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POSTERIOR PITUITARY ACTIVITY FROM AN ANATOMICAL STANDPOINT *

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Since representatives of all departments of medicine are now in pursuit of the manifold activities of the pituitary body it may not be untimely to reconsider the histological evidences of the source and nature more particularly of the posterior lobe secretion and its pathway of discharge.

Because of the great interest aroused by the discovery in extracts of the anterior lobe of separable growth-promoting and sex-maturing hormones, attention of late has been focussed chiefly on the activities of that part of the gland. The posterior lobe meanwhile has been largely ignored and the impression has gained ground that it is a relatively unimportant structure. It has been separately extirpated in dogs without recognizable consequences (doubtless because it was not known what effects to look for), and the recently aroused interest in the hypothalamus and its functions has served more than ever to throw it into the shade.

Herring's Hyaline Bodies: After Howell's demonstration (1898) that the previously discovered haemodynamic effects of pituitary extracts were a property of the posterior lobe alone, ten years elapsed before the publication of P. T. Herring's illuminating studies^{9,10} of this particular subdivision of the gland. He described, in the pars nervosa of cats, what he called hyaline bodies, † which were looked upon as the secretory product of the pars intermedia.

* Received for publication June 9, 1933.

† It was possibly an unfortunate designation as the term "hyaline" suggests to pathologists a form of tissue degeneration. Others speak of the same substance as "colloid."

These bodies or masses made their way through the nervous tissue, along what were taken to be lymph spaces, in the direction of the infundibular cavity into which some of them appeared to pass.

This conception of posterior lobe secretion, though accepted wholly or in part by a few observers (*e.g.*, Cushing and Goetsch,⁷ da Costa,⁵ Remy Collin,⁴ Biedl³), has been looked upon in most quarters as wholly fantastic. Attempts on the part of many to establish the actual presence of posterior lobe hormone in the cerebrospinal fluid have led to contradictory results. Possibly the two most convincing recent observations in support of this view have been: (1) by Karplus and Peczenik¹¹ (1930), who found a pressor substance in the cisternal fluid only after electrical stimulation of the tuber; and (2) by Zondek and Krohn²² (1932), who have shown that a melanophore-expanding substance (*Intermedin*) proves not only to be abundant in extracts of the pars intermedia, of stalk and of tuber, but is also demonstrable in small amounts in the fluid of the third ventricle. In the cerebrospinal fluid elsewhere it is not detectable.

Important information regarding the tubulo-infundibular apparatus has meanwhile been secured from two sources. One of them has been the demonstration (1925), independently by Greving⁸ and by Pines,¹⁴ of the rich network of unmyelinated fibres from supra-optic and tuberal nuclei which arborize in the posterior lobe, thereby confirming Tello's observation²⁰ (1912) on the human gland of what Ramón y Cajal¹⁸ had originally (1894) described in the mouse. The other has been the description by Popa and Fielding^{15, 16, 17} (1930-1933) and Basir² (1932) of an "hypophysio-portal" circulation whose main venous trunks, having gathered blood from the sinusoids of the pars distalis, ascend in the pars tuberalis to break up in a vascular capillary plexus in the tuber cinereum (*cf.* Figs. 2-12). It is assumed that these ascending veins, which were independently described by Pietsch¹⁸ (1930), serve to carry the products of pars anterior secretion, colloidal masses of which may occasionally be demonstrated¹⁷ in the lumina of the vessels.

There thus appear to be two routes, both probably under nervous control, whereby the products of pituitary secretion are transported to the tuberal and possibly to other nuclei of the anterior hypothalamus: (1) from pars anterior by way of the "hypophysio-portal" vessels; and (2) from pars intermedia by way of the tissue

spaces in the pars nervosa. Though something will be said of the former route of secretion, it is with the latter that this paper will chiefly deal.

Among those who have described the course of the hyaline bodies through the pars nervosa and who believe that it has a stimulatory effect on the tuberal nuclei, only a few (Herring in the cat, Cushing and Goetsch in the dog, and Remy Collin in birds) appear to have noted that hyaline masses may actually be seen squeezing their way between the ependymal cells to enter the infundibular cavity. Observations of this kind are fortuitous because there is no certain method of preserving the secretory product in the tissues. For owing to the ready solubility of the substance it is usually dissolved out in the process of tissue fixation, leaving only an occasional hyalinoid mass still retained in the empty spaces in the open glial meshwork. That these empty tissue spaces which comprise the greater part of pars nervosa, stalk, tuber and infundibular ependyma serve as a tell-tale of the former presence of the secretory product, an effort will be made herein to show.

The Source of the Posterior Lobe Hormone: Preparations of the active principle of the posterior lobe are customarily made from the glands of animals in which there is a residual cleft. Hence, the extracts are not solely of pars nervosa, as generally assumed, but of pars intermedia as well. It is scarcely conceivable that the neural core of the lobe is capable independently of elaborating a hormone, which obviously must be produced by its inseparable epithelial investment. The two are in intimate functional contact, for the infundibular projection represents the only portion of the central nervous system that remains unprotected by an essentially impermeable pial covering.

Because of the absence of a distinct cleft in the glands of man and higher apes certain writers disclaim the existence in them of a separately recognizable pars intermedia. This, however, is an academic point of view that has been well answered by Rasmussen¹⁹ (1930), who believes with others that the elements comprising the pars intermedia are clearly distinguishable. Even under normal conditions, when the lobe is relatively inactive, the chromophobe mother cells of the juxtaneural investment tend to arrange themselves into colloid-holding vesiculi, from which an occasional ripened cell may be seen invading the adjacent neural tissue.

In the process of their ripening the cells of the pars intermedia invariably become transformed into basophilic elements which in their mature stage are indistinguishable from the ripened basophiles of the pars distalis. The cells may occasionally be seen in the process of disgoring their cytoplasm in apocrine fashion, but more often the entire cell body is cast off in the manner of a holocrine secretion (*cf.* Fig. 14). The highly vacuolated elements thus discharged soon lose their tinctorial affinity and each separate mass as it becomes "hyalinized" in its passage into the lobe may long retain the recognizable ghost of the swollen nucleus (*cf.* Figs. 15-16). These so-called hyaline bodies of Herring are certainly not the degenerated end-bulbs of nerves as some writers, under the influence of Tello's paper, have come to believe.

Basophilic Activation of Posterior Lobe: When the normal activity of the pars intermedia is exaggerated in certain pathological states there occurs a marked hyperplasia of the basophilic elements. Not only do they discharge their secretory product into the relics of the original cleft, which can be partly reestablished thereby, but the ripened elements wander deeply into the neural tissue after the manner of a malignant epithelial invasion, to which the process first described by Thom²¹ (1901) has often been likened. While this infiltrative tendency has been observed by many, it has been commonly supposed to be a peculiarity of the glands of aged persons (more particularly of those victimized by arteriosclerosis and renal disease) and to have no functional significance.

These infiltrating elements, which are apparently unrelated to the tubulo-racemose glands recently redescribed by Lewis and Lee¹² (1927), are accompanied by a great increase in the hyalinoid secretory product that gives to the lobe, stalk and tuber its "juicy" appearance to the naked eye. And when sections are cut and the pars nervosa is found to be composed of a widely opened mesh (from which the hyalin has been largely dissolