THE AMERICAN JOURNAL OF PATHOLOGY

VOLUME X MARCH, 1934 NUMBER 2

# HYPERACTIVATION OF THE NEUROHYPOPHYSIS AS THE PATHOLOGICAL BASIS OF ECLAMPSIA AND OTHER HYPERTENSIVE STATES *

HARVEY CUSHING, M.D.

(*New Haven, Conn.*)

An excessive infiltration of the neurohypophysis by epithelial elements, bearing a certain resemblance to the cellular invasion of a malignant tumor, appears to have been first mentioned by Thom in 1901,[45] since when the condition has been observed and commented on from one aspect or another by many others. There has, however, been a difference of opinion regarding the precise nature as well as source of origin of the inwandering cells, and still less agreement as to the meaning of the process. Indeed, it has not been generally assumed to have any physiological or pathological significance.

In the lower animals a patent cleft, the relic of Rathke's pouch, divides the epithelial portion of the pituitary body into a bulky pars distalis and a thin pars intermedia, which serves closely to envelop the pars nervosa proper. The posterior lobe or neurohypophysis is thus composed of two easily recognizable but mechanically inseparable portions.†

* These studies, made in the Surgical Laboratory of the Peter Bent Brigham Hospital with the assistance of Dr. Louise Eisenhardt, were the basis of the first lecture before the Medical Research Society delivered at University College, London, November 2, 1933.

† Closely embracing the pituitary stalk and lower tuber, both in animals and in man, is a tongue-like prolongation of the epithelial lobe known as the pars tuberalis, of whose independent secretory function even less is known than of the pars intermedia. The chief difficulty encountered by those who have attempted, by study of its extracts, to determine the separate function of the pars tuberalis has possibly lain in the fact that the large venous trunks which pass through it contain variable amounts of the secretory product both of pars distalis and of pars intermedia in the process of transport to the tuberal nuclei.

Received for publication December 12, 1933.

In the higher anthropoids and in man, on the other hand, because of the practical disappearance of the cleft there exists no such clear anatomical distinction between pars distalis and pars intermedia. Consequently, many writers (*e. g.*, Plaut[36] in 1922, Erdheim[17] in 1925, Dayton[14] in 1926, Benda[5] in 1927, and Kraus[27] in 1928) have expressed the belief that the latter has become so rudimentary or vestigial it is futile to consider the two epithelial parts of the human gland other than as a whole. This has been particularly emphasized during the past several years by Berblinger,[6, 7] who distinguishes glandular hypophysis from neural hypophysis but disclaims any recognizable subdivisions of the former. Hence, in accordance with this view, any cells that wander into the pars nervosa must come from the pars distalis or anterior lobe proper.

Several of the authors who adhere to this opinion, more especially Kraus and Berblinger, have examined large numbers of human glands removed at autopsy and have made detailed estimates of the relative percentage of basophilic elements present in the pituitary body as a whole under various conditions of disease. Berblinger's computations of an increase or diminution of these elements are based on their relative number, irrespective of the lobe in which they occur. Kraus,[27] on the other hand, lists those of anterior and posterior lobe separately and it would appear from his tables that the pars nervosa often harbors basophilic elements, particularly in association with what he calls the hypersthenic constitution.[28]

However, from my reading of their papers it does not appear that either of these distinguished writers on the subject looks upon the basophilic infiltration of the pars nervosa as anything more than a fortuitous overflow of these elements from the pars anterior. Berblinger, indeed, emphatically insists that pituitary disease is entirely an anterior lobe problem. Just why the acidophilic elements of this lobe, which in man are heavily massed in the region adjacent to the site of the original cleft, fail similarly to infiltrate the nervous tissue is not explained.

A contrary view, with which the writer sides, is held by another group (*e. g.*, Tölken[46] in 1912, Schönig[40] in 1926, Lewis and Lee[30] in 1927, Marburg[31] in 1929, Biedl[8] in 1929, Aschoff[3] in 1930, Rasmussen[38] in 1930, Orlandi[34] in 1930, Guizzetti[20] in 1933). While granting its relatively inconspicuous nature in man, most of these authors nevertheless maintain that the pars intermedia is anatomi-

cally recognizable by the distinctive character of its cells, which acquire basophilic granules in the process of maturation and migrate into the pars nervosa. Though the basophils arising from this source possibly tend to be somewhat smaller, to have a more pyknotic type of nucleus and a less heavily granular and less abundantly vacuolated cytoplasm than the basophilic elements of the pars distalis, in the terminal stages of ripening the basophils from either source are morphologically indistinguishable.

These differing points of view regarding the source of origin of the basophilic elements occasionally observed in the pars nervosa would seem to be of less importance than the physiological significance of the process; and it does not appear to have been suggested, or at least not to have been emphasized, by either party in this contention that *the degree of basophilic infiltration may represent a measure of neurohypophysial activation*. It is proposed herein to lay stress on this fundamentally important point.

That the posterior lobe contains an active principle, not found in the anterior lobe, has been known since Howell's discovery in 1898 of a pressor substance in its extracts. However, all posterior lobe extracts obtained from the lower animals are necessarily products of both pars intermedia and pars nervosa. And since it is inconceivable that the neural tissue composing the tubero-infundibular apparatus is capable independently of elaborating a hormone, the active principle in extracts of the lobe must obviously be derived from its cellular investment. It certainly could not come from the pars distalis, for in the lower animals from which these extracts are customarily made the two lobes of the gland are readily separated.

Herring [21] was the first to study and describe the peculiar manner of posterior lobe secretion. In the gland of the cat he observed the casting off from the pars intermedia of cells which in their passage through the pars nervosa become transformed into hyaline-like masses. These masses of secretory product, in favourable preparations, not only are discernible in the posterior lobe of normal glands but may be increased visibly under certain experimental conditions such, for example, as after a preceding thyroidectomy.[22] While Herring's conception of the process has been looked upon with skepticism in many quarters and may need some slight reinterpretation, a number of authors (*e. g.*, Sharpey-Schafer,[41] Cushing and Goetsch,[13] da Costa,[10] and Remy Collin [9]) have agreed with him in

all essential points. His views unquestionably furnish the only satisfactory explanation of the normal manner of neurohypophysial activity.

As mentioned in the introductory paragraph, a massive infiltration by basophilic elements is not infrequently seen in the posterior lobe of man. However, not even by those who believe in a persistent pars intermedia and look upon the invading elements as derived from it does the suggestion appear to have been made that the degree of infiltration is a measure of functional activity and that an excess of posterior lobe (*i. e.* pars intermedia) secretion should be recoverable from glands in which the process is marked.

It has been pointed out separately by Erdheim, Tölken, Kraus and Berblinger that an increase of basophilic elements in the gland as a whole is an accompaniment of advancing years of life when naturally enough it is often associated with atherosclerosis and renal disease. They appear, however, to regard the process as merely coincidental with these disorders and do not look upon it as in any sense an aetiological factor in their production, unless such a statement has been overlooked. In his recent monograph Berblinger [7] emphatically states (page 936): "Neither Hoeppli nor I ever claimed that the increase in the basophilic cells represents a pathological finding in the hypophysis but on the contrary, we regarded the cellular variation as a reaction that supposedly bears some sort of relationship to the altered renal activity."

Of the several pathologists who have dealt with the subject Skubiszewski [42] (1925) appears to have been the only one to have grasped the idea that posterior lobe basophilia might be an indication of hyperfunction. He expressed the belief that the cardiac hypertrophy and diuresis accompanying chronic interstitial nephritis might thus be accounted for. This view appears to have been based on the assumption that the posterior lobe principle had a diuretic rather than an antidiuretic action. But however this may be, the time was not ripe for such an interpretation and Berblinger promptly opposed it on the ground that in uraemia with lowered diuresis the same picture is particularly frequent. As a matter of fact, only in the past few years through the discovery of a posterior lobe-like substance in the blood in certain hypertensive states could the full significance of hyperactivation of the posterior lobe by the invading elements have been thoroughly grasped.

## 1. Neurohypophysial Activation in Pituitary Basophilism

What has led to a revival of interest in this particular matter has been the postmortem disclosure, in a case of what has been termed pituitary basophilism,[11] not only of a definite basophilic adenoma in the pars distalis, but of an excessive invasion of the pars nervosa by elements of the same type (Fig. 1). This strongly suggested a dual source of the symptom-complex as partly anterior hypophysial and partly posterior hypophysial. For in these clinical states not only is there evidence of gonadal dysfunction but the adiposity, glycosuria, pigmentation of the skin, hypertension and ultimate atherosclerosis might well be ascribed to hyperfunction of the posterior lobe.

This disclosure naturally led to the re-examination of sections of the pituitary glands from the known victims of the disorder obtained from various sources; and though in the single sections from the Anderson case, the Parkes Weber case, and one or two others, no notable basophilic invasion of the posterior lobe is seen, it is very marked in the gland from the Raab-Kraus case, of which Professor Kraus has kindly submitted four sections. Indeed, on further study of this case, the interpretation of which has been thoroughly discussed in the literature both by Kraus[26] and by Raab,[37] it is my impression that the tumor is an actual adenoma of the pars intermedia (Fig. 2).

While this interpretation of the lesion is not in accord with that held by Dr. Kraus, to whose opinion and wide experience I should naturally wish to defer, certain reasons in its favour may be given. Not only is a rich basophilic invasion of the pars nervosa taking place from the periphery of the adenoma, as he has clearly pointed out, but there is also a tendency in this direction in areas remote from the tumor where the investing pars intermedia is separated from the pars anterior by a large Rathke's cyst (Fig. 3). It would seem, therefore, that the cells must come from the pars intermedia rather than the pars distalis from which, indeed, the adenoma itself is sharply delimited. A further reason lies in the fact that an adenoma of similar sort, unmistakably from pars intermedia, has been observed in a fatal case of eclampsia to be described (p. 156).

The vasculo-renal changes incidental to old age have, as already stated, been shown to be accompanied by an increase of basophilic elements of the pituitary body as a whole. But since hypertension

and atherosclerosis of pituitary basophilism occur in young persons, it was natural to assume that the basophilic adenoma was the causal agent rather than a resultant effect. What is more, since extracts of the posterior lobe alone contain a demonstrable pressor substance, the conclusion was inescapable that the posterior lobe basophilia was the important factor in the hypertension, rather than the numerical increase of these cells in the pars distalis.

### 2. Neurohypophysial Activation in Eclampsia

We may now turn to evidence from another source. Several years ago (1918) it was pointed out by Hofbauer [23] that the diminished output of urine, the oedemas, convulsions and vascular hypertension characterizing eclampsia strongly suggested an intoxication by excess of posterior lobe secretion. In pursuit of this hypothesis Anselmino and his collaborators [1, 2] have found an antidiuretic substance in the blood of patients with eclampsia, and also a pressor substance in all instances when systolic blood pressures of 180 or over were a feature of the syndrome.

In view of these interesting observations it was anticipated that the same excessive infiltration of the pars nervosa, which was so striking in the case of pituitary basophilism with hypertension and nephrosclerosis, might also be present in the pituitary glands of patients with eclampsia.

A hint that this idea might be worth pursuing was afforded by the sections of a gland in which such an infiltration had been observed (Fig. 4). The specimen came from the Boston Lying-In Hospital and the sections have been filed in our laboratory since 1921, when Percival Bailey [4] was in search of a tinctorial method of distinguishing the granules in basophilic and acidophilic cells. There unfortunately is no history of the specimen and it is not definitely known to have come from an eclamptic patient, but considering its source the probabilities are that it did.

Since Erdheim and Stumme's classical paper [18] (1909), in which the pregnancy cells were first described, most pathologists who have studied the pituitary body in pregnancy have been more interested in the condition of the glandular than of the neural hypophysis. Though Erdheim had been among the first to describe the basophilic invasion of the posterior lobe no reference is made to its occurrence in any of the eighteen cases of eclampsia that he and Stumme in-

cluded in their important monograph. On the other hand, in three of the twenty-five glands in their control series (two cases of nephritis and one of biliary carcinoma) such an invasion is specifically mentioned. The professor of pathology in another university has kindly forwarded for study single sections of the pituitary bodies from eleven cases of eclampsia in his collection. Five of them fail to show the posterior lobe at all, and in none of those that happen to retain portions of it does any active cellular invasion appear. All this would seem to constitute overwhelming evidence against the view that posterior lobe activation by basophils might be a factor in the toxaemias of pregnancy.

Not only are pituitary glands of eclampsia difficult to come by, but it would appear that the "toxicoses of pregnancy" and "eclampsia" are exceedingly vague terms in obstetrical parlance. During the past few months we have succeeded in securing nine uncut glands supposedly from fatal cases of the disorder. While not all of them show basophilia of the posterior lobe, some of them do, and in a few instances it is excessive. To a consideration of these cases we may now turn.

For the first two specimens which came from the pathological department of the Boston Lying-In Hospital I am indebted to my colleague, Professor S. B. Wolbach.

CASE 1. The patient, 28 years of age, had been under treatment for advanced diabetes mellitus for a period of 6 years. She was sent to the hospital a few hours after a normal parturition because of a sudden convulsion with subsequent coma. The systolic blood pressure was 170; the urine showed large traces of albumin and the blood a marked hyperglycaemia. She was twice subjected to plasmapheresis with fatal issue. While the diagnosis was "puerperal toxaemia with convulsions," there was some question as to whether the death might not have been due to diabetic coma.

The serial sections of the *pituitary body* show no posterior lobe invasion whatsoever.

The history of the second case from the same source is as follows.

CASE 2. On March 29, 1931, an 8 months pregnant primipara, aged 34 years, was brought to the hospital in a comatose condition after having had three consecutive convulsions. The urine drawn by catheter was small in amount and showed a large trace of albumin. Plasmapheresis was performed and she was given hypertonic glucose and saline solution. The blood pressure was variable, the highest reading having been 190/100. The lowest reading of 50/38 was taken shortly before death, which occurred on the day after admission, the patient never having regained consciousness.

The postmortem examination showed: an 8 months undelivered fetus, acute tubular nephritis, slight fatty infiltration of the liver with central congestion and necrosis, acute toxic splenitis, pulmonary congestion and oedema with (?) terminal bronchopneumonia, generalized slight arteriosclerosis, and follicular desquamation of the thyroid.

On its removal in 1931 the *pituitary body* had been cut sagittally in halves, one of which was preserved in alcohol, the other in Zenker's fluid. On being sectioned serially the *anterior lobe* shows a great abundance of basophils, often in large clusters, some of almost adenomatous-like character. There is no necrosis, scarring or round-cell infiltration.

In the *posterior lobe* (evidently cut into and partly lost in process of removal) the distinction between pars distalis and pars intermedia is easily drawn by long, narrow, colloid-containing cavities representing the original cleft. In the more lateral regions the cleft may be followed all the way through to its open mouth in the dura. Because of this separation it is difficult to imagine that the fairly abundant basophilic infiltration of the posterior lobe (Fig. 5) represents an overflow from the pars distalis.

The colloid-filled cleft extends from the base of the gland four-fifths of the way up toward the stalk. Above this level the distinction between pars distalis and pars intermedia is less clear. Below this level signs of reactive hyperplasia of the pars intermedia are everywhere evident; the acini have increased in number and ripened basophilic elements are being cast off to invade the adjacent nervous tissue. Fortunately the hyaline masses have not been wholly dissolved out of the tissue and the pars nervosa is everywhere heavily charged with them, large accumulations being present in certain regions (Fig. 6).

For the next three specimens to be described thanks are due to Dr. G. Elliott May of the Boston City Hospital.

CASE 3. On Jan. 30, 1933, Mrs. A. F., a primipara 42 years of age, first consulted Dr. May when about 7 months pregnant. For 2 months she had been having frequent vomiting attacks, which were ascribed to indigestion from which she had suffered for years. Latterly she had voided infrequently and for the past week only very small amounts.

She was emaciated and dehydrated, having a dry, coated tongue, slight oedema of the ankles and a blood pressure of 160/100. The urine showed a trace

of albumin, a few red cells and occasional granular casts. Test of renal function showed it to be low; the non-protein nitrogen was 36 mg. per cent. She was immediately sent to the hospital with the diagnosis of toxaemia of pregnancy and hyperemesis gravidarum.

During the next week under forced fluids she improved greatly. The urine increased in amount, the oedema disappeared and the vomiting ceased. Her blood pressure, however, progressively rose to 184/128 by February 7th, on which day she began having labour pains. Of these she complained so bitterly she was given phenobarbital and scopolamine in small doses. Later in the day she passed into a coma from which she never aroused. On the afternoon of February 8th she was delivered normally, with the aid of an injection of pituitrin, of a still-born foetus. The systolic blood pressure dropped from 182 to 138 and 2 hours later to 90/70. She remained comatose, in spite of all efforts to relieve the condition, until her death on the afternoon of Febuary 10th.

