis of the cavernous sinus, sometimes bilateral, is found occasionally in obstetric autopsies, and is a remarkably symptomless condition. In the cases personally observed, it was a quite accidental finding during the routine removal of pituitary glands. One of the cases was associated with, and possibly secondary to, a pituitary necrosis, but in the others the pituitary gland was quite healthy. Thus a bland thrombosis of the cavernous sinus in obstetric patients can not be linked aetiologically with pituitary necrosis. On the other hand there are several cases in the literature where septic thrombosis of the cavernous sinus has resulted from infection of the middle ear, the sphenoid sinus or the orbit, and has produced either simple necrosis or an abscess of the pituitary gland. There do not happen to be any recorded cases of this condition occurring in pregnancy.

In this connection, it may be mentioned that Gotshalk & Tilden (1940) having observed a case of post-partum pituitary necrosis where the pars interlroralis projected considerably above the opening of the diaphragma sellae and was not involved in the necrosis, raised the question as to whether the enlargement of the pituitary gland in pregnancy might so compress the vessels, presumably the veins, as to occlude them and cause pituitary necrosis. This is not an attractive theory. In obstetric autopsies it is not uncommon to find a pituitary gland so large that the pars interlroralis projects as a small knob above the diaphragm, but pituitary necrosis is no more common in these patients than in those with relatively small pituitary glands.

THE NATURE OF THE VASCULAR DISTURBANCE

The principal conclusion from the study of the development of the histological changes is that there is an initial period of ischaemia of the anterior lobe followed by an unsuccessful attempt at reflow of blood into the area. This
implies that the local cause of the initial ischaemia is a functional and not an organic obstruction.

The most obvious hypothesis, though an unsatisfactory one, is that the ischaemia of the pituitary gland is a simple haemodynamic result of the low pulse pressure and low blood pressure during the period of general circulatory collapse, so that a satisfactory flow can not be maintained through the double capillary bed of the pituitary portal system, or even through the direct arterial supply to the gland. This explanation encounters two major difficulties. The first is that any general impairment of the circulation sufficient to arrest the portal blood-flow in the pituitary gland should equally affect other portal circuits in the body, such as those in the liver and the kidney. The usual causes of the general circulatory collapse which gives rise to pituitary necrosis in an obstetric patient are retained placenta and post-partum haemorrhage, and, in fact, these disturbances are not followed by necrosis in the liver or the kidney. Secondly, if the general circulation is so poor that it can not provide a blood-flow along the direct arterial supply of the anterior lobe, there should be a corresponding arrest of arterial blood-flow to many or all of the other organs.

A more tenable explanation is that the local ischaemia is produced by an occlusive spasm of the arteries to the anterior lobe and the stalk. This cuts off the arterial supply to the gomitoli and thus leads to an arrest of the portal circulation, and it also cuts off the direct arterial supply to the anterior lobe. As a result, there is ischaemic death of all the affected area of the anterior lobe. When the spasm of the arteries passes off, morphological changes occur in the vessels, but these are purely secondary to the damage produced in the initial stage of ischaemia. The differences in the extent of the necrosis of the anterior lobe are explicable as due to differences in the severity or duration of the spasm in the arterial tree.

The presumed spasm is peculiarly localised to the arteries which supply the anterior lobe, either directly or via the portal circuit. In large necroses there is clear evidence of an arrest of blood-flow in the loral arteries where they enter the anterior lobe. The blood-flow is greatly reduced in most of the arteries which enter the stalk from the superior hypophyseal plexus, though the stalk has some continuing circulation, either by a few of the short stalk arteries or by the genual arteries. In the great majority of cases there is no significant impairment of blood-flow in the inferior hypophyseal circulation, but there is no blood-flow along the communicating artery which passes from the inferior hypophyseal circle into the anterior lobe. The inferior capsular artery ceases to supply the lateral pole. Thus the arrest of the blood-flow, and the site of the presumed spasm, seems to occur at the points where the arteries enter the anterior lobe. In addition, it is certainly possible that there could also be a spasm in the short arterioles of the gomitoli, or in the muscle sphincters around the portal vessels, but this is not a necessary postulate.
It seems probable that the spasm in the branches of the superior hypophyseal artery does not extend far back towards the origin of the artery. The proximal part of the artery provides branches to the optic nerve and optic chiasma, and these structures almost always survive, though there is one case in the literature (Stewart 1936) where the patient became blind at the same time as the pituitary necrosis occurred. However this is an involved problem; blindness is a rare but well-recognised complication of severe haematemesis.

In a large necrosis the site of the lesion and of the areas of surviving parenchyma is fairly clearly related to the distribution of the vascular supply of the anterior lobe. The smaller necroses present a special case.

The anastomoses among the capillaries and small sinusoids of the anterior lobe are very extensive, and a local vascular spasm around the site of a small necrosis would be difficult to envisage. The probable course of events is that there is a great reduction of blood-flow to the entire anterior lobe, though not a complete arrest. The blood pressure in the capillaries of the anterior lobe is insufficient to provide a uniform circulation, and certain small areas become totally ischaemic. The condition is analogous to the necrosis of one toe in a patient who has obstruction of the femoral artery.

The conclusion that there is a spasm of the arteries to the anterior lobe and stalk leads on to the question of why this spasm occurs, and particularly why it is relatively common and severe in obstetric patients. No satisfying explanation can be given. The following remarks and speculations are intended merely as indications of lines for future study, and do not clarify the problem.

(a) There is considerable obscurity about the physiology of the pituitary stalk.

The gomitoli are very peculiar structures whose real function is completely unknown. However, their histological appearance suggests that one of their actions is to govern the flow of blood into the capillary network of the stalk; this might conceivably be under nervous control from the hypothalamus.

The capillary network of the stalk appears histologically to be of relatively banal type, but there is presumably some important physiological reason for the interposition of this vascular bed into the main blood supply of the anterior lobe. The tissue of the neural stalk can certainly take up considerable amounts of various substances from the circulation (thyroxine and adrenalin are well-known examples), and it may possibly secrete release-factors or other hormones. Any of these could theoretically give rise to local effects on the gomitoli, or could be passed on via the portal system to exert control on the function of the anterior lobe or on its blood supply (Harris 1951; Zuckerman 1954).

At normal parturition there is a sudden change in the endocrine balance which has been maintained during pregnancy, and this may well involve an adjustment of the blood supply to the pituitary gland. When any patient has
a severe general circulatory collapse, various endocrine reactions occur, such as the rapid secretion of adrenalin or of adrenal steroids, and some of these might accumulate in the stalk in abnormal amounts. The association of the two clinical states (delivery and shock) might thus produce specific disturbances in the blood supply to the pituitary gland.

(b) In obstetric patients certain particular parts of the arterial system respond in an extreme degree to specific clinical disturbances. For example, concealed accidental haemorrhage (abruptio, or premature separation of the placenta) gives rise to a transient spasm localised to the intralobular arteries of the kidney, and thus causes renal cortical necrosis. Hypertensive toxaemia causes marked vasomotor disturbances in small hepatic arterioles, and produces the characteristic liver lesions. Certain bacteria or their toxins affect the arteries to the adrenal cortex and produce haemorrhagic infarction there. Thus, for some unknown reason, the effects of each individual type of stimulus are almost entirely confined to one corresponding part of the arterial system. These analogies illustrate, though they do not explain, the problem of pituitary necrosis; a general circulatory collapse at the time of delivery produces the standard generalised vasoconstriction of «shock», but this vasoconstriction is of extreme degree only in the vessels of the anterior pituitary gland.

There have been two reports of the experimental production of pituitary necrosis in animals by non-surgical methods, such as by the administration of ergot (Nassar et al. 1950) or by the administration of chorionic gonadotrophin (Orcoyen & Cano 1954). The illustrations of the lesions in both these papers are unconvincing. In the present series of human cases, ergot had sometimes been used, but the great majority of the patients had not been given this drug.

(c) McKay et al. (1953) suggest that the disturbance leading to the pituitary necrosis is essentially a sudden intravascular deposit of fibrin caused by a mechanism which is similar to, if not identifiable with, the Shwartzman phenomenon in experimental animals. Thus they link it with their explanation of the lesions of eclampsia and of bilateral renal cortical necrosis. They point out that the thrombi may form and then quickly lyse in vivo; a process which might account for the transient nature of the pituitary ischaemia. However, in the cases where there is renal cortical necrosis associated with a pituitary necrosis, the association seems to be purely coincidental: retroplacental haemorrhage can give rise to renal cortical necrosis and can at the same time also give rise to a severe circulatory collapse, and this latter may in turn cause a pituitary necrosis (Sheehan 1948). The explanation offered by McKay et al. (1953) does not account for the fact that the great majority of cases of pituitary necrosis in obstetric patients are due to post-partum haemorrhage or retained placenta, and are not accompanied by renal cortical necrosis or by toxaemic lesions in the liver or kidney.

(d) Small areas of necrosis in the anterior lobe are not uncommon in routine
autopsies on non-obstetric patients, but they are easily missed unless numerous sections are made through the gland. The reported incidence is about 3 per cent: Simonds (1925) found them in 6 out of 200 autopsies, Cavallero (1946) in 4 out of 300 autopsies, Plaut (1952) in 13 out of 149 autopsies, Wagner & Sharrett (1956) in 30 out of 1735 autopsies, and Wolman (1956) in 12 out of 270 autopsies. Rather larger areas of necrosis may be due to various conditions: tumours or inflammatory processes near the sella, damage to the stalk in cases of fractured base, arteritis, epidemic haemorrhagic fever, or in association with raised intracranial pressure, sometimes due to gliomas. The earlier literature has been reviewed elsewhere (Sheehan 1937; Sheehan & Summers 1949); further cases have been reported by various authors (Plies 1955; Shelling & Remsen 1935; Coulter & Morey 1953; Hullingshorst & Steer 1953; Powell 1954; Lukes 1954; Aring 1955; Joseph & Levin 1956; Fassbender 1957). Larger necroses are rather common in diabetes mellitus, and can be of clinical importance. The literature on this subject up to 1957 has been analysed in detail (Sheehan 1957); several further cases have since been reported (Calvert & Caplin 1957; Kemp 1957; Moore 1957; Grunberg & Blair 1957; Shafar & Dutton 1957; Elliott et al. 1958; Nyiri 1958; Dingman et al. 1958; de Graeff et al. 1959; Frey 1959; Vague et al. 1959; Mićić 1960; Boulet et al. 1960; Martin et al. 1960).

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