PITUITARY NECROSIS IN ROUTINE NECROPSIES*

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Subtotal necrosis of the anterior pituitary body, as it is observed after childbirth, is ascribed to the anoxemia of circulatory disturbance associated with shock and severe hemorrhage. It is not to be expected that an "all or none" law governs this process; one might rather expect intermediate phases between subtotal necrosis and the normal condition. Since severe, irreversible circulatory disturbance naturally may precede death, such necrosis could occur not only in women who have died after childbirth but also in those who have succumbed under other conditions.

Many of the authors who have examined numerous sections of the pituitary gland in various pursuits either do not mention necrosis, or mention it more or less casually. Kraus,[1] in 1926, stated that pituitary necrosis is "by no means rare." Finding small foci of necrosis accidentally in various necropsies induced me to study this problem.

MATERIAL, METHODS, AND FINDINGS

The pituitary glands from 149 necropsies were removed in the usual fashion. They were sectioned horizontally or sagittally, depending upon their shape. Sections were cut at 6 or 7 μ and stained with hematoxylin and eosin. Routinely, 2 sections were taken from each block. There were 2 blocks when the pituitary gland was cut horizontally, and generally 4 when it was cut sagittally.

Necrosis was found 12 times in the routine sections; in one case it was detected on serial sectioning. Numerous sections were cut from most blocks. In many cases series or step series were examined.

The suspicion that such necrotic areas represent post-mortem change will hardly arise. They are surrounded by well preserved tissue and they are present in necropsies done as early as 4 hours, 2 hours, even 1½ hours after death. Neither can they be explained, even the smallest ones, as an exhaustion phase in the secretory cycle.

In 7 cases, only one necrotic focus was found. Serial sections were

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available in 2 of these cases; in 3 others, 100, 70, and 55 sections, respectively. Of the 2 remaining cases, 18 sections each were examined. Three pituitary glands contained 3 foci each; in 3 other cases the number of necrotic foci was 4, 5, and 6, respectively.

Most of the necrotic foci were situated near one of the connective tissue structures, mainly the capsule, but also near the border of the two lobes and near the hilar connective tissue. Twice necrotic glandular tissue occupied a narrow space between capsule and hilum, thus being near a connective tissue structure on more than one side. Necrosis was found also in the cells of the anterior lobe that had migrated into the posterior lobe. The central portion of the anterior lobe seldom was the seat of necrosis. A thin, sometimes very thin, layer of well preserved epithelial cells generally was interposed between the connective tissue structure and the necrotic area. The total volume of necrotic tissue in no case exceeded 1 cc.; it generally was much less. The largest necrotic focus measured 5 mm. in diameter; 2 others, 3 mm.; one, 2 mm. In 4, the size was 1.5 mm.; in 5 others, about 1 mm. Many of the foci were smaller.

There was much variation in shape; most of the subcapsular foci were flat and curved; those near the region of the pars intermedia were mostly round or ovoid. Some were irregular with finger-like protrusions. It was difficult, in such cases, to know whether small necrotic spots were discrete or formed part of one larger focus. None of the foci, when studied in serial sections, was definitely wedge-shaped or pyramidal. The spherical or ellipsoid shape of some was astonishingly regular.

The necrosis mainly involved the epithelial cells; the blood vessels in many foci were more or less preserved and had conspicuous endothelial nuclei. The cytoplasm generally was more severely damaged than the nuclei, but occasionally the reverse was seen. The three cell types showed no difference in their relation to necrosis. The capillaries within the necrotic foci did not differ much from those of the surrounding tissue. They were in most cases wide and filled with well preserved red blood cells. One large necrotic area was surrounded by a thin layer of tissue with narrow capillaries, while capillaries in the necrotic area and in the more remote surroundings were distended.

Necrosis in the masses of basophilic epithelial cells that have migrated into the posterior lobe results in a slightly different picture because the posterior lobe has no network of sinusoids. One necrotic area (2 mm. in diameter) appeared homogeneous. Some of the posterior lobe tissue proper between the epithelial cells had become necrotic also, and its nuclei did not take the stain. No leukocytes were seen,

and there were few red blood cells. The posterior lobe outside the area invaded by the epithelial cells did not show necrosis. In another case, several very small patches of necrosis were scattered through a large area of invading basophils. These small necrotic spots stained intensely with eosin. Such a picture never results from the normal disintegration of the basophilic epithelial cells in the posterior lobe.

Leukocytes were absent in one-third of the lesions; in some cases they were scattered through the dead tissue in various numbers, and were easily recognized by their well stained nuclei. They were situated more in the necrotic tissue itself than in the lumina of the capillaries. In one sharply outlined, round, subcapsular focus the sinusoids were filled with leukocytes. This focus differed from the others in having a narrow zone of edema surrounding it. The tissue around necrotic foci showed very little cellular reaction; usually none at all. No lymphocytes or plasma cells were found. No attempt was made to determine the age of the necrotic process. There were no scars that could be interpreted as the result of necrosis, nor were there any crescent-shaped, subcapsular, fibrous spots. Large, flat, subcapsular areas, which in distribution and shape resembled the foci of necrosis, were present in one specimen. They seemed to consist essentially of wide, blood-filled vessels without leukocytes, of deeply stained colloid, and of various interspersed, non-characteristic nuclei. The remnants of the cytoplasm of the dead epithelial cells were much less conspicuous than in other foci.

The larger and medium-sized blood vessels of the pituitary gland were best studied in the angle between the lobes, and in the hilar connective tissue. With one exception, no important narrowing and no occlusion were found in the cases with necrosis or in those without. In one pituitary gland a small artery in the posterior lobe was narrowed by thrombosis, but the necrosis was in the anterior lobe. No thrombi were found in the necrotic areas, in their neighborhood, or in other portions of the pituitary body.

Up to the age of 50 years (all males, none under 21), the distribution of positive cases over the decades was fairly even (2 of 12 in the third, 2 of 13 in the fourth, 3 of 11 in the fifth). There were 29 pituitary glands from men between 51 and 55 years with 4 positive cases, against only one positive case in the 38 specimens from the second half of the sixth decade. There were 11 cases with necrosis among 60 patients under 55 years, but only 2 cases with necrosis among 94 pituitary glands from men over 55 years of age.

Necrosis caused by tumor masses or by meningitic exudate around the pituitary gland was not included in this paper. In a group of 16

cases with space-occupying intracranial lesions, necrosis was present 3 times. Six of these patients had undergone craniotomy, and necrosis was found in one. Of the 32 cancer cases, 2 had necrosis; of 9 cirrhosis cases and of 19 cases of encephalomalacia, 1 each. Hypertension had been an outstanding symptom in 11 patients and 4 of them had necrosis, 2 after sympathectomy.

The clinical conditions in the last days of life were not uniform. While in some patients shock and severe peripheral circulatory failure were noted, necrotic areas were present in 2 patients who had died unexpectedly and rapidly.

Microscopic sections and some data of 11 other cases of pituitary necrosis (from Beth Israel Hospital, New York City) were available. They could not be evaluated statistically because the data on the corresponding negative cases were lacking. But it may be useful to enumerate the diseases and conditions mentioned in all 24 cases in which pituitary necrosis was found: diabetes, 2; chronic renal disease, 3; essential hypertension, 2; intracranial hemorrhage, 2; encephalomalacia, 3; severe acute hemorrhage, 4; major operation in the last 2 weeks of life, 6 (3 of these craniotomy); shock in the last 2 weeks of life, 4.

Comment

Comment on clinical correlations can be short. The material, in most respects, is too small for detailed statistical evaluation. The older age groups and those with encephalomalacia yielded far fewer cases of pituitary necrosis than hypertensive patients and those of younger age groups. This may indicate that anatomical narrowing of arteries is less conducive to pituitary necrosis than vascular dysfunction, notably hyper-reactivity. It remains to be seen whether the occurrence in 2 patients following sympathectomy is accidental or meaningful. One died 8 hours after operation. According to Sheehan and Murdoch,[2] pituitary necrosis takes at least 14 hours to develop.

Scars in the pituitary gland are rare because the necrosis generally occurs under conditions that lead to death. Sheehan and Murdoch,[2] however, have found small scars in women who, years before, had gone through severe obstetric illness. Probably, the pituitary gland during pregnancy is so susceptible that necrosis can take place in it even under non-fatal conditions.

The rôle of embolization in the genesis of pituitary necrosis will be discussed on the assumption that subtotal necrosis after delivery and small foci of asymptomatic necrosis represent different degrees of the same process. Before Sheehan's[3] work, it was almost generally assumed that pituitary necrosis was caused by embolic occlusion of blood

vessels. The terms necrosis, ischemic necrosis, embolic necrosis, and infarct are used interchangeably in the older literature. In his classical paper on fatal destruction of the pituitary gland, Simmonds[4] took it for granted that the lesion in the pituitary gland was embolic. He stated, however, that the larger vessels were normal. In several papers, Simmonds[5-8] referred to septic diseases in which he found emboli of bacteria and foci of necrosis in the pituitary body. He designated the lesion in one of his cases as embolic necrosis. He stressed the absence of changes in the walls of blood vessels.

Simmonds[8] was aware of the multiple blood supply of the pituitary gland as found by Luschka[9] and by Dandy and Goetsch.[10] With Luschka he believed that the numerous small vessels that run to the anterior lobe from the stalk were arteries. He realized that the occurrence of infarcts is inconsistent with multiple blood supply. He therefore asked Benda to reinvestigate the blood supply of the pituitary gland. Benda[11] came to the conclusion that the small vessels running along the stalk enter only the posterior lobe, and that the anterior lobe receives its blood mainly through one small artery coming from the carotid within the cavernous sinus. In this Simmonds found confirmation of his opinion that the pituitary lesions described by him were embolic. He wrote that this new statement pleased him very much because now larger embolic lesions of the anterior lobe became understandable.