The postmortem examination disclosed an apopleptic clot in the right frontal lobe of the cerebrum, a duodenal ulcer, and multiple small abscesses of liver and kidneys. There was no atherosclerosis. The diagnosis was "non-convulsive eclampsia without typical autopsy findings."

The *pituitary body* had been cut in two in a sagittal plane, the stalk having been destroyed in the process; one-half had been fixed in Zenker's fluid, the other in formalin. Serial sections of each block were made in the vertical plane of the original cut.

The *pars distalis* shows near its anterior edge an irregularly marginal area of necrosis about 3 mm. in diameter. Infiltration with polymorphonuclear leukocytes has begun to take place in the necrotic area, which is encircled by alveolated clusters of basophilic cells more sharply outlined than usual because of their separation by oedematous strands of interstitial tissue.

Throughout the pars distalis basophils far outnumber the acidophilic elements, the latter being largely confined to a broad juxtaneural crescentic strip. Many large chromophobe elements (gestation cells?) are scattered through the lobe and one gains the impression that they are ripening into pale staining basophils.

The *pars intermedia* is clearly separated from the pars distalis, throughout most of the sections, by the overabundance of colloid in the cleft. There is an extensive posterior lobe invasion (Fig. 7) by basophilic elements from the pars intermedia, more particularly from the lower third of the cleft. The column of cells extends in the usual conical fashion halfway through the lobe.

Throughout the *pars nervosa* the hyaline masses happen to have been unusually well retained in the interstices of the neural tissue

(Fig. 8), many of them adjacent to the tongues of the still living cells showing ghosts of nuclei. The hyaline masses can be followed easily as they stream toward the direction of the stalk. The abundant hyalin (colloid) in the cleft appears to come from the same cellular elements. It can be seen emerging from the mouth of the cleft into the subarachnoid spaces.

In all three of the foregoing cases the gland, before it was received, had been divided on a sagittal plane, the two halves having been placed in different fixatives. This procedure, for reasons given elsewhere,[2] adds difficulties of interpretation to the study of the serial sections from the loss of topographical relations. Wishing to obtain an entire gland with its hypothalamic attachment intact, Dr. May kindly notified me of the autopsy on the following case and I was permitted to remove and preserve the block of tissue in the desired way.

CASE 4. The patient, an exceedingly adipose multipara 38 years of age, was admitted to the Boston City Hospital June 6, 1933. Three years before she had been attended by her local physician in her ninth pregnancy. At that time she had a normal parturition, though she was found to have a blood pressure of 180/100. As this condition subsequently persisted, it was looked upon as an essential hypertension.

During this, her tenth pregnancy, the systolic pressures had varied from 200 to 220. She latterly had been having much nausea and vomiting with swelling of the hands and feet.

Before her admission she had been in labour for several hours with a breech presentation and, becoming hysterical, she was finally taken to the hospital. There she was found to have a blood pressure of 210/120, going up to 260/120 during her pains. The delivery of the child was tardy and subsequently the mother passed into a comatose state without convulsions and died in a few hours. The clinical diagnosis was "toxaemia of pregnancy."

The autopsy showed very little apart from a moderate cardiac hypertrophy and dilatation, slight atherosclerosis, fatty infiltration of the liver and acute pulmonary congestion.

The *pituitary body*, a large, succulent gland (not separately weighed) with its stalk, tuber and block of the hypothalamic region, was removed in one piece (Fig. 9), fixed in formalin, serially sectioned in the horizontal plane and stained with haematoxylin and eosin.

The posterior lobe in its lower portion shows a cellular invasion by basophilic elements that almost surround its circumference (Fig. 10). A large excess of colloid in certain parts of the cleft has broken widely

into the pars distalis. In many areas the infiltration is massive (Fig. 11) and strands of normally staining basophils can be followed well up into the stalk (Fig. 12). The holocrine secretion has been well preserved in between the infiltrating tongues of viable cells (Fig. 13). The tuber is broken up into widely opened spaces as the tip of the infundibular cavity is approached. This, as usual, shows a highly defective ependymal cuticle.

The story of Dr. May's third case is briefly as follows.

CASE 5. On Aug. 12, 1933, a 23 year old Polish woman, about 7 months pregnant, who had had no prenatal care, was admitted to the Boston City Hospital with the story that she had recently shown some swelling of the face and ankles, and for 24 hours had been having a series of convulsive seizures. She was unconscious on admission and about 3 ounces of urine were obtained by catheter, showing a heavy trace of albumin, hyaline and granular casts and red cells. Her blood pressure was 170/110. She remained in deep coma in spite of treatment and died 36 hours later.

The postmortem examination showed lesions in the liver and kidneys typical of eclampsia. There was also an intense venous congestion of the cortical vessels of the brain with a small subarachnoid hemorrhage over the right occipito-parietal region.

The *pituitary body* with the hypothalamus had been removed in a single block, fixed in formalin and forwarded for study. The gland was large; both stalk and tuber were swollen and succulent. After serial sectioning in the horizontal plane not only are basophiles found to be abundant in the pars distalis, but from the pars intermedia two cones of these same elements project into the pars nervosa (Fig. 14), from one of which ripened cells can be traced well into the center of the lobe. The pars intermedia in other regions shows an abundance of Rathke's cysts lined by ripened basophiles (Fig. 15) which have broken into the cysts as well as the cleft and are scantily invading the pars nervosa.

In the Kraus-Raab case of pituitary basophilism, as previously stated, there was found what I have ventured to interpret as a basophilic adenoma of the pars intermedia (*cf.* Fig. 2). Some hesitation was felt in regard to this for the reason that no such adenoma of this epithelial zone had been definitely described. However, the disclosure of a similar lesion in the gland of a patient with eclampsia makes the given interpretation of the case seem the more probable.

Through my one-time pupil, Dr. Benno Schlesinger, some inquiries were made regarding the prevalence of eclampsia in Vienna. Desiring to interest Professor Erdheim in the subject at hand and with the hope that his old eclampsia sections might be gone over to see what proportion of them showed invasion of the type in question, a photomicrograph of one of our sections was sent in illustration of what was to be looked for. He replied that he had never seen any corresponding degree of "spreading out" of basophilic cells in the posterior lobe, except in the glands of old persons. Unfortunately his old slides had been thrown away and for years he had had no opportunity further to pursue his studies of pregnancy.

Dr. Schlesinger made further inquiries and learned at the Allgemeines Krankenhaus that they do not have more than one or two fatal cases of eclampsia each year. He subsequently, from another source, had the good fortune to secure and forward to me the gland to be described.

CASE 6. The patient, a primipara aged 37 years, was admitted to the Brigittaspital of Vienna May 2, 1933. She had marked hypertension, the systolic registrations ranging between 210 to 180 during the next 10 days. On May 13th she had six convulsive seizures and at 6 P.M. the child was delivered by forceps extraction. In spite of stimulants she failed to rally and died 8 hours later.

The postmortem examination disclosed a "gray and fragile" liver, a parenchymatous and fatty degeneration of the kidneys, excentric hypertrophy of the left ventricle, acute oedema of the lungs, and oedema of the leptomeninges.

The *pituitary body* was large, ovoid, and weighed *circa* 960 mg. The prominent posterior lobe had been slightly damaged in removal; there was an obvious extrusion of a large hyaline globule in the cleft between the posterior and anterior lobes.

Serial sections on a horizontal plane were cut at 8 microns, every tenth section being mounted and stained with haematoxylin and eosin. The first thing noticeable is the large, full pars distalis which shows no areas of necrosis or round-cell infiltration. Basophilic elements abound, many of them in large clusters. The transverse cleft is distended with colloid which has burst through into the meninges. It cleanly separates pars distalis from pars intermedia (Fig. 16). The posterior lobe at this level is defective but an extensive invasion from pars intermedia is clearly apparent (Fig. 17).

The cells from this low-level invasion pass upward and backward toward the posterior portion of the pars nervosa where they become

merged with a large, sharply defined cellular mass (Fig. 18). This globular lesion is readily visible to the naked eye from the 8 micron sections No. 720 to 2250 (Fig. 19), its maximal diameters being about 3 by 4 mm. It proves on higher magnification to have the architectural features of an adenoma (Fig. 20) and its component elements are unmistakably fully ripened basophilic cells (Fig. 21).

The glands of the two following cases were received through the courtesy of Dr. C. B. Courville of Los Angeles.

CASE 7. The patient, an obese woman aged 35 years, and 7 months pregnant, was admitted to the Los Angeles General Hospital May 13, 1933, having had three convulsions the previous day. She had had no prenatal care. There was some oedema of the ankles, feet and face. The urine showed a large trace of albumin and finely granular casts. The blood pressure was only 130/90. On May 18th she was delivered of a premature child. On May 19th she became comatose with Cheyne-Stokes respiration and was found to have a bilateral papilloedema. On May 22nd she died. The case was looked upon as one of typical postpartum eclampsia.

At autopsy changes in the liver and kidneys were found consistent with eclampsia and there were in addition multiple focal haemorrhages in the brain.

The *pituitary body* shows very little change. Posterior lobe invasion is slight, occurs in one small area only (Fig. 22) and there is no colloid in the cleft.

In the following, the second of Dr. Courville's cases, there was doubt of the diagnosis.

CASE 8. The patient, a multipara 7 months pregnant, was admitted to the Los Angeles General Hospital on June 15, 1933, in status epilepticus from rapidly recurring right-sided fits. She had been known to have convulsions previously of Jacksonian type beginning on the right side. The blood pressure was 165/100. The urine showed a trace of albumin and a few casts. The cerebrospinal fluid was blood-tinged and under tension. A diagnosis of subdural haemorrhage was made and an operation performed without disclosing a clot.

The autopsy showed cerebral oedema with petechial haemorrhages, a thickened arachnoid and an apparent thrombosis of the left middle cerebral artery. The case was looked upon as "atypical eclampsia."

The *pituitary body* on section shows (Fig. 23) only a very slight degree of posterior lobe invasion in one place. There is certainly no excessive basophilia in either anterior or posterior lobe.

The records and specimen from the last of the cases have been kindly forwarded by Dr. Frank Forry of the Indiana University Medical School.

CASE 9. The patient, 44 years of age, was an obese multipara in the 8th month of her ninth pregnancy. She had been known to have hypertension for several years. She was admitted to the hospital Aug. 16, 1931, in deep coma with cyanosis. There was oedema of the extremities. The urine showed a large trace of sugar, albumin, red cells and granular casts. The blood pressure, taken frequently, ranged from 238/130 to 190/110. She was spontaneously delivered of a still-born child and died 3 days after admission in a state of hyperthermia (107° F).

At autopsy focal necroses of the liver, chronic nephritis and bronchopneumonia were found. There was no question of the diagnosis of eclampsia gravidarum.

The *pituitary body* shows a massive posterior lobe invasion, as heavy as that shown in Figure 5. The gland unfortunately was fragmented in removal and the sections stain so feebly the photomicrograph is not worth reproducing.

## *Summary*

Briefly summarized, six of these nine cases (Nos. 2, 4, 5, 6, 7 and 9) were typical of eclampsia and in the four (Nos. 2, 4, 6 and 9) that had shown marked hypertension an excessive basophilic invasion was present; Case 5 showed only a moderate invasion with the systolic pressure not above 170, and in Case 7 there was no hypertension and very slight invasion.

In the other three cases (Nos. 1, 3 and 8) the diagnosis of eclampsia was questionable or the condition atypical. There was no invasion in Case 1 with a systolic pressure of 170, and in Case 8 with a pressure of 165 it was slight. In Case 3, on the other hand, with a pressure of 184, the posterior lobe basophilia was marked. In all the cases, therefore, in which blood pressure registrations were 180 or over, there was marked basophilic infiltration of the posterior lobe. It will be recalled that Anselmino and Hoffmann found a pressor substance in the blood of eclamptics only when systolic pressures exceeding 180 were recorded.

### 3. Essential Hypertension in the Prime of Life

If I am correctly informed, it is generally recognized by obstetricians that when the toxaemias of pregnancy are accompanied by hypertension their victims are apt to retain an abnormally high blood pressure which is likely to be increased in each subsequent period of child-bearing. Alongside of this goes a tendency toward adiposity, examples of such a sequence being given by Cases 4 and 9 in the preceding series. So-called essential hypertension, however, is a common disorder by no means limited to such a small group, for it may victimize women who have never borne children and no less frequently men in the prime of life.

The postmortem examination on such cases often fails to show any satisfactory explanation for the patient's death. The usual finding on which the pathological diagnosis is based is a chronic progressive renal lesion characterized by hyalinoid thickening of the terminal arterioles. While these vascular changes may be more pronounced in the kidney than elsewhere and may possibly first be detected there, the process nevertheless is universal and similar arteriolar changes are found in all other organs. This was clearly pointed out sixty years ago by Gull and Sutton, whose important studies were the starting point of the vast amount of work that has since been done on arteriosclerosis and hypertension. Nevertheless, many clinicians are still inclined to regard essential hypertension (the "hyperpiesia" of Clifford Allbutt) as primarily a nephrovascular disorder, in view of the presence of albumin and casts in the urine.

While Gull and Sutton admitted complete ignorance as to the cause of their "arterio-capillary fibrosis" other than that it was common in old age and premature senility, it would have interested them to know that posterior lobe extract exerts its constricting effects on the peripheral arterioles and capillaries where the pathological changes they described primarily appear. What is more, as pointed out by Professor Harold E. MacMahon, precisely the same renal lesion, variously called progressive vascular nephritis and malignant nephrosclerosis, may be seen to follow both hyperpiesia and pituitary basophilism, and it is quite possible that the more acute renal lesions of eclampsia are of the same order.

In view of what has gone before, it was natural enough to suspect that posterior lobe basophilia might also accompany these conditions

of so-called essential hypertension. The first opportunity to examine the pituitary body from such a case in the desired way was afforded by Dr. George Hass, the resident pathologist of the Peter Bent Brigham Hospital, who removed the gland and anterior hypothalamus in one piece from the body of the man whose story follows.

CASE 10. Edward M., aged 45 years, a negro chef of good family history and exemplary habits, entered the medical wards of the hospital Feb. 8, 1933, complaining of precordial pain, shortness of breath, inappetence, and recent loss of weight. For *2 years* he had been having morning headaches regressing during the day; for *3 months* dyspnoea on exertion, often associated with substernal pain radiating to the left shoulder and ceasing abruptly; also attacks of nocturnal dyspnoea with productive cough; for *2 months* transient attacks of blindness in the right eye, lasting a few hours; for *2 weeks* occasional slight epistaxis.

The physical examination revealed a cardiac enlargement and an expanded aorta (shown by the X-ray), with soft systolic murmur and accentuated second sound. The blood pressure was high, varying around 230/160. The urine showed the slightest possible trace of albumin, an occasional red blood corpuscle, rarely a hyaline cast. The Wassermann reaction was positive for the blood (repeated), negative for the spinal fluid. There was no history of a syphilitic infection.

He was abundantly studied by many observers during the following 6 weeks with the diagnosis of syphilitic aortitis chiefly favoured, though some thought it was coronary disease, others a nephrovascular disorder. He had occasional attacks of severe pain, substernal or epigastric, during which his blood pressure would usually fall, on one occasion to 135/80. For these attacks he was given nitroglycerine and often required morphia.

In the early morning of March 25th he was taken with a typical attack of agonizing epigastric pain, which sedatives failed to relieve. This continued during the day, with periodic vomiting and frequent watery bowel movements containing blood. His blood pressure gradually fell to low levels, he became dyspnoeic, and died 24 hours later.

The postmortem examination showed a moderate cardiac hypertrophy, a slight degree of atherosclerosis, a progressive vascular nephritis and acute haemorrhagic colitis. It otherwise was essentially negative. There was nothing to support the clinical diagnosis of luetic aortitis, coronary thrombosis or myocarditis, and no cause for the "anginal" attacks was apparent.

Grossly the *pituitary body* was small, concave above, and its two lobes easily distinguishable, the posterior lobe being unusually prominent. Serial sections were taken through the entire block, including the hypothalamus, from below upward.*

The *pars distalis* shows no discernible abnormalities. The clusters of basophils are as usual principally disposed toward the anterior

* The sections from this case were the basis of a recent paper on the secretory activity of the two lobes of the gland and manner of their discharge.[12]

surface of the lobe and are not pathologically numerous. The acidophils are chiefly massed in the deeper portions of the lobe.

The *pars intermedia*, despite the almost total absence of a cleft, is clearly distinguishable from the pars distalis by the well marked limiting zone of basophilic elements which almost everywhere, even up to the root of the stalk, are actively invading the pars nervosa, here and there sending heavy wedge-shaped columns of cells deeply into the lobe (Fig. 24).

The *arterioles* encountered in the sections of the hypothalamus show precisely the same changes as those affecting the vessels of the kidneys, so that the process is a general rather than a local one. Numerous minute capillary haemorrhages have occurred in the pars nervosa, stalk and tuber.

This case is one of several in which very similar conditions have been found. The patients have usually been of middle age, often obese, have shown marked vascular hypertension, enlargement of the heart, traces of albumin with a few casts, and rare renal elements in the urine. They have usually succumbed with symptoms of acute pulmonary oedema. The postmortem examination has shown malignant nephrosclerosis with cardiac hypertrophy and a more or less marked atherosclerosis. Fatty infiltration of the liver has been common, also macular or ulcerative lesions of the gastro-duodenal mucosa.

### 4. Hypertension with Atherosclerosis in the Aged

These are the conditions in which an increase of basophilic elements sometimes invading the posterior lobe have already been described by Kraus, Berblinger, Erdheim and others. Nowhere, however, does it appear to have been suggested that the cellular invasion of the neurohypophysis was an indication of posterior lobe activation that might be the primary factor in the hypertension, causing in its turn the progressive vascular and renal changes so frequent in aged persons.

The cases are so common specific examples need scarcely be given. Not only have several instances been met with in our own series but during the past few months, since local attention has been drawn to the matter, some of the younger pathologists in the several hospitals associated with the Harvard Medical School have begun routinely to study the *pituitary body* in all autopsies. Some of them have brought

specimens showing marked basophilia of the posterior lobe. Good examples of massive invasion occur in the following two cases submitted by Dr. John I. Bradley of the Massachusetts General Hospital.

CASE 11. The patient, a 60 year old labourer, had been known to have a high blood pressure for some time before his admission to the hospital on Sept. 21, 1932, following a cerebral accident. Though conscious and alert, his speech was thick and unintelligible. The blood pressure was 180/110 and the eyegrounds showed moderate tortuosity and sclerosis of the arteries. On the morning following his admission he suddenly became unconscious, the blood pressure fell to 60/50, and the body temperature rose to 108.2° F just before death.

The autopsy showed hypertrophy and dilatation of the left ventricle with marked generalized atherosclerosis. A thrombus was found occluding the basilar and right vertebral arteries, causing an infarct of the pons and multiple organized infarcts of the basal ganglia. There was also a pulmonary infarct with secondary oedema and congestion. The posterior hypophysis shows a marked basophilic invasion (Fig. 25) with distention by colloid of the adjacent Rathke's cysts.

CASE 12. A 67 year old multiparous Irish housewife was admitted to the hospital on April 1, 1933, because of intermittent vaginal bleeding for the preceding few weeks.

Examination showed an obese, arteriosclerotic woman with a blood pressure of 190/100. There was some swelling of the ankles and a slight trace of albumin in the urine without casts, and the phthalein excretion was 50 per cent in an hour. The cause of her complaint was found to be a large cervical polyp, and her hypertensive disorder was thought to be sufficiently well compensated to justify the risk of surgical intervention.

An operation accordingly was carried out on April 8th under gas oxygen and ether anaesthesia. Convalescence was uneventful and a few days later the patient was about to be discharged from the hospital when she suddenly collapsed, became unconscious, cyanotic and dyspnoeic. It was recognized that she probably had a pulmonary thrombosis and an emergency operation was carried out with the removal of a small embolus from the right branch of the pulmonary artery. This operation failed to accomplish its purpose.

The autopsy confirmed the clinical diagnosis of arteriosclerotic heart disease, endometrial polyp, and acute pulmonary embolism. In addition there was found a duodenal ulcer, a slightly enlarged heart, slight atheroma of the coronary arteries without constriction, and a moderate atheroma of the aorta.

The *pituitary body*, which was found to occupy a definitely enlarged sella, was small and flattened. It shows (Figs. 26 and 28) a massive basophilic invasion from the pars intermedia which is

visible to the naked eye. Everywhere between the viable cells the holocrine product is well preserved (Fig. 27), the shadows of the swollen nuclei being still discernible in many of the cast-off cytoplasmic masses.

Sections from a gland showing a degree of posterior lobe infiltration perhaps even more marked than in the preceding example have been kindly sent to me by Dr. John F. Noble, through the intermediation of Professor Rasmussen. The history of the case is as follows.

CASE 13. The patient, 90 years of age, was admitted to the Ancker Hospital of St. Paul on Jan. 13, 1933. Her past health had always been good and in her active years she had been the mother of twelve children. She was extremely obese and had a blood pressure of 176/110. She showed evidence of mental deterioration with marked excitation. Albumin was occasionally but not invariably present in the urine with a few hyaline casts. She died suddenly on March 16, 1933, supposedly from a coronary occlusion.

Postmortem examination showed excessive obesity, hypertrophy of the right heart, generalized atherosclerosis, and a terminal pulmonary thrombosis with marked oedema and congestion of the lungs.

The *pituitary body*, cut sagittally, proves to be a cup-shaped gland (Fig. 29) with a massive basophilic invasion occupying practically the entire anterior half of the pars nervosa (Fig. 30). The invading cells bud off in characteristic fashion from the vascular stalks (Figs. 31 and 32). These stalks show a larger amount of perivascular connective tissue than is usual and this may conceivably represent the consequences of a long-standing process with fluctuation in activity.

## DISCUSSION

In venturing to interpret the posterior lobe basophilia of eclampsia, of essential hypertension, and of the atheroscleroses and nephropathies of the aged in terms of neurohypophysial activation, questions immediately arise which some attempt must be made to answer. How often does the process occur in persons of supposedly normal health? What, if any, is the relation of these basophilic elements of the pars nervosa to the cells of the pars distalis which appear to be identical in their tinctorial reactions and morphology? Are the invading basophils the source of all the recognized activities of extracts derived from the posterior lobe?

1. *The Frequency of the Process*: Doubtless some meaure of posterior lobe activity is constantly maintained. And if, as is assumed, the pars intermedia is responsible for it and the number of free basophils is an indication of its degree, few glands would, if serially cut, fail to show here and there an occasioned ripened cell wandering into the pars nervosa. But how often there occurs a massive invasion, as in some of the cases that have been cited, is impossible to say for want of routine postmortem studies of the gland with this particular point in view.

Only a few writers on the pathology of the hypophysis specifically mention these "inwandering" elements. Those who do, like Kiyono [25] (1926), merely allude to the fact without interpretation. Nor could there scarcely be any, for in his brief protocols of fifty-three cases thirty-two showed no invasion, twelve a slight invasion, and only nine a copious invasion. In this last group, four were examples of vascular disease, three of carcinoma of the breast, one had a brain tumor, and the ninth (the only subject below middle age) was a suicide. Rasmussen, in his valuable paper [38] (1930) dealing with the pars intermedia, depicts a single example of heavy infiltration without commenting on its possible significance. In a personal communication he states that in his collection of 240 serially cut glands a corresponding degree of invasion has been observed only half a dozen times.

The late Dr. Ernest Southard, for a number of years when pathologist to the Department of Mental Diseases, methodically collected and sectioned the pituitary bodies of the patients who had died in the Massachusetts state hospitals. His successor, Dr. Canavan, who continued to add to the material, has kindly permitted my coworker, Dr. Eisenhardt, to go through these sections to get a general idea of what they show. The glands were uniformly cut through the middle on the horizontal plane so the single sections of each that have been preserved are apt to transect the outer angles of the posterior lobe, where the cellular invasion in question is most likely to be seen.

Unfortunately the case histories that go with the specimens are brief. They chiefly relate to the mental status of the patients, and when factors such as blood pressure are mentioned it is difficult to tell when the reading may have been taken, for many of the patients had long been inmates of the institutions in which they died. But

leaving all else aside, in a series of 100 of these glands, 64 per cent showed no basophilic invasion of the pars nervosa whatsoever, 23 per cent showed a slight invasion, and 13 per cent showed a marked invasion. The average age of the thirteen cases was 56 years, the ages ranging from 34 to 83. In only two instances was the age below 40: one was a man of 34 who died of lobar pneumonia, the other a woman of 38 with a blood pressure of 170/90 and a postencephalitic syndrome. The conditions in the other cases were so variable as to baffle analysis. Naturally many of the older patients were found at autopsy to have had arteriovascular disease.*

As a check on this series of Dr. Southard's, sections from a large collection of pituitary bodies made at the Johns Hopkins Hospital many years ago have been gone over, those in which the posterior lobe does not happen to be well shown having been excluded. A consecutive series of 100 of these sections from different glands shows in sixty-two no basophilic infiltration, in twenty-two a few invading elements, in nine a moderately well marked invasion, and in only seven a heavy invasion. Serial sections would of course have increased the number of positive cases. As matters stand the percentages in this and in the Southard series are surprisingly close.

Much depends naturally on what the terms "slight," "moderate" and "heavy" indicate, and without suitable illustrations different writers might have different views on the matter. However this may be, it may be gathered that in the general run of autopsies a heavy posterior lobe invasion is not infrequent. For though Rasmussen's estimate is low, namely, 2.5 per cent, my series showed 7 per cent and the Southard series 13 per cent, while in Kiyono's smaller group of cases 17 per cent showed marked invasion.

2. *The Function of the Pars Intermedia*: In accordance with the view that the pars intermedia must be the sole source of whatever active principle can be extracted from the posterior lobe, the pars nervosa is merely the carrier for the secretory product. This is assumed to find its way in the loose tissue toward the tuberal nuclei, and the broken-up appearance of the ependymal cuticle of the infundibulum [12] strongly suggests its partial passage into the cavity of the ventricle.

* In a small selected group of forty-two imbeciles and idiots, in whose study Dr. Southard was particularly interested, thirteen (or 31 per cent) showed marked invasion. The ages ranged from 24 to 72 years, many of the patients having been institutionalized for a long period of years.

Whether the secretion of the pars intermedia under variable stimuli is capable of being chemically altered, or whether its pharmacological action can be *qualitatively* modified during its transit through the nervous tissue, is now impossible to say. But there can be little doubt that under different physiological stresses or differing conditions of disease it is *quantitatively* variable, the degree of basophilia, as already indicated, being looked upon as a measure of posterior lobe activity.

Granted that a few invading basophils may normally be found in every gland that is completely studied, how rapidly their number may multiply under proper stimulation is unknown. Karplus and Peczenik,[24] to be sure, have shown that electrical excitation of the tuber will promptly increase the amount of a posterior lobe-like substance in the ventricular fluids. But whether such a stimulus long continued would actually lead to histological changes indicating activation of the pars intermedia does not appear to have been put to the test.

From Cannon's experiments it is known that the adrenal medulla may be quickly activated and there is no reason to believe that the response of the neurohypophysis to an electrical or emotional stimulation would be any less slow. In the case of the adrenal glands, however, we do not yet know just where to look microscopically for the cytological source of the pressor principle, whereas in the neurohypophysis we apparently now do.

The several pathologists whose opinion has been consulted in regard to these matters have mostly raised the objection that a posterior lobe basophilia may occasionally be encountered in supposedly normal glands. Professor W. G. MacCallum and Professor H. M. Turnbull have both sent me sections from the pituitary bodies of persons who have died in consequence of accidents, the glands showing (Figs. 33 and 34) as rich a basophilic invasion as was present in some of the cases of eclampsia herein described.

Just what form of neurohumoral stimulation calls forth the basophilic invasion in the first place is undetermined. But it is known that the posterior lobe receives a richly arborized, non-myelinated nerve supply from the anterior hypothalamic nuclei and its functional activity is probably controlled by a diencephalic mechanism that is highly sensitive to the primitive emotions. And if, as Cannon has shown, the sympathico-adrenal apparatus can be discharged

by fright, there is every reason to suppose that the neurohypophysis is just as likely, if not more likely, to respond to crude stimuli of similar kind.

That the pars intermedia cells, under profound or prolonged nervous impulses, can multiply and ripen with sufficient rapidity to invade the lobe and discharge their secretion so as to produce in the course of a few hours the pathological picture under discussion may be assuming too much. Granting that there was no preëxisting hypertension of which the postmortem examinations gave no evidence, and being unaware of how long the patients survived, this is the only possible present explanation to offer for the basophilic infiltration of the posterior lobe in these fatal accident cases. However this may be, and some better explanation may be forthcoming, it is the purpose of this paper to offer an interpretation of those instances of posterior lobe basophilia that are associated with a *known* disorder, rather than to attempt an explanation for all conditions in which a similar process is found to occur.

3. *Posterior Lobe Secretion and the Invading Elements*: What are these basophilic elements that are taken to be activators of the posterior lobe, and what is their relation to the basophilic cells of the pars distalis? From the fact that in the case of pituitary basophilism not only was there a basophilic adenoma of the pars distalis but at the same time a marked invasion of the posterior lobe, it might be assumed that the elements in both regions had been simultaneously affected by the same stimulus, whatever it might be. A wholly similar dual basophilia affecting both lobes has also characterized some of the eclamptic glands that have been studied. Histological similarity, however, does not necessarily imply that the chemical nature of the secretory product of the cells is identical. While loth to get entangled in the highly controversial subject of the relation of the anterior pituitary-like substance, prolan, to the actual gonadotropic hormone of the anterior hypophysis, something nevertheless must be said regarding it in connection with the subject in hand.

Emphasis up to this point has been laid on hypertension as a manifestation of the posterior lobe activation, rather than on other less striking and less easily measurable symptoms, but this does not mean that other effects, such for example as disturbances of carbohydrate and fat metabolism, which are equally well ascribable to posterior lobe over-activity, may not at the same time be produced. The associa-

tion of diabetes mellitus with adiposity and subsequent hypertension has long been appreciated in the clinic and the suspicion of a concomitant (possibly primary) pituitary disorder been aroused. That all three of these conditions are striking features of pituitary basophilism can scarcely fail to be of significance.

That the posterior lobe might contain a gonadotropic substance, however, would scarcely be expected. Pighini [35] (1932) has reported that extracts of the human anterior hypophysis and tuber, as well as the cerebrospinal fluid from the third ventricle, give positive Aschheim-Zondek tests in immature rats. There would, however, be no way of telling whether the gonadotropic substance in tuber and cerebrospinal fluid had been transported from pars distalis by the hypophysio-portal veins or whether it had come from the pars intermedia. To this question with great profit Zondek and his collaborators have recently turned their attention.

One of the well known properties of posterior lobe extracts obtained from the glands of animals is its melanophore-expanding capacity when tested on batrachians. While the posterior lobe hormone or hormones are not normally present in sufficient amounts in the blood to be definitely detectable it had, however, been observed by Küstner, by Ehrhardt, by Dietel and others, that a melanophore-expanding substance appears in the blood serum of pregnancy and can be found in high concentration in the serum of eclamptics.

Zondek and Krohn [46] a year ago (1932), after a series of ingenious experiments in which the European minnow was used as a highly satisfactory test object for the melanophore reaction, announced that the juxtaneural strip of both the human and bovine hypophysis contains an excess of this component of posterior lobe extracts which is neither detectable in the pars distalis nor in the remote portions of the pars nervosa. The active substance, which was called "intermedin," can be traced through the stalk and the tuber, and it is demonstrable in small amounts in the fluid content of the third ventricle, though not elsewhere in the cerebrospinal fluid spaces.

Thus one at least of the constituent properties of posterior lobe extracts has been shown to be more highly concentrated in the zone of the pars intermedia from which it is in all certainty elaborated. But Zondek has gone still further and in the present year (1933) has shown [47] that in the human (but not in the bovine) hypophysis a sex-

maturing substance identical with prolan A is present in this same strip of posterior lobe which lies adjacent to its epithelial investment. Traces of it are also found in the stalk but not in the third ventricle, in which respect it differs from intermedin. Under the influence of Berblinger, Zondek concludes that this substance represents the inwandering basophils from the pars distalis (*sic*). Prolan, he believes, must therefore be derived from the basophilic elements of the anterior lobe.

From what source the human glands used in these experiments by Zondek were obtained and to what maladies the subjects may have succumbed is not mentioned. Nor could the tissues have been used both for the making of an extract and for the histological demonstration or otherwise of an active posterior lobe basophilia. It is quite probable, however, that had the posterior lobe activation by basophils in these glands been sufficiently marked, the sex-maturing substance might also have been demonstrable in the fluid of the third ventricle. Hints suggesting this possibility have been provided from another source, namely, from the studies by certain gynaecologists. The evidence at hand has been summarized briefly as follows by Eugen Kulka.[29]

Aschheim, in searching for follicle-ripening substances in various fluids and tissues of pregnant women, failed to find any trace of such a substance in the cerebrospinal fluid. Califonza, on the other hand, believed that he had detected its presence in fifteen out of the twenty-eight fluids examined. Ehrhardt [16] found prolan A in the cerebrospinal fluid in three cases of eclampsia, in one preëclamptic, and in a gravid woman suffering from carcinoma; and Heim states briefly that he had corroborated these findings in eclamptics. Kulka investigated the lumbar fluid from twenty-five gravid patients, seven of them with symptoms of marked eclampsia. The Aschheim-Zondek test was negative in the fluid in all but six of the patients. Of the six cases showing a positive reaction one had intra partum eclampsia with a blood pressure of 190, labour having been induced by forceps. Another was a postpartum eclamptic with a blood pressure of 200, oedema of the extremities and albumin in the urine. The third patient had a cystic chorionepithelioma and three others were examples of marked hyperemesis gravidarum.

While the evidence given by these several writers is suggestive rather than conclusive, it is remarkable that under any circum-

stances of posterior lobe activation an active principle should be found in the cerebrospinal fluid obtained by lumbar puncture. Could the fluid from the ventricles have been examined, or even that from the posterior cistern, the chance of detecting the substance looked for would have been vastly greater.

More important are the recent biochemical studies by Anselmino and his collaborators, to which allusion has already been made. In their more recent paper [2] (1932) it is claimed that the active substances found in the blood of eclamptics are identical with the corresponding fractions of posterior lobe extract and that their amount varies quantitatively with the severity of the symptoms. They assume that the combination of excessive pressor and antidiuretic effects leads to arteriolar and capillary spasm with water retention and oedema of the tissues. When the brain becomes oedematous convulsions and coma are produced and there is usually a terminal oedema of the lungs. They believe that overproduction of the posterior pituitary hormone affords the only consistent explanation of these phenomena. All this seems the more plausible in view of certain observations such as those by Rowntree,[39] by Dietel,[15] and by McQuarrie and Peeler [32] on the clinical and pathological consequences of experimental water intoxication, whether produced by administering excessive amounts of water or by the antidiuretic effect of posterior pituitary extracts.*

While the studies mentioned above are highly suggestive, they are concerned with some of the better known properties of posterior lobe extracts and have no apparent bearing on the possible production by the posterior lobe of the sex-maturing substance that Zondek has found to be present in the juxtaneural portion of human glands. In this connection the following observations would seem to be of great significance.

Drs. G. Van S. and O. W. Smith of Boston have recently shown [43] that the blood and urine of toxaemic patients in late pregnancy contain a far larger amount of the anterior pituitary-like substance (prolan) than ordinarily occurs in pregnancy. They have further demonstrated [44] in a second communication that a quantitative imbalance between prolan and oestrin is characteristic of the

* Efforts to produce in animals lesions in the liver and kidneys comparable to those characterizing human eclampsia by administering posterior lobe extracts have been highly contradictory (*e. g.*, the papers by Dietel,[15] by Fauvet,[19] and by Ohligmacher [33]).

toxaemias of late pregnancy. The number of rat units per 100 cc. of blood serum in twelve gravid women without symptoms averaged 50, in eighteen toxaemic patients 250, and in five eclamptics 480. The amount of oestrin was correspondingly diminished. In the course of this study the interesting observation was made on a gravid woman with diabetes insipidus that the amount of pituitrin necessary to control the polyuria was greatly diminished during the months of child-bearing.

It can be gathered from all this that information from many sources points toward a hyperactivation of the posterior lobe in these hypertensive states. And if we are to believe, as some of the observations strongly suggest, that prolan is a product of posterior lobe basophilia, while the gonadotropic substance extracted from the anterior lobe is derived from the basophils of that part of the gland, the difference in the reactions of these two sex-maturing substances, which so many have pointed out, may thus be accounted for.

## Summary and Conclusions

The active principle of the posterior lobe and its several fractions must under all circumstances primarily be derived not from the pars nervosa but from its epithelial investment — the pars intermedia.

When the posterior lobe of man is functionally dormant the pars intermedia is inconspicuous, but so soon as it is activated the investing cells become transformed into basophilic elements, which in certain areas invade the pars nervosa. When their cytoplasm becomes fully ripened the cells eventually lose their staining qualities, change first into discernible "hyaline bodies" and then into a fluid product, which apparently makes its way through the loose tissue spaces of stalk and tuber in the direction of the infundibular ventricle and the adjacent hypothalamic nuclei.

Under certain circumstances the invading basophils with their desquamated products are greatly increased in number and the cellular infiltration assumes a massive character. This is looked upon merely as a pathological exaggeration of the normal secretory process and its degree is regarded as a measure of the hyperactivation.

An extreme example of posterior lobe basophilia of this sort has been observed in a case of so-called "pituitary basophilism," associated with a functionally active basophilic adenoma of the pars distalis. This polyglandular disorder chiefly affects young persons and

is characterized, among other symptoms, by vascular hypertension together with disturbances of carbohydrate and fat metabolism. As these symptoms suggest a posterior rather than an anterior lobe effect, it was assumed that the posterior lobe basophilia represented something more than an overflow of these elements from the anterior lobe.

It has been shown by Anselmino and his collaborators that the blood of eclamptics with oedema and marked hypertension contains antidiuretic and pressor substances, whose effects correspond to those produced by posterior lobe extracts. They therefore claim to have proved what others had suggested, that the toxaemias of pregnancy were due to the overproduction of the posterior lobe hormones.

In serial sections of six out of nine pituitary bodies from fatal cases of eclampsia a heavy infiltration of basophilic elements in the posterior lobe has been disclosed, and the same condition has been observed in a number of glands from cases of essential or nephrovascular hypertension, also serially cut and examined. That in advancing years there is a tendency for the basophilic cells thus to wander in large numbers into the posterior lobe has long been known. It has been looked upon merely as a concomitant of old age, particularly when attended by atherosclerosis and renal disease.

Pathologists have recognized in eclampsia distinctive lesions in the liver to which the disorder has customarily been ascribed. In essential hypertension, likewise, lesions affecting the terminal arterioles of the kidneys have been thought to indicate a primary nephrovascular disorder. Necroses in eclampsia, however, are not limited to the liver, nor are the terminal arteriolar lesions in essential hypertension confined to the kidneys. In neither instance do the histopathological findings satisfactorily account for the clinical symptoms.

From the observations presented the conclusions are drawn: (1) that the source of these hypertensive disorders lies in the posterior lobe of the pituitary body; (2) that the extent of basophilic invasion from the pars intermedia is a measure of posterior lobe activity; and (3) that excessive infiltration by these elements represents the histopathological basis of eclampsia and essential hypertension in young persons and may possibly also be related aetiologically to the atherosclerosis of old age.

Whether the general hypothesis herein advanced should or should not prove on further study to be in all its features wholly correct, it will nevertheless provide an incentive to include a detailed study of the neurohypophysis in forthcoming postmortem studies of disorders in which hypertension is a distinguishing feature.

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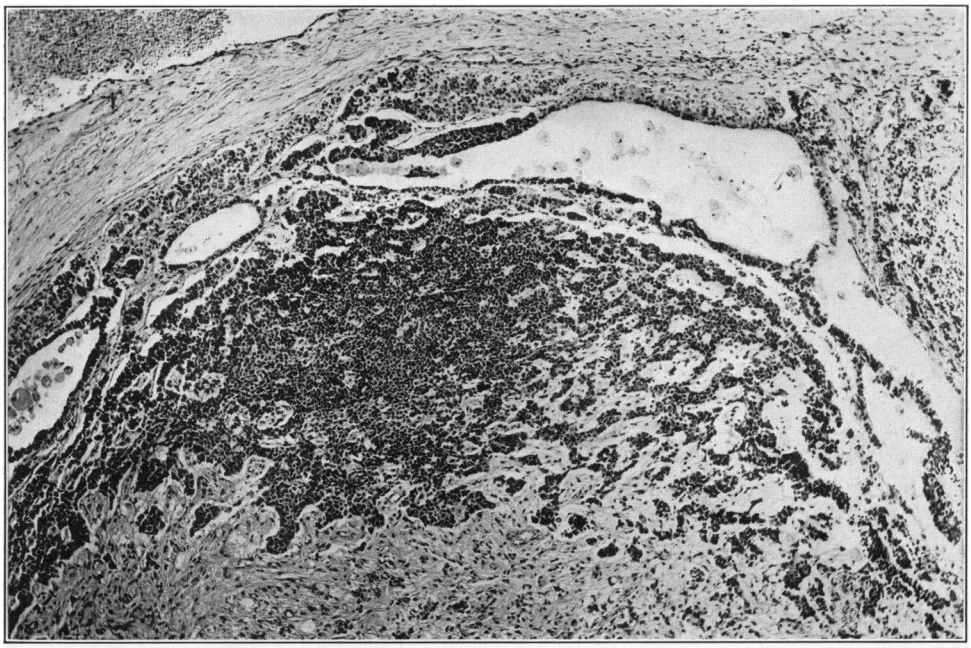
## DESCRIPTION OF PLATES

### PLATE 54

FIG. 1. Massive posterior lobe invasion from a case of pituitary basophilism (mag. × 60).

FIG. 2. Section (mag. × 9) from the Raab-Kraus case of basophilic adenoma presumably arising from pars intermedia (*cf.* Fig. 3).



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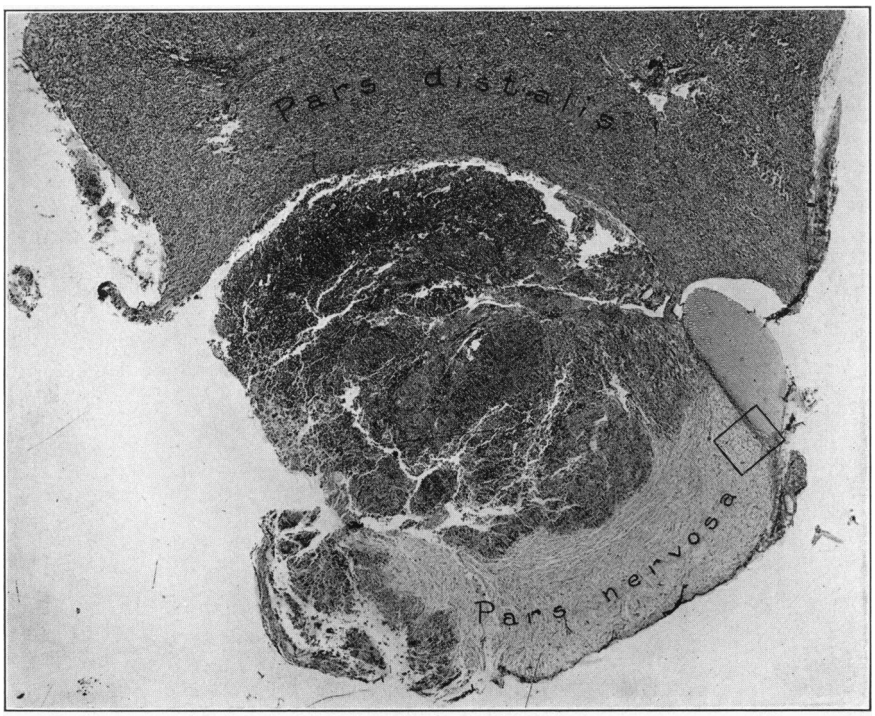


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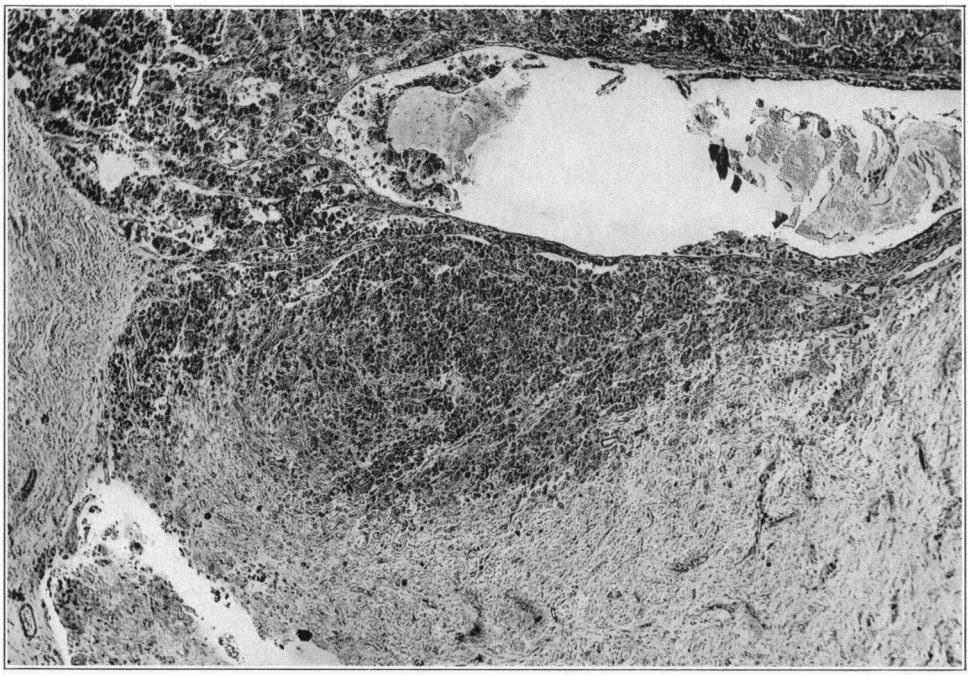
PLATE 55

FIG. 3. Squared area from Fig. 2 (mag. × 80) showing infiltrating basophils in a zone remote from the adenoma.

FIG. 4. Typical cone-shaped area of basophilic invasion from outer angle of pars intermedia in a case of presumed eclampsia (mag. × 80).



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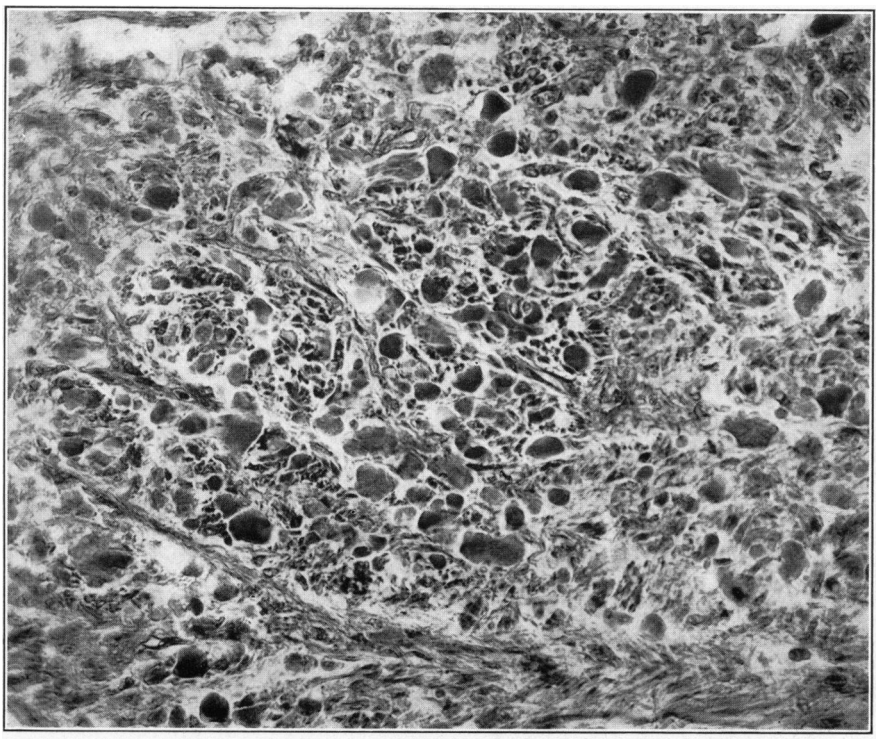

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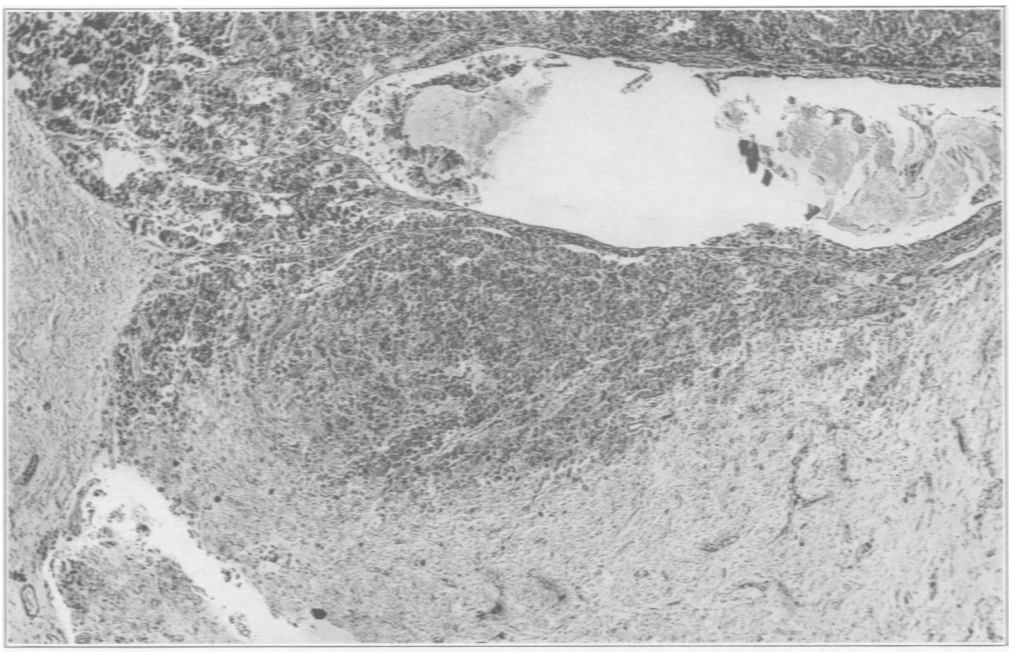
PLATE 56

FIG. 5. (Case 2.) Posterior lobe infiltration by basophils from a case of eclampsia with hypertension (mag. × 60).