A glance at the photographs of lesions described by Simmonds as embolic indicates that many of them are identical with the ones described in this paper. The septic nature of Simmonds' cases may have been a factor in the causation of necrosis, but I do not believe that the lesions were embolic. One of Simmonds' papers[7] on embolic processes in the hypophysis included a case of complete necrosis of the anterior half of the anterior lobe. This patient had died of heart disease 7 days after delivery, and there was no sepsis. The lesion was called anemic infarct occasioned by childbirth. None of the illustrations in Simmonds' papers shows a plug in a pituitary vessel of adequate size.

Among the pituitary lesions which I[12] described in 1922, only 2 were examples of necrosis in the anterior lobe (cases 9 and 16). I called them infarcts, erroneously, as I think today. Baló[13] mentioned arteries obliterated by emboli in one case of pituitary necrosis, and postulated them in another one. Both were young diabetic patients with pulmonary tuberculosis. Kraus,[1] in a pituitary gland with necrosis, found an artery occluded by intimal overgrowth. The patient was a woman, 61 years of age, with diabetes and hypertension. Kraus

stated that necrosis in young diabetic patients with an intact vascular system is entirely unexplained. He stressed the discrepancy between the two facts that the anterior lobe is so rich in blood vessels, and that necrosis is found mainly in circulatory disorders.*

Kaminsky,[14] to my knowledge, was the first to deny the embolic origin of pituitary necrosis. He mentioned the possible importance of difficult deliveries and uterine hemorrhage. Sheehan, in his paper of 1937,[3] explained post-partum necrosis by thrombosis of the sinusoids in the anterior lobe. He found some sinusoids thrombosed, but never a larger vessel, and he did not see widespread capillary thrombosis. He realized the difficulty of proving the causative rôle of the thrombi. In a later paper,[2] he gave an explanation—which he considered quite speculative—namely, that the blood flow to the involuting anterior lobe is physiologically reduced at the time of delivery and that shock reduces it further, bringing on thrombosis. The extent of thrombosis as described by Sheehan makes it appear more as a concomitant of the necrosis than as its cause. It also is difficult to think that capillary thrombosis sufficient to bring on almost complete necrosis should be restricted to the anterior pituitary lobe. Such selectivity is more easily understood as corresponding to metabolic than to circulatory properties.

With the confirmation that Luschka's concept of the blood supply of the pituitary gland has received by modern anatomists,[15] the doubts are revived which Simmonds originally entertained concerning the possibility of infarction in the pituitary gland. The modifications of Luschka's concept which resulted from the work of Wislocki[15] do not alter the situation; the fact remains that blood reaches the anterior lobe by many channels. In addition to arteries which enter the groove between the lobes, a number of vessels run alongside the stalk and enter the anterior lobe. They are veins, but the blood in them flows toward the pituitary gland; they are called the hypophyseo-portal vessels.

The early work on pituitary necrosis was largely done on septic diseases. This fact in itself made an embolic origin plausible. Today I do not understand why the blandness of the lesions in the anterior lobe, as opposed to the abscess-like metastases in the posterior lobe, did not deter pathologists from the embolization theory. The thin layer of well preserved tissue which often lies between the area of necrosis and the capsule enhances the similarity to infarction, but several considerations speak against infarction, in addition to the fact that occlusion

* No attempt is made to enumerate all papers on pituitary necrosis. For a detailed discussion of the older literature see Sheehan.[3]

of a hypophyseal artery has seldom been found. The necrotic areas are not hemorrhagic, and it is improbable that infarction in an organ with so many wide, thin-walled sinusoids should not lead to diapedesis of red blood cells. The regularly ellipsoid, sometimes spherical shape speaks against infarction. In most cases of pituitary necrosis there are no embolic phenomena in other organs, especially not in the brain. We would have to assume that embolization restricted to one small organ occurs frequently in a variety of cases and in the absence of a manifest source of the emboli. Such predilection of emboli for the anterior pituitary gland would, *a fortiori,* make us expect them in pituitary vessels when other branches of the internal carotid do contain emboli. But I searched, without success, 50 sections of the pituitary gland in a case of septic (endocarditic) embolization of both middle cerebral arteries. If occlusion of arteries was the main factor, one should expect an increase with age and with cerebral vascular disease. This, to judge from the material at hand, is not the case.

Two instances may further illustrate the fact that pituitary necrosis and mechanical occlusion of pituitary vessels do not go hand in hand: When a patient dies in malarial coma and pituitary necrosis is found, one would expect the pituitary sinusoids to be blocked by parasites, but Guccione[16] stated that there were no parasites in the sinusoids. He thought of a toxic factor causing the necrosis. In a patient who had died of clinically latent gastric carcinoma with generalized arterial metastases, I found numerous capillaries filled with carcinoma in the anterior lobe. There was no tissue reaction around the tumor emboli, but a small area of necrosis was found in a portion of the anterior lobe that was free of emboli. In each case, the seemingly obvious connection between necrosis and occlusion of capillaries did not exist.