FIG. 6. (Case 2.) Showing (mag. × 300) in center of pars nervosa accumulations of hyaline masses (Herring) in the spaces that are bounded by the "baskets" of neurofibrils.



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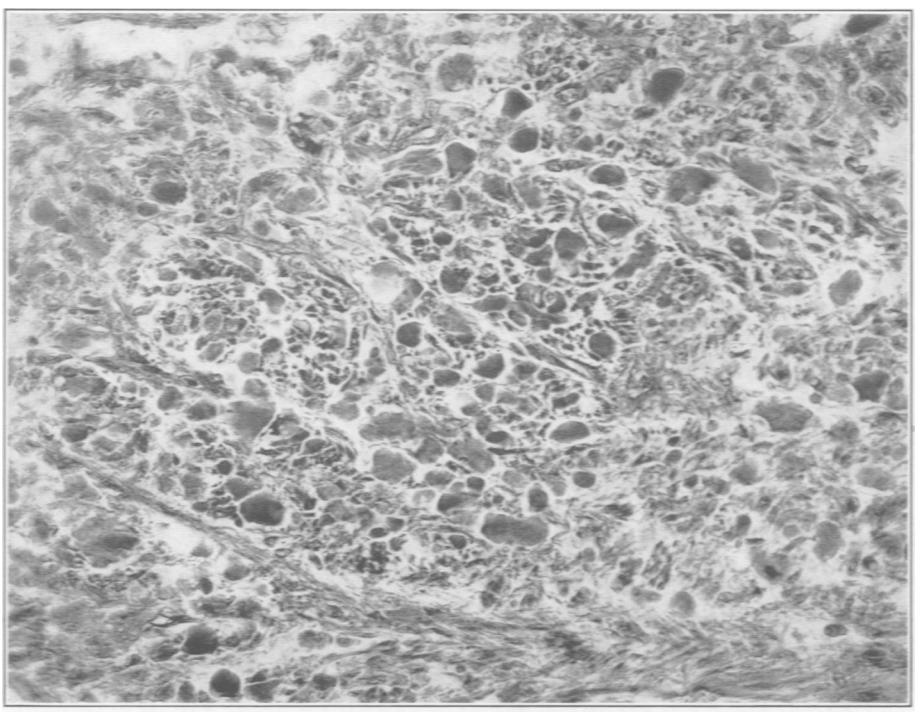

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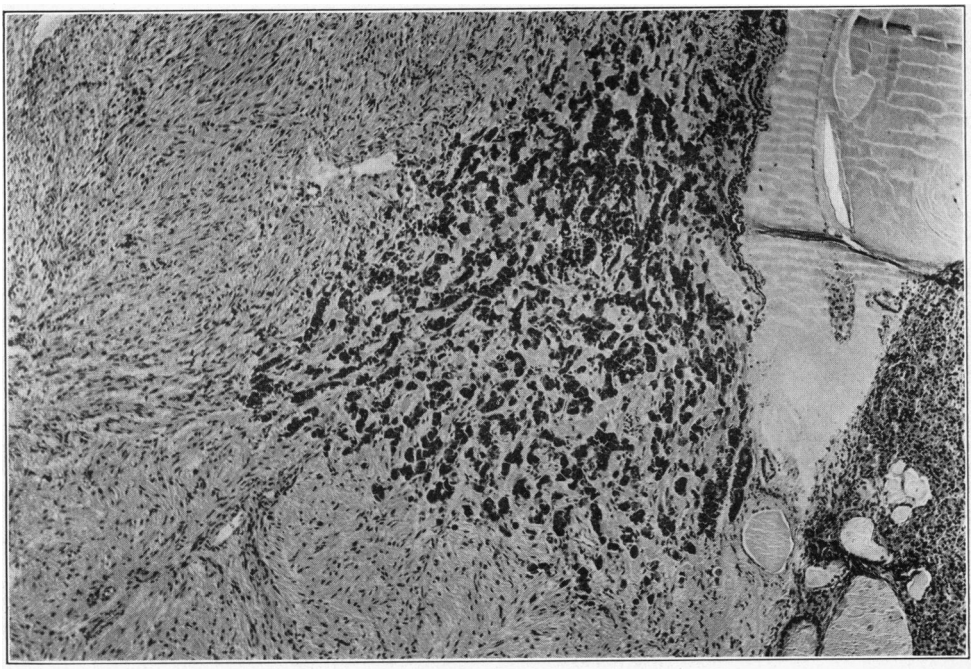
## PLATE 57

FIG. 7. (Case 3.) Invasion of basophilic elements from pars intermedia in a case of eclampsia. Note separation from pars anterior (upper left) by large colloidal mass reopening residual cleft (mag. × 60).

FIG. 8. (Case 3.) Showing (mag. × 560) masses of granular holocrine secretion in and among tongues of invading basophilic elements.



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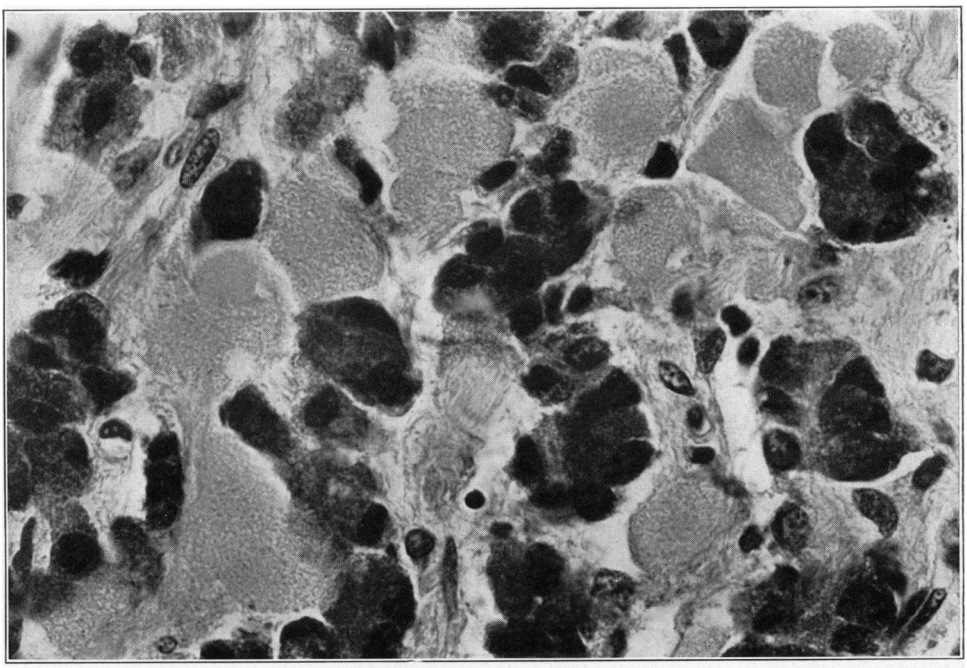

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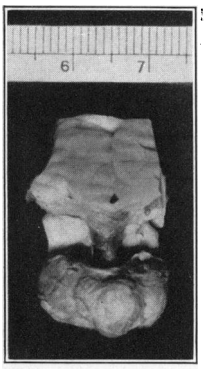
Cushing Hyperactivation of the Neurohypophysis

PLATE 58

FIG. 9. (Case 4.) Posterior view of block of tissue with large gland, bulging posterior lobe and juicy tuber in case of eclampsia.

FIG. 10. (Case 4.) Horizontal section (Section 1260) through lower portion of posterior lobe to show widespread encirclement by actively invading basophils (mag. × 20).

FIG. 11. (Case 4.) Showing area (mag. × 60) squared in Fig. 10.



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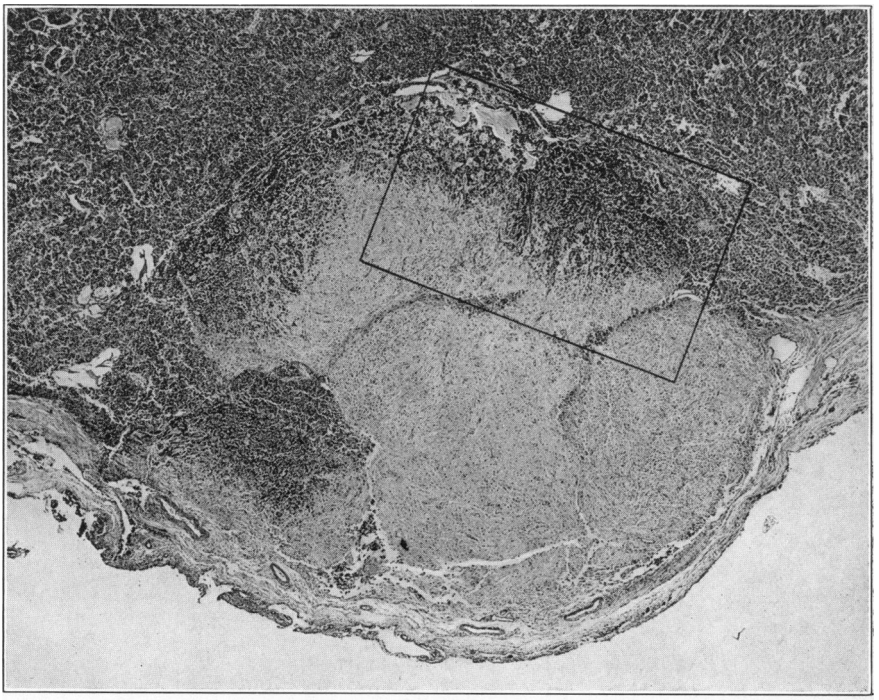

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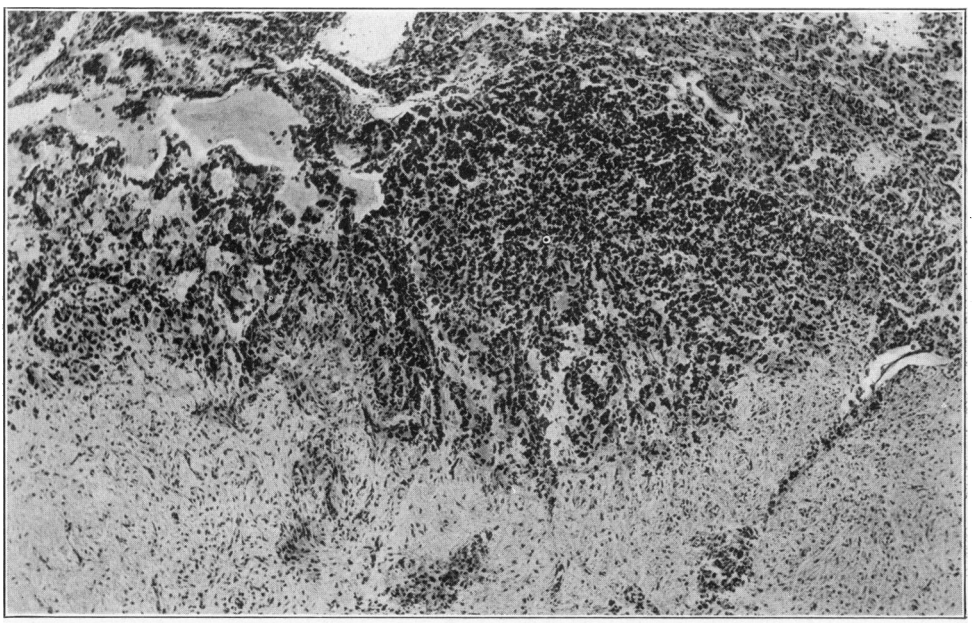

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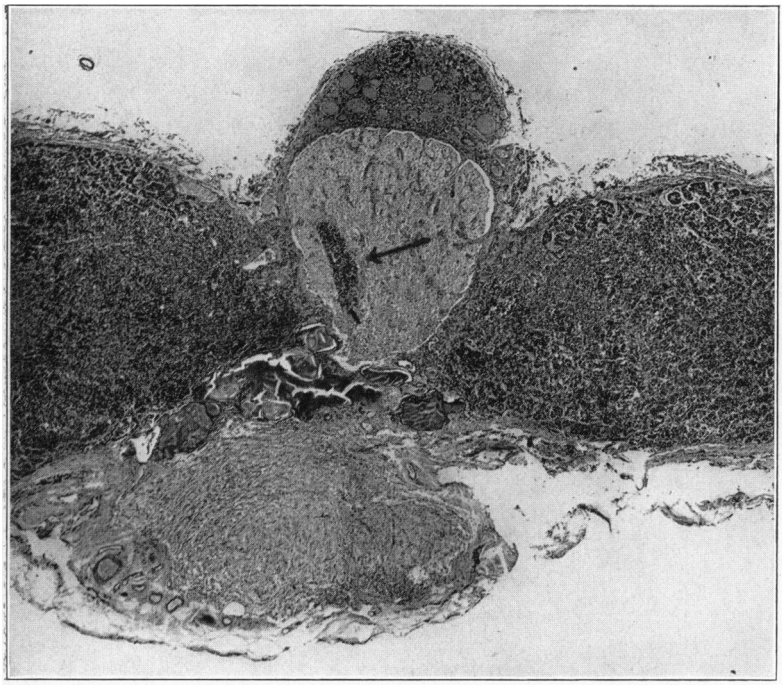
## PLATE 59

FIG. 12. (Case 4.) Showing (Section 3060, mag. × 15) strand of basophils (arrow) in lower stalk. At this level through upper part of gland the pars tuberalis showing above has just become free from pars distalis. Insert (Fig. 12a) shows (Section 3510, mag. × 15) same strand of viable cells still traceable in free stalk.

FIG. 13. (Case 4.) To show (mag. × 600) the holocrine discharge of ripened cells between invading elements. Note ghosts of nuclei in several of the secretory masses.



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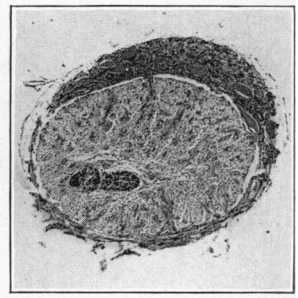

12a

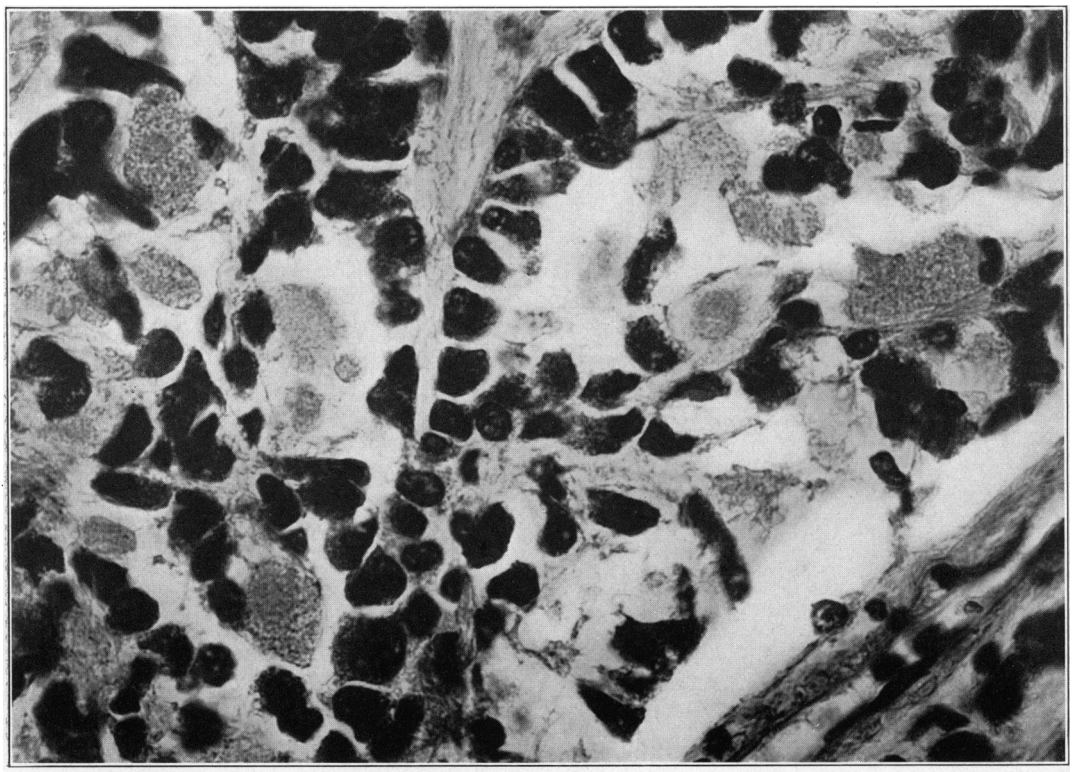

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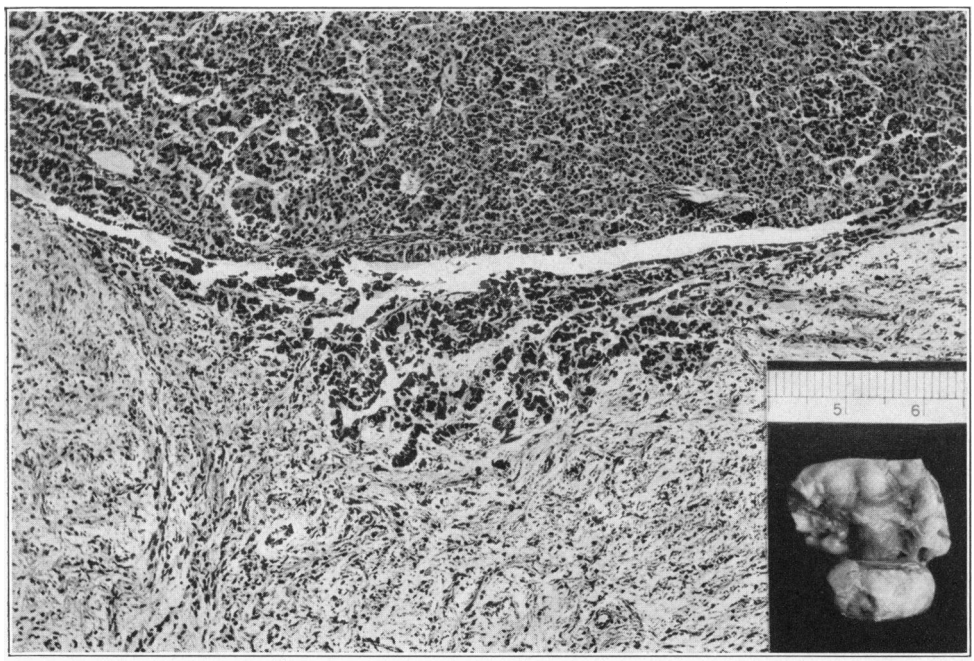
PLATE 60

FIG. 14. (Case 5.) Showing (mag. × 80) one of two areas of moderate conical infiltration traceable in other sections into center of pars nervosa. Insert shows the posterior view of the specimen (natural size) with pituitary body below.

FIG. 15. (Case 5.) Showing (mag. × 230) pars intermedia activity with formation of Rathke's cysts lined by ripened basophils. Pars distalis (above) separated by cleft from posterior lobe (below).

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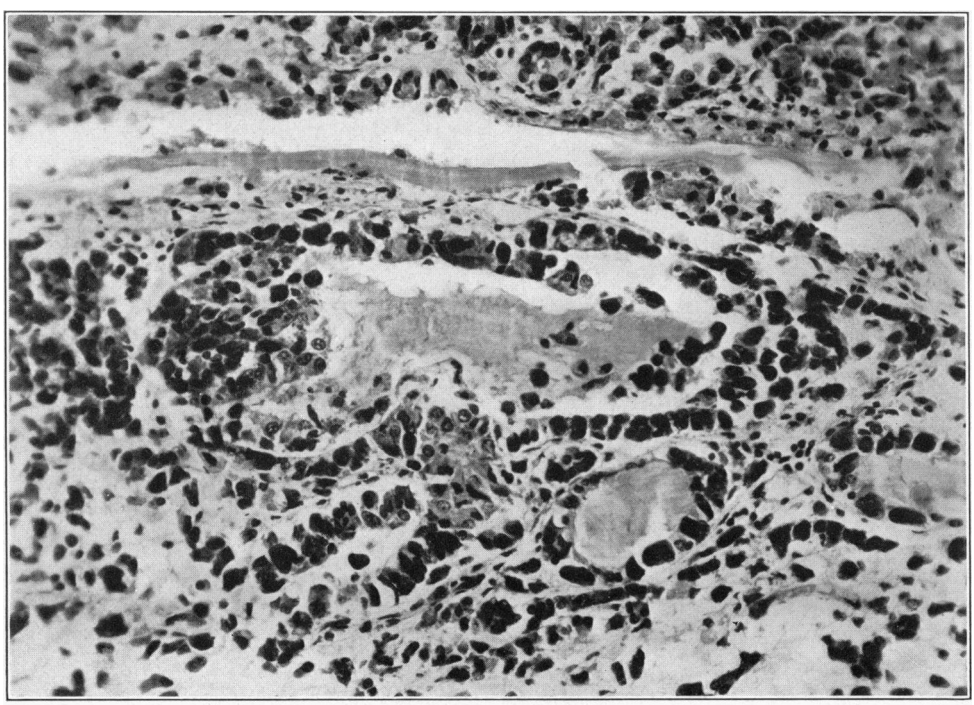

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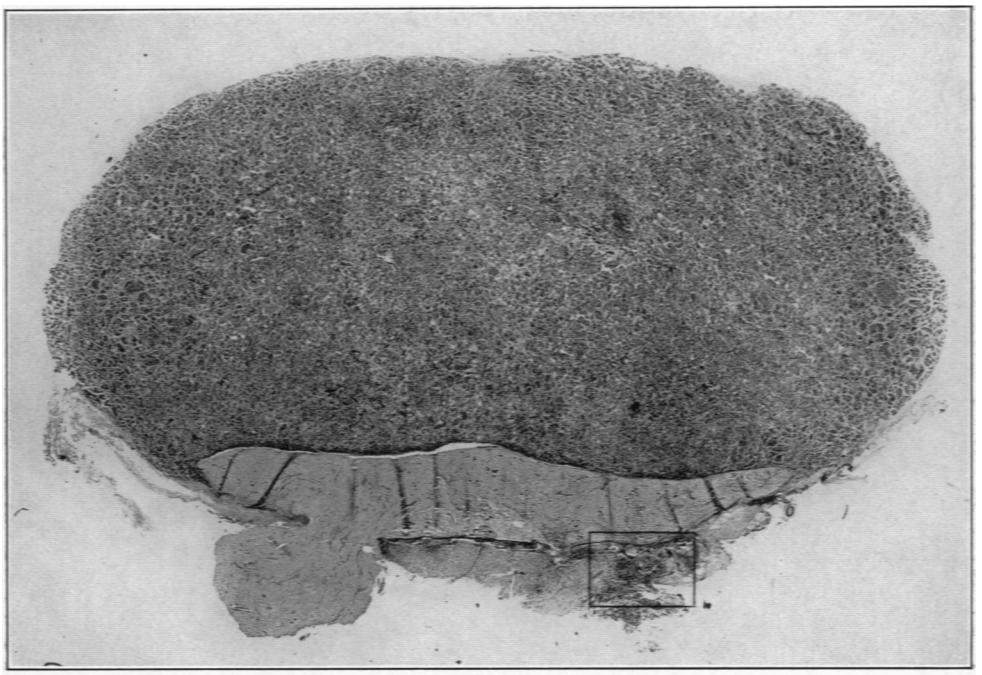
Cushing Hyperactivation of the Neurohypophysis

## PLATE 61

FIG. 16. (Case 6.) Section 630 (mag. × 8) showing large anterior lobe with entire cleft distended by colloid. Posterior lobe somewhat damaged in removal. Basophilic invasion from pars intermedia in squared area.

FIG. 17. (Case 6.) Squared area from above (mag. × 70) showing invasion from pars intermedia.



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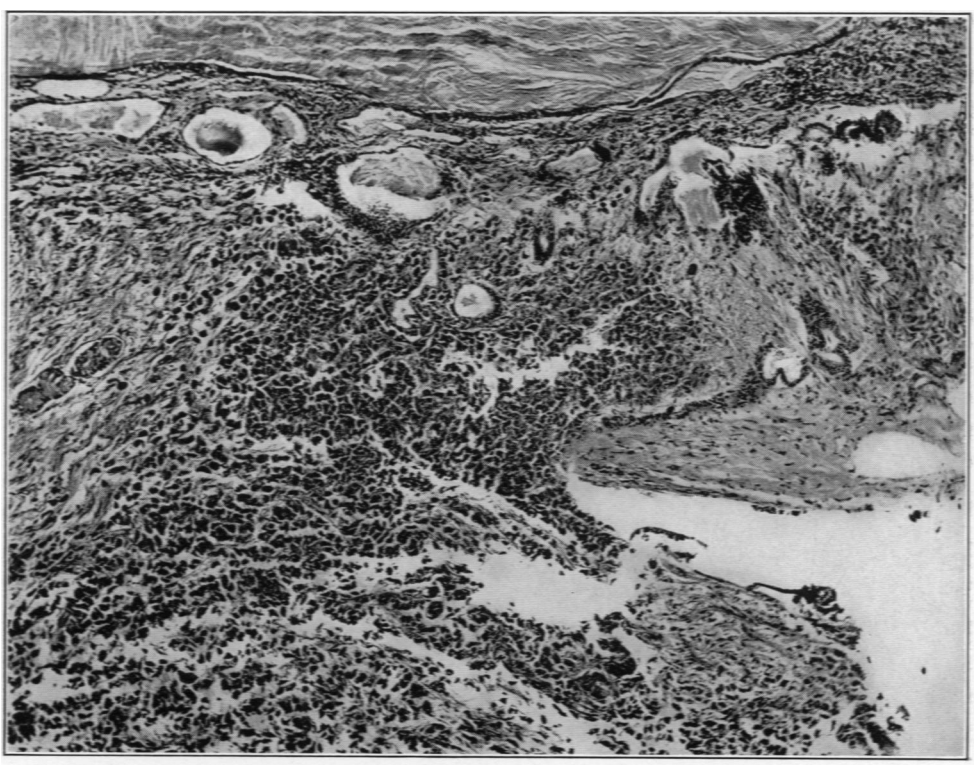

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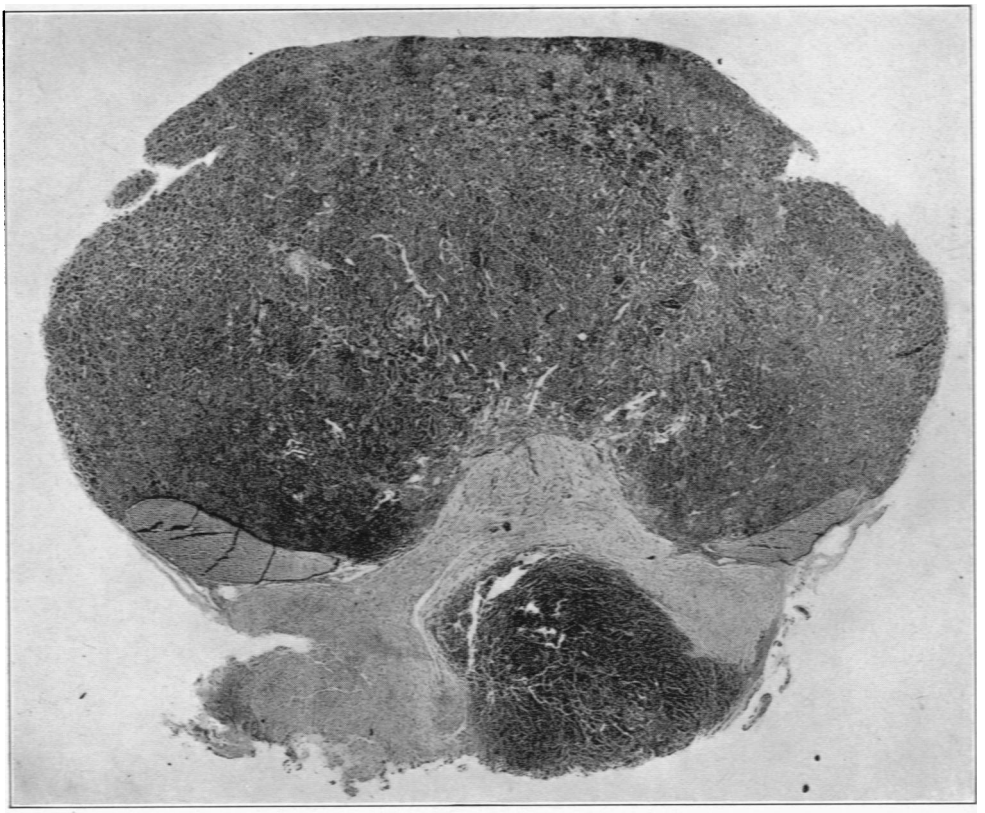
PLATE 62

FIG. 18. (Case 6.) Section 1710 (mag. × 8) taken at level where stalk of posterior lobe is forming and large portal sinusoids are congregating toward it. Note large basophilic adenoma in posterior lobe.

FIG. 19. (Case 6.) Section 2250 (mag. × 8) showing adenoma fading off at posterior edge of pars nervosa. At this level the pituitary stalk has already formed and the portal vessels are clearly shown radiating backward toward it in what will become pars tuberalis.