Pituitary lesions might be expected in so-called temporal arteritis which affects the carotid system especially. In a paper on temporal arteritis[17] a report on a necropsy contains the statement, "pituitary gland appears necrotic" (no details given). Dr. Jennings,[18] at my request, had new sections made of the pituitary gland. He found "very small foci of necrosis" and "no marked vascular change." He thinks, however, that the pathologist who first studied this gland did find changes in the vessels and ascribed the necrosis to them. These small foci of necrosis probably were accidental, but one should pay attention to the pituitary vessels in cranial arteritis; the neighboring ophthalmic vessels are often affected.

It would be unwise to deny that vascular occlusion can lead to necrosis in the pituitary gland. When, for instance, in an 81-year-old man one large hypophyseal artery was almost occluded by the thick-

ened intima, it might be assumed that this could have been one factor in the genesis of the necrotic areas in the anterior lobe; but, since necrosis occurs when all vessels are normal, we cannot attach much importance to the narrowing or occlusion of single arteries. Necrosis could not be detected in the pituitary gland of a young man who died 1 week after ligation of the right internal carotid artery. Necrosis does not occur in the posterior lobe under ordinary conditions. The basophilic epithelial cells, which normally invade the posterior lobe, do not bring blood vessels with them, but migrate individually. Thus, being in an organ in which necrosis does not occur, these cells should be immune from necrosis. The fact that they do become necrotic clearly shows that the cause of necrosis lies in the cells themselves and not in embolic or thrombotic occlusion of blood vessels.

It was to be expected that pituitary necrosis, when found in unusual or unexplained diseases, would be considered an essential part of the picture. But, in my opinion, the necrotic lesions reported in beriberi,[19] as well as in renal rickets,[20] were accidental findings.

The idea presents itself that pituitary necrosis might be related to altered endocrine function. It is supported by the severity and relative frequency in the puerperal state when the organ has gone through the changes of pregnancy. Endocrinologic diseases, however, as far as I know, do not supply many instances of pituitary necrosis. Diabetes is an exception. The number of examples in diabetic patients in the older reports is astonishing, and some of these necrotic lesions were unusually large. At least 4 cases are on record in which the urine of a diabetic patient became free of sugar some time before death, insulin was discontinued, the blood sugar was normal, and at necropsy the anterior pituitary gland was found widely necrotic.[21-23]

The question arises whether such necrosis occurring in the last days of life, independently from occlusion of vessels, is a prerogative of the master gland. The one other organ that shows similar necrosis is the adrenal cortex, which is functionally related to the pituitary gland and which has several anatomical features in common with it: the relation between cells and sinusoids, the combination with a nerve structure, and the multiple blood supply. In my material, such necrosis was found only once in the adrenal gland. The main finding in that 63-year-old man was aneurysm of the left ventricle with massive pulmonary infarction. Necrosis was not found in the carefully examined pituitary gland. The adrenal gland was searched for vascular lesions, but none was found. Focal necrosis of the adrenal cortex was found 18 times in the single routine sections of 3,080 necropsies (Mitchell and Angrist[24]). Nine of these may be comparable to pituitary necro-

sis. Mitchell and Angrist do not state if they ever found necrosis in the pituitary and adrenal glands in the same necropsy. An infectious disease process was present in most of their cases.

The hemorrhagic necrosis which Crawford[25] found in the suprarenal glands of 14 pregnant women belongs to another chapter.

The condition of the blood vessels presents an important difference between renal cortical necrosis and pituitary necrosis, which have been found together repeatedly. In the latter, no anatomical vascular lesions exist; in the former, most cases show fibrinoid change in the vessels, necrosis, or true arteritis. Obviously the sets of conditions that are responsible for each lesion have several items in common, pregnancy being the most important. The extent of the pituitary necrosis found in cases of renal cortical necrosis varies from subtotal (Doniach[26]) to small areas similar to those with which this paper is dealing (MacGillivray,[27] case 3).

The foregoing observations and considerations that speak against an embolic or thrombotic origin for pituitary necrosis are given additional weight by the occurrence of necrosis in the masses of epithelium which extend into the posterior lobe. The posterior lobe tissue itself does not participate to any marked degree in the necrosis, even in very severe cases. Since we thus cannot incriminate the vasculature of the posterior lobe, we must find the main cause for the necrosis in the cells themselves. Probably the pituitary epithelial cells are in a precariously labile equilibrium, sensitive to deficiency of oxygen or to accumulating products of metabolism. As Victor and Andersen[28] pointed out, the metabolic rate of the rat's pituitary gland at the time of parturition is about three times as high as in any other phase of reproduction in the rat. If it is the same with the human pituitary gland, we have an explanation for the massiveness of the post-partum necrosis.[29] In the less susceptible pituitary glands of non-pregnant women and of men, shock-like conditions which precede death cause only small foci of necrosis. I do not know if the oxygen consumption of the anterior pituitary gland is higher than that of other organs, especially endocrine organs. The anterior lobe cells are at a disadvantage as far as metabolism is concerned because they receive much venous blood through the hypophyseo-portal vessels. It is a matter of speculation how far vasospasm, as part of the shock syndrome, is a causative factor (Giornelli,[30] Plaut[31]).

Finally, among the probably multiple causative factors, a mechanical one may be active. The small necrotic foci are mostly near one of the non-yielding connective tissue structures, and the pituitary gland at the end of pregnancy is tightly squeezed into the sella. In one case

of subtotal post-partum necrosis (Gotshalk and Tilden[32]), a portion of the anterior lobe protruded from the sella and did not participate in the necrosis. In another condition, however, which leads to hyperplastic enlargement of the pituitary gland, namely, increased intracranial pressure, necrosis of the anterior lobe is not conspicuous.

SUMMARY

In 149 unselected necropsies of adult males, necrosis in the anterior pituitary gland was found 13 times.

In none could necrosis be explained by embolic or thrombotic occlusion of blood vessels. It appears that most of the necrotic lesions in the anterior lobe which might have been described as embolic or thrombotic are not of such origin.

Necrosis was less frequent after the age of 55; it seemed to be frequent in hypertension. Otherwise, no correlation with clinical disease was evident.

The subtotal post-partum necrosis of the anterior pituitary gland (Sheehan[2]) represents an exaggerated degree of a process that takes place frequently during the last days of life, in non-pregnant women and in males, without a close relationship to the disease from which the patient is dying.

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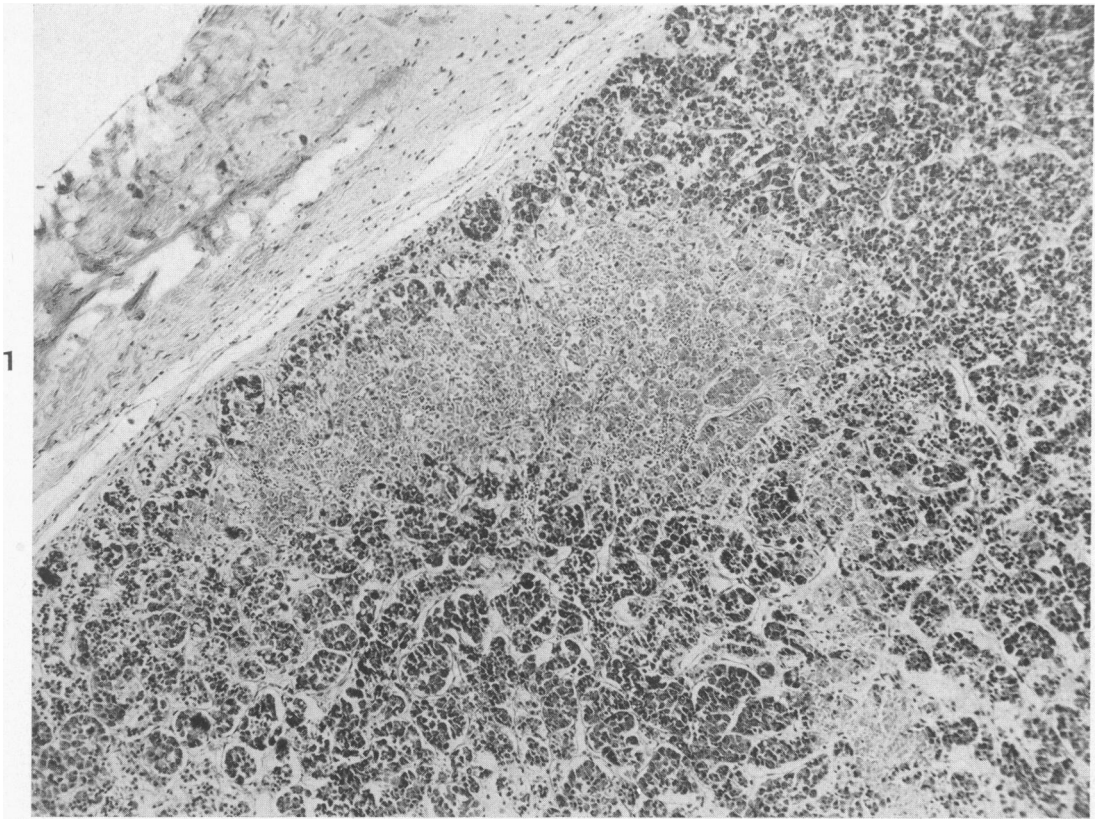
[*Illustrations follow*]

DESCRIPTION OF PLATES

PLATE 136

FIG. 1. Typical subcapsular necrosis. A thin, somewhat interrupted layer of well preserved tissue lies between the region of necrosis and the capsule. In the right lower corner, necrosis extends deeper into the tissue. Male, 51 years old, with abdominal carcinomatosis. Hematoxylin and eosin stain. × 77.

FIG. 2. Irregularly rounded area of necrosis in anterior lobe near the base of the stalk. The necrotic tissue is deeply stained with eosin and, therefore, appears dark. The clear area near the necrotic focus is normal connective tissue. Male, 46 years of age, with essential hypertension; sympathectomy. Hematoxylin and eosin stain. × 18.



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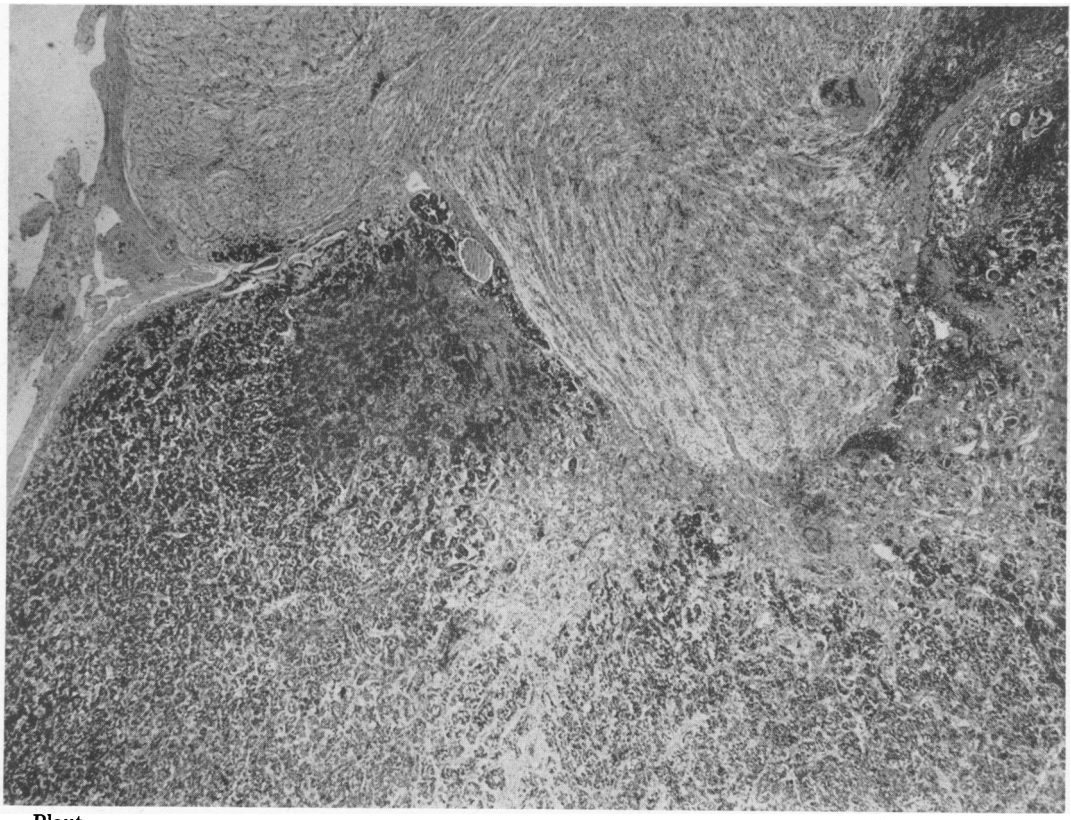

2

Plaut Pituitary Necrosis

PLATE 137

FIG. 3. The posterior lobe (above) is widely invaded by epithelial cells; a large portion of this epithelium is necrotic (center of field). The surrounding posterior lobe tissue is normal. Female, 70 years old, with carcinoma of the bladder. Hematoxylin and eosin stain. × 18.

FIG. 4. Edge of necrotic focus. Single nuclei are preserved. A capillary in the necrotic area is distended with red cells. There is no inflammatory reaction. Female, 36 years of age, with peritonitis. Hematoxylin and eosin stain. × 385.

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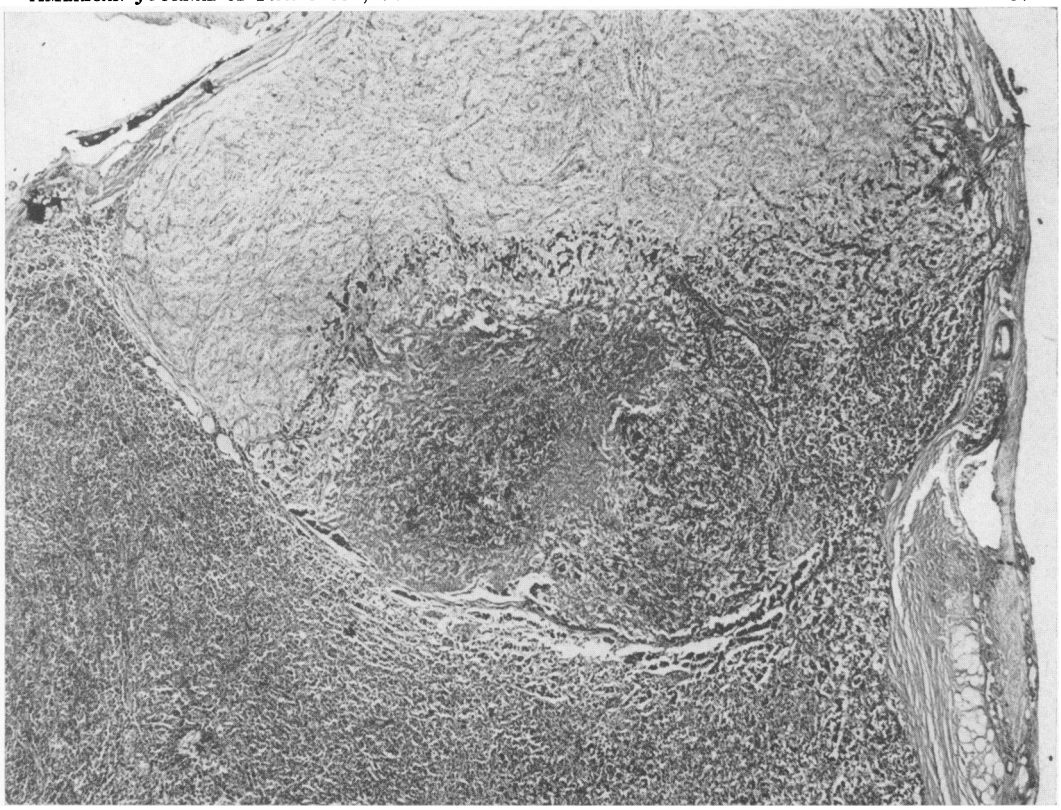

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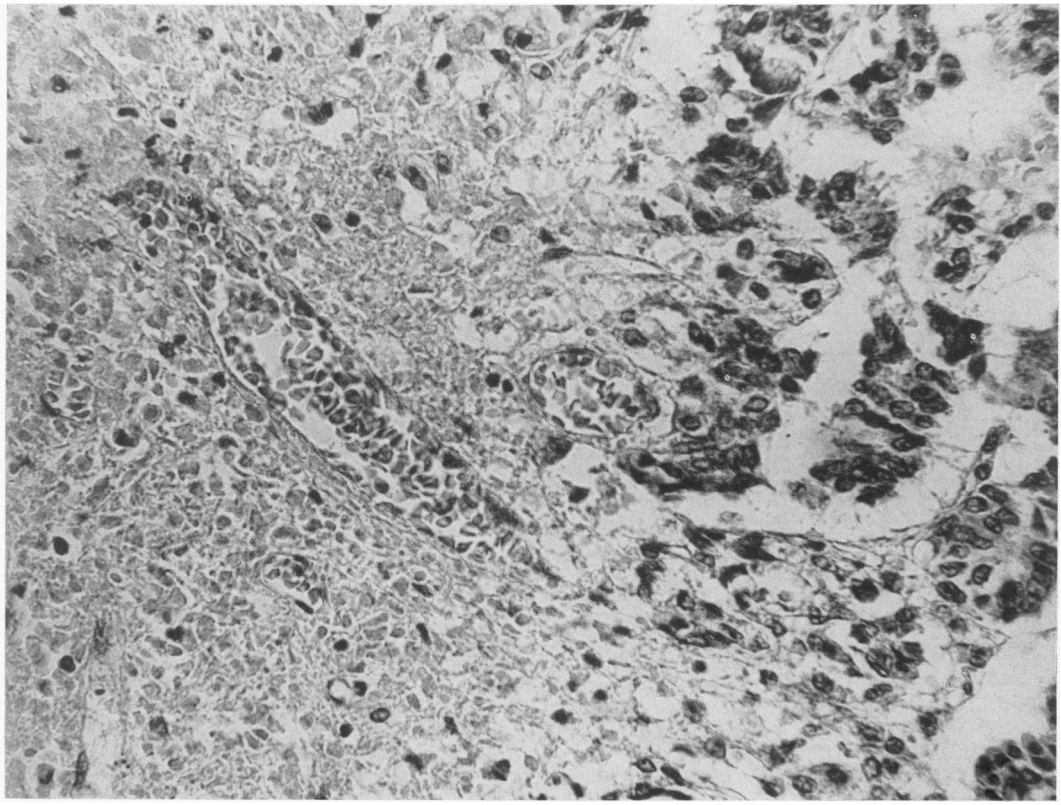

Plaut Pituitary Necrosis

PLATE 138

FIG. 5. Necrosis in anterior lobe, similar to that shown in Figure 1. Necropsy 1,435/1919 (Eppendorf Hospital, Hamburg); male, 18 years old, with otogenous septic thrombosis of transverse sinus. Inflammation is absent. This focus was erroneously considered as embolic. Iron hematoxylin stain. × 110.

FIG. 6. Subcapsular necrosis in adrenal cortex. There is a similarity to pituitary necrosis. Male, 63 years old, with aneurysm of left ventricle and massive pulmonary infarction. No necrotic foci were found in the pituitary gland. Iron hematoxylin stain. × 40.

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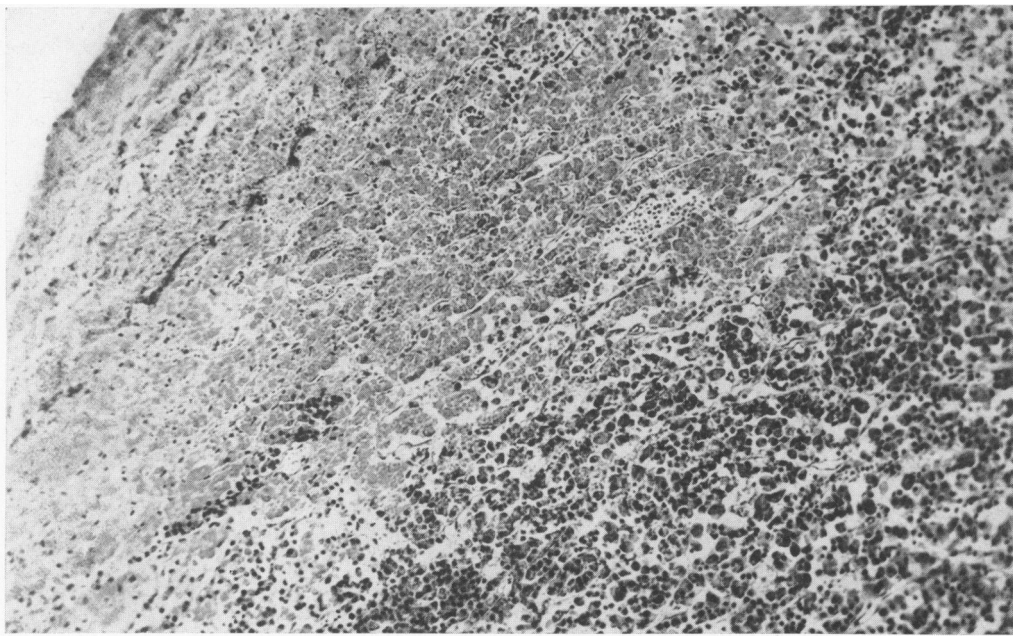

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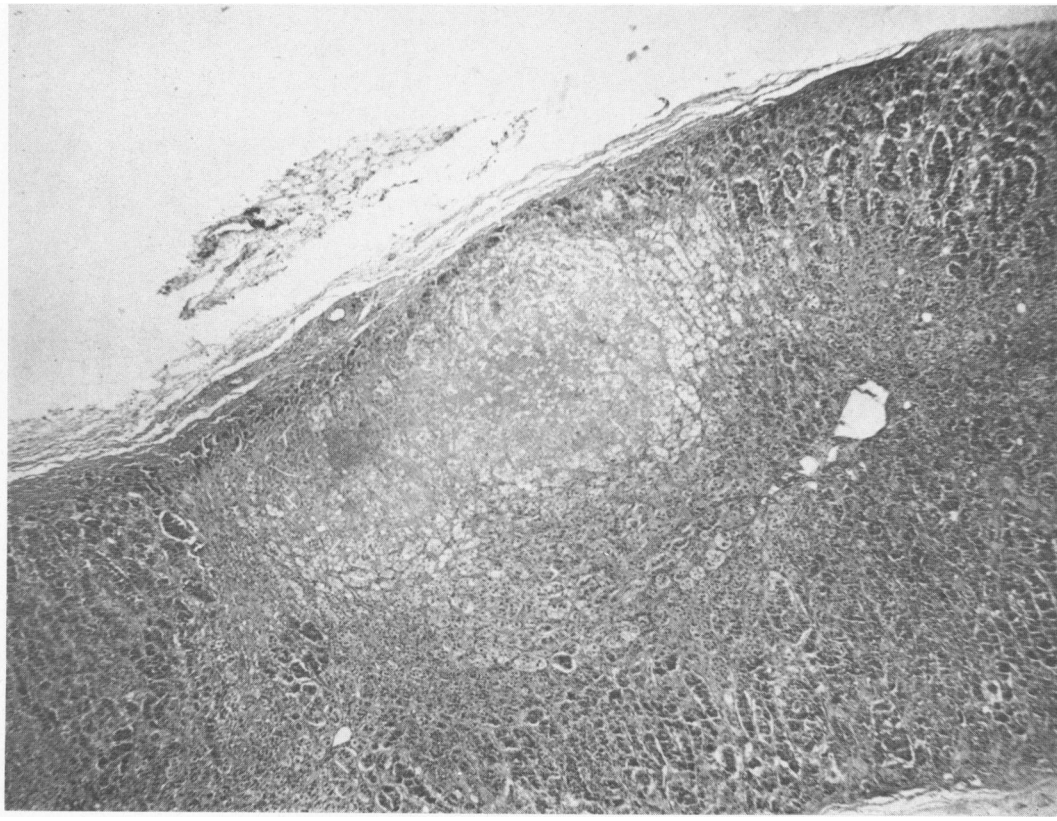

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Pituitary Necrosis