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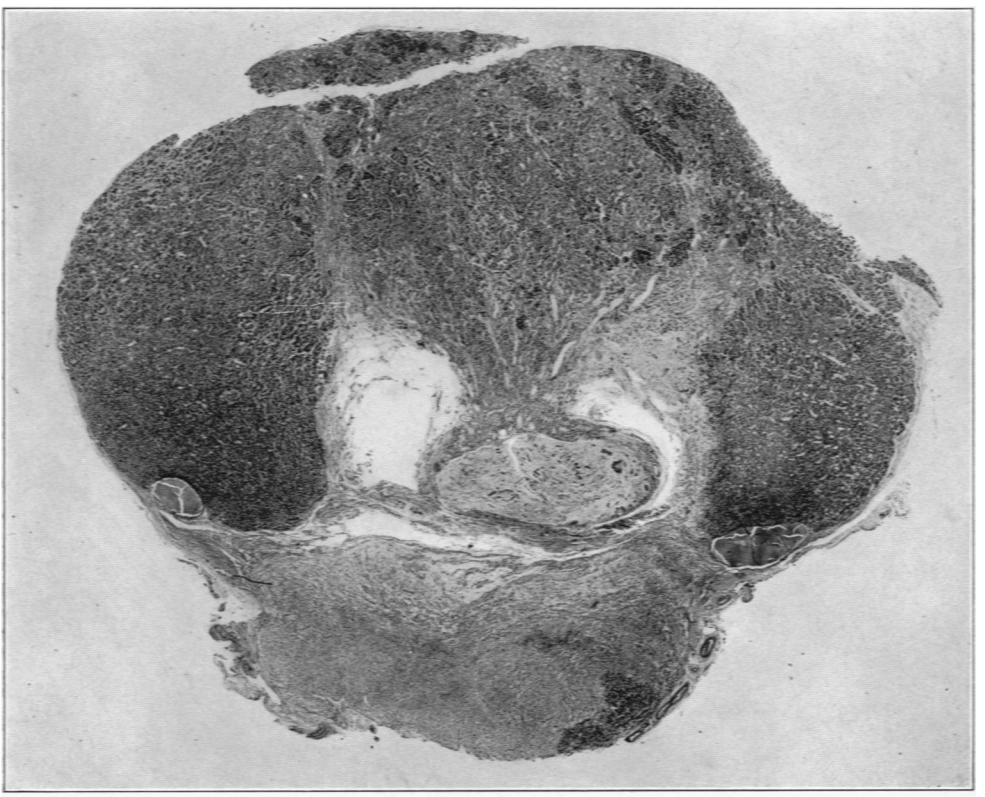

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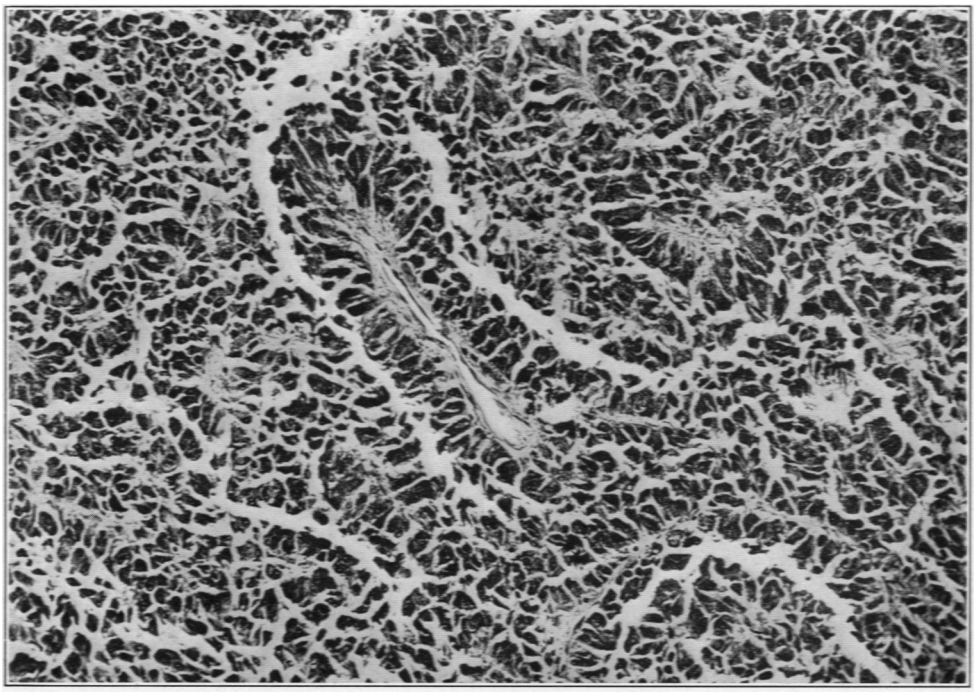
## PLATE 63

FIG. 20. (Case 6.) To show (mag. × 150) general character of adenoma whose cells bud off from capillary stalks.

FIG. 21. (Case 6.) Showing on higher magnification (× 600) the typically vacuolated basophilic elements of the adenoma.



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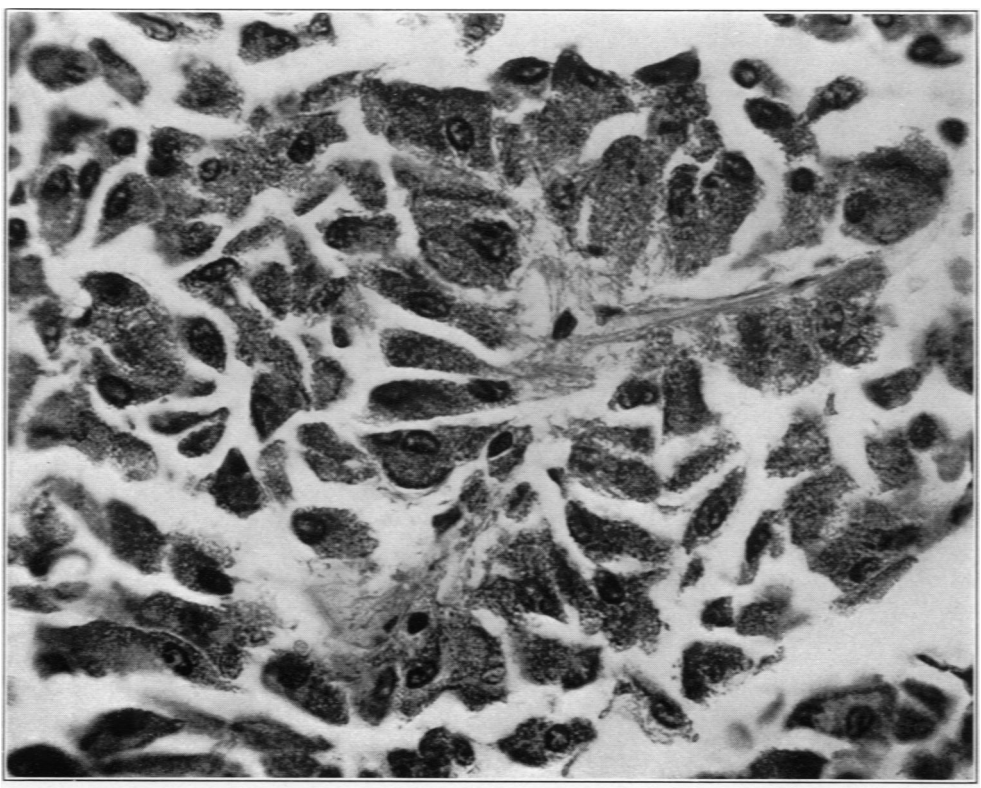

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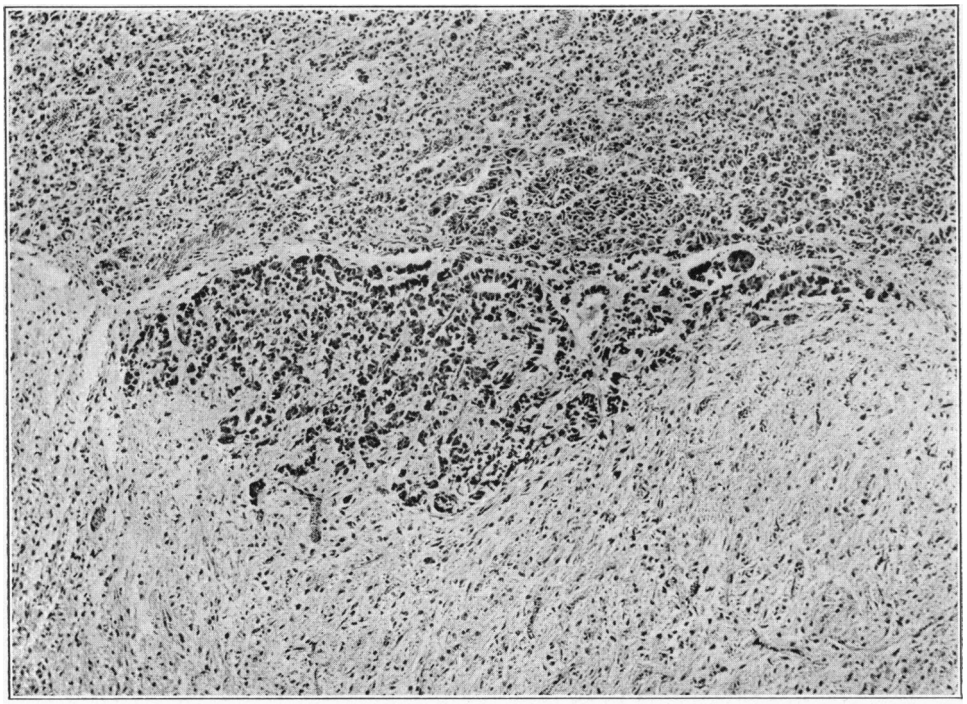
PLATE 64

FIGS. 22 and 23. Showing (mag. × 80) the relatively slight degree of invasion in Case 7 (above) and Case 8 (below).



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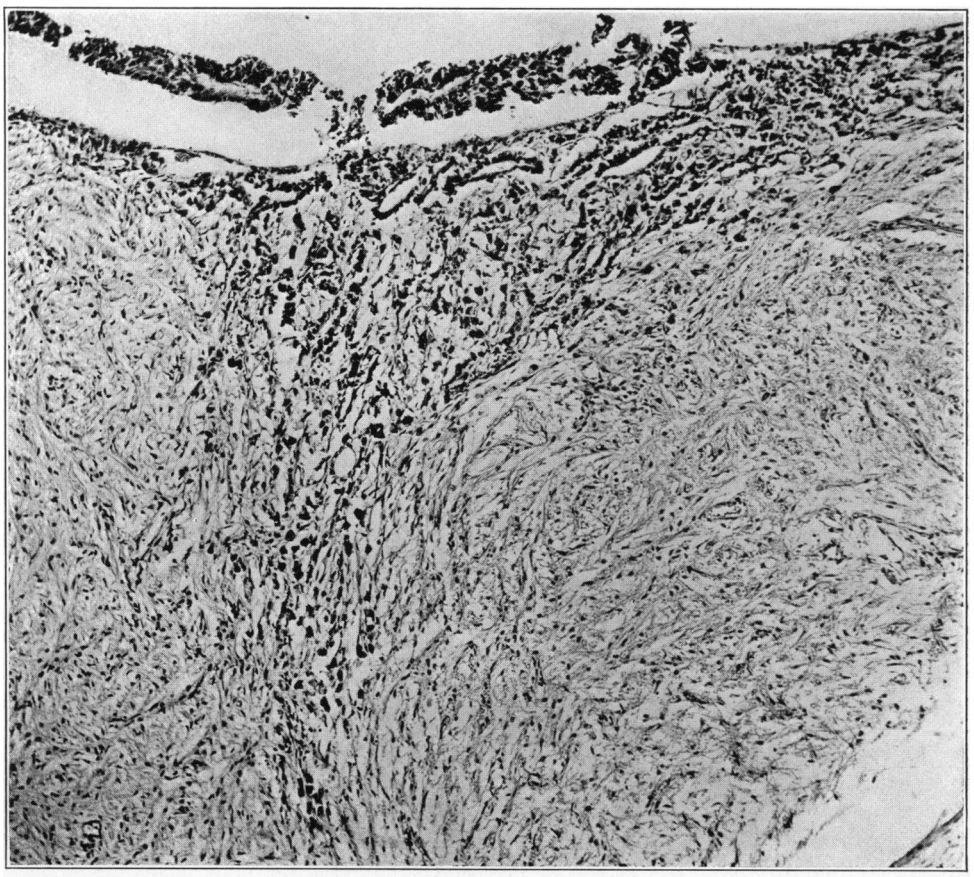
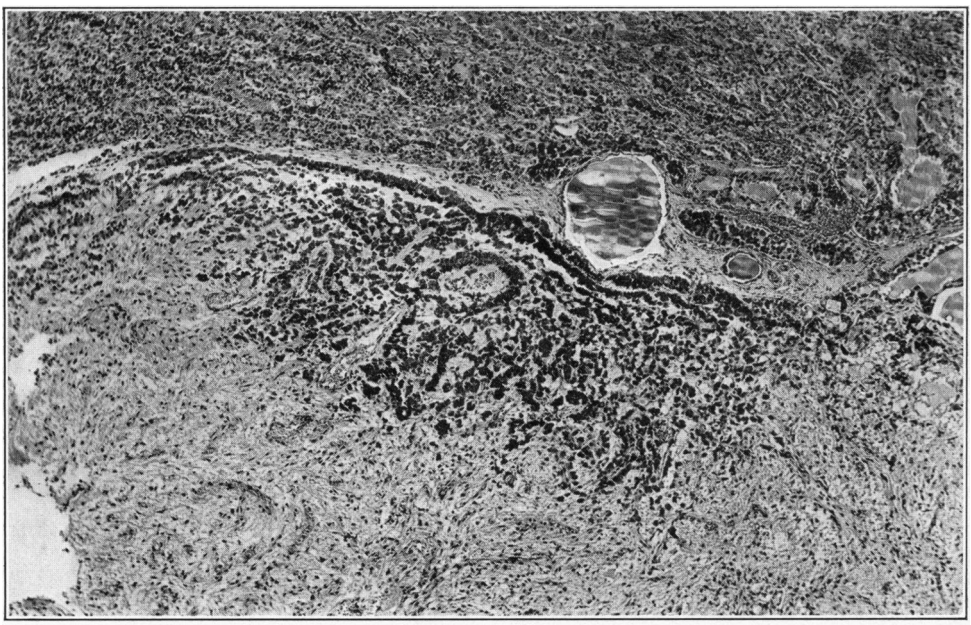


23

## Plate 65

Fig. 24. (Case 10.) Zone of activated basophils from pars intermedia from a case of essential hypertension (mag. × 60) in a man of middle age.

Fig. 25. (Case 11.) Showing (mag. × 60) posterior lobe invasion in a 60 year old man with hypertension and atherosclerosis.



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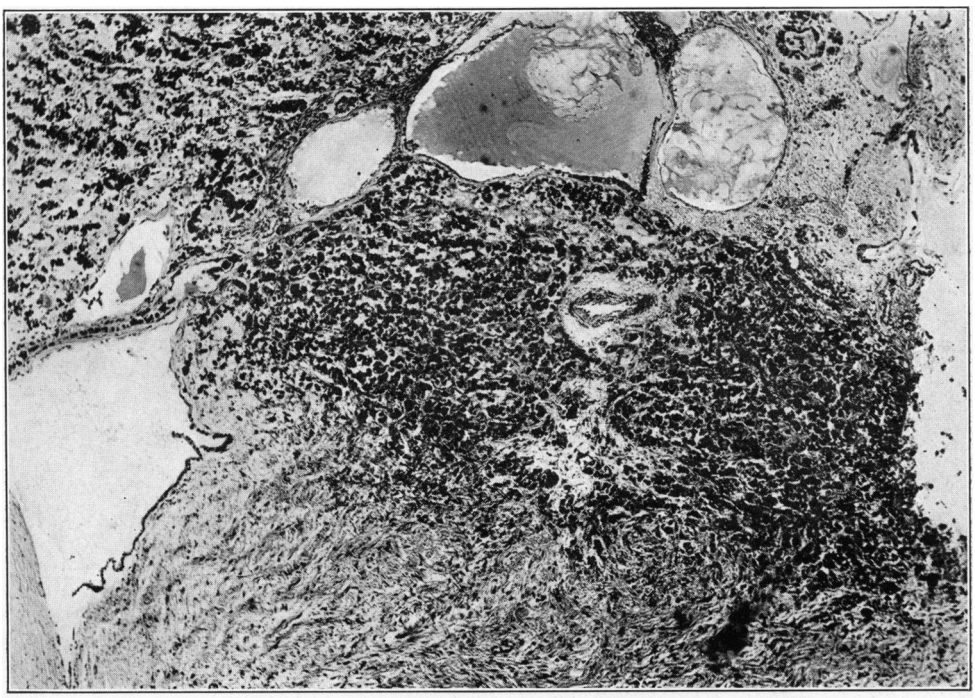

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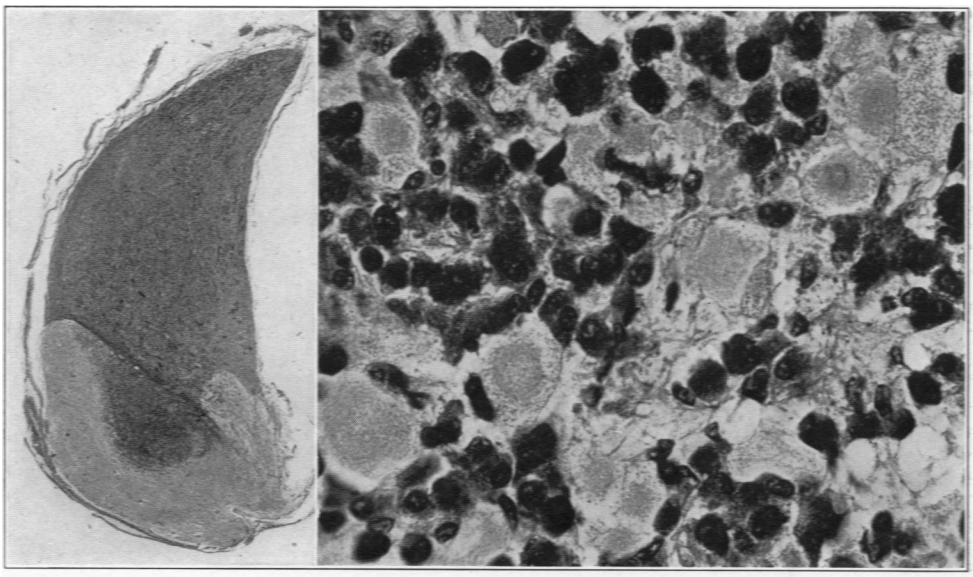
## PLATE 66

FIGS. 26 and 27. (Case 12.) Sagittal section (mag. × 8) of small gland from 67 year old woman with marked hypertension and heavy posterior lobe invasion. In Fig. 27 (mag. × 600) are seen well preserved masses of holocrine secretion showing ghosts of swollen nuclei.

FIG. 28. (Case 12.) Showing (mag. × 40) the area of massive invasion easily visible to the unaided eye (*cf.* Fig. 26).



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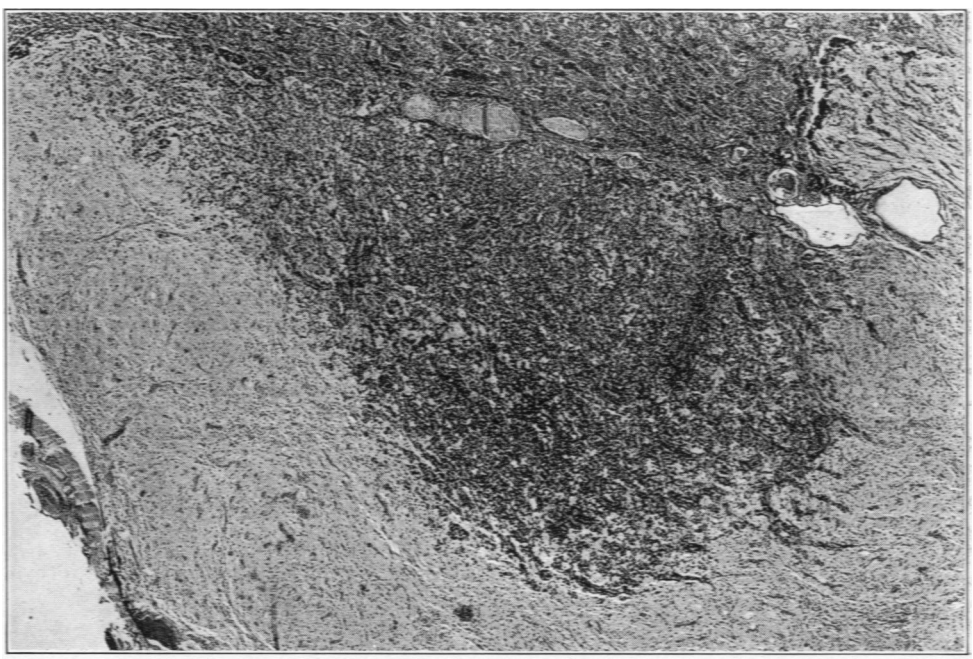

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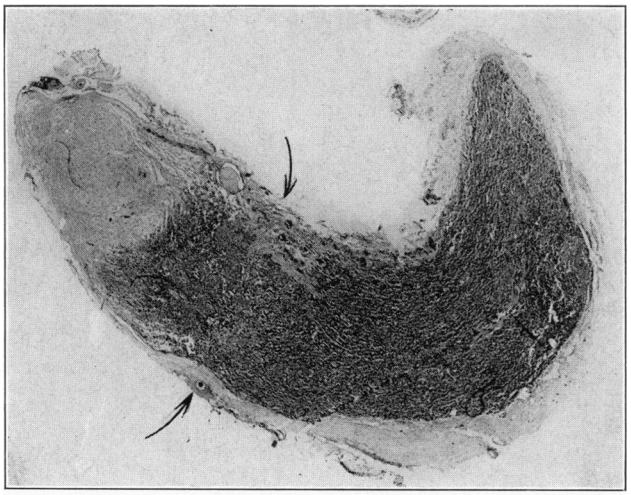
## PLATE 67

FIG. 29. (Case 13.) Sagittal section (mag. × 8) from gland of an aged woman with atherosclerosis, showing massive posterior lobe invasion. Arrows point to position of cleft.

FIG. 30. (Case 13.) Showing on higher magnification ( × 30) the full extent of the infiltration. A corner of pars distalis shows in the lower left corner.



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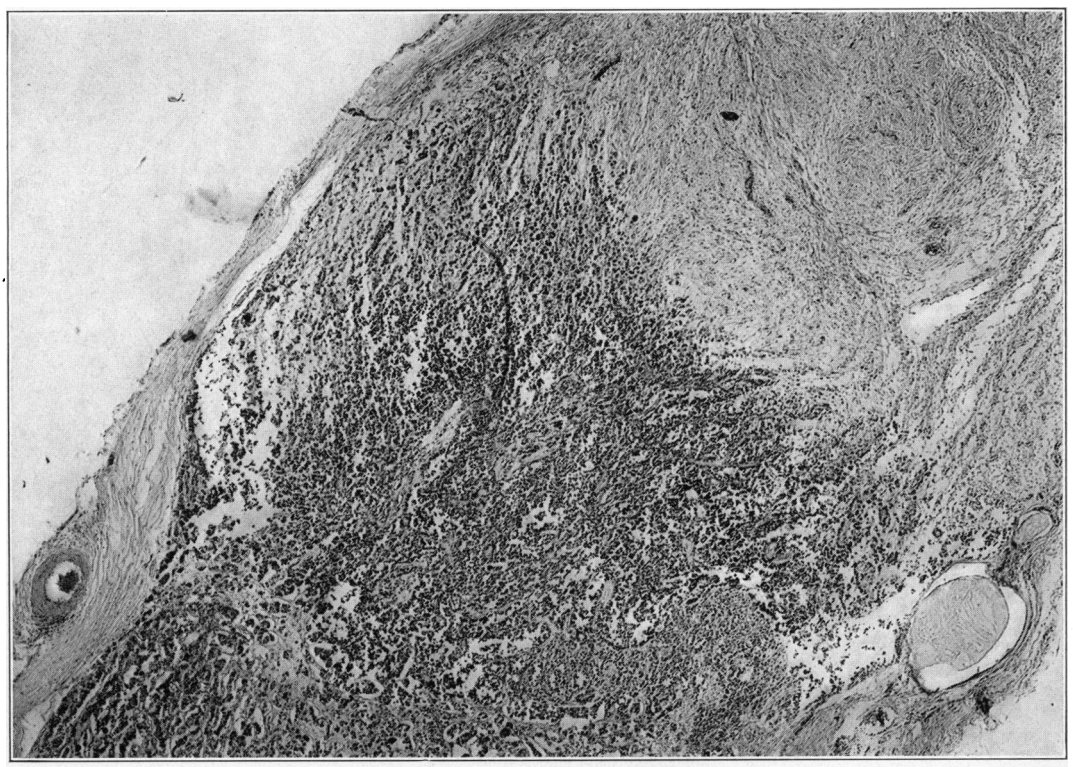

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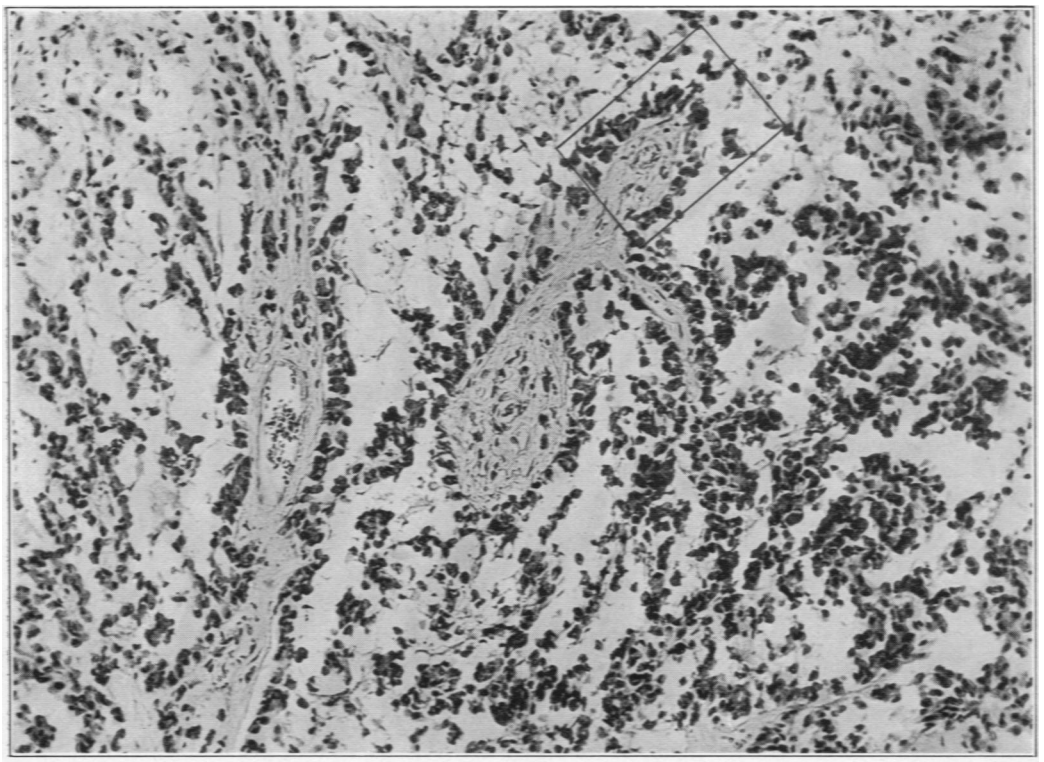
## PLATE 68

FIG. 31. (Case 13.) Posterior fringe of invading elements.

FIG. 32. (Case 13.) Squared area from Fig. 31 (mag. × 850) to show typical vacuolated cytoplasm of basophilic elements.



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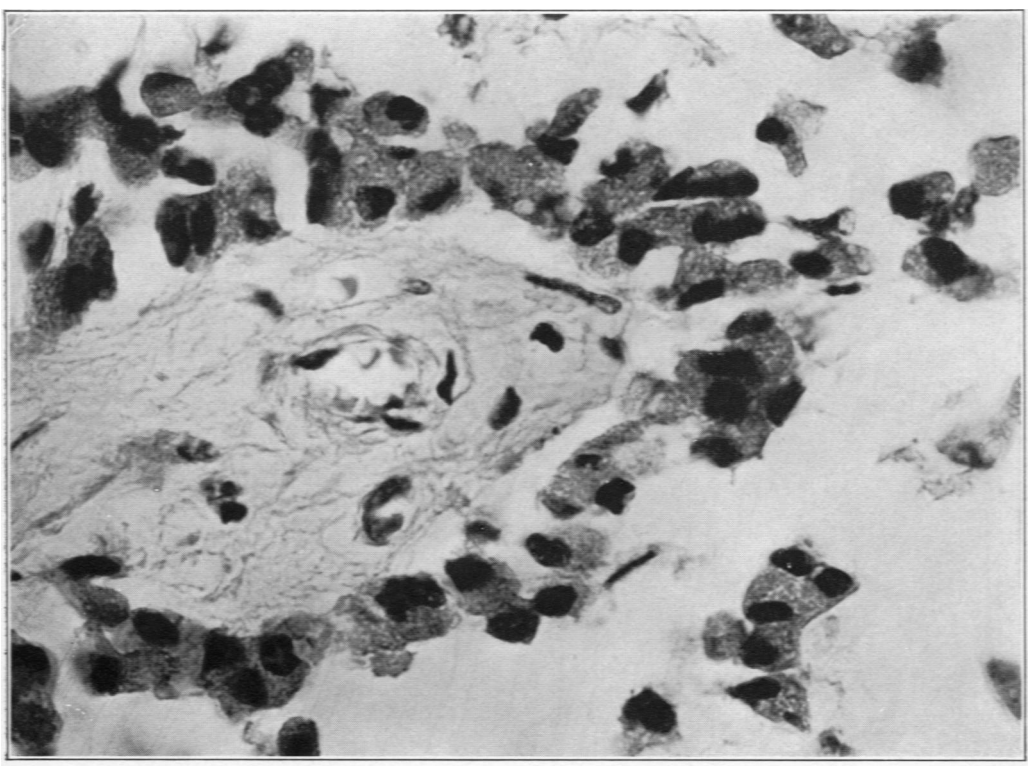

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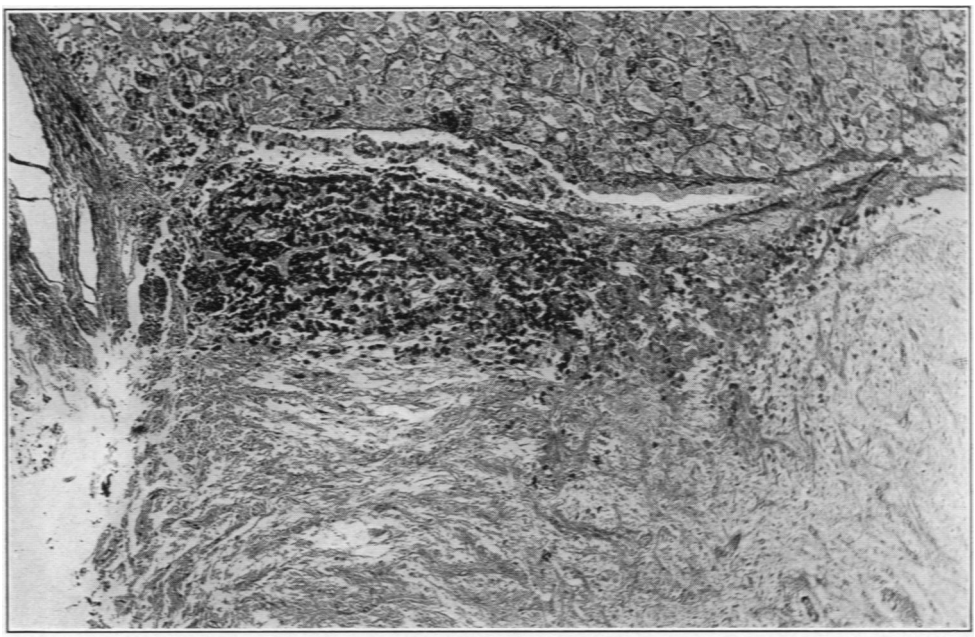
PLATE 69

FIGS. 33 and 34. Moderate invasion ( x 60) in two cases of accidental death. (Kindness of Professor Turnbull.)



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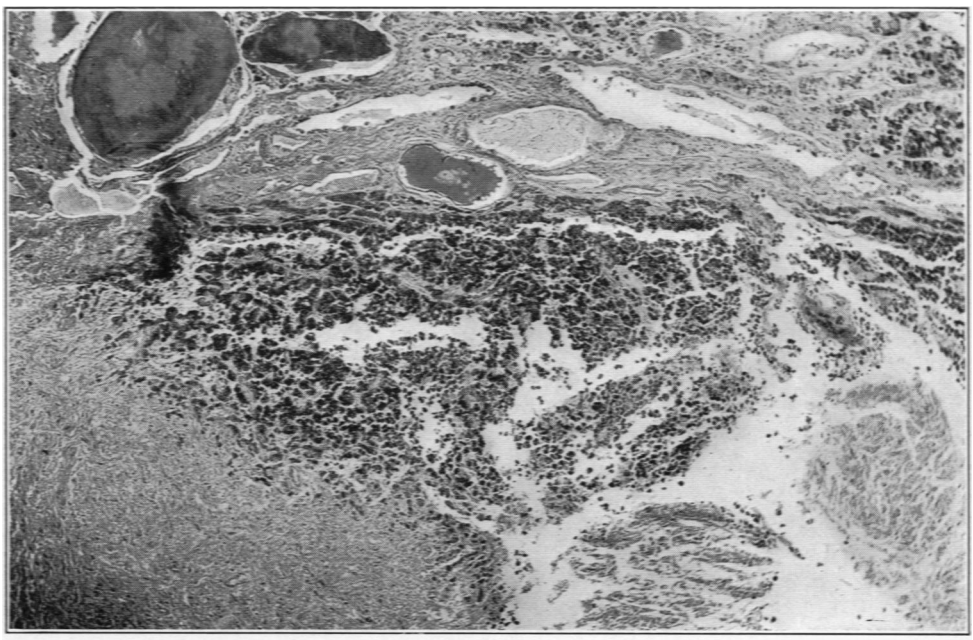

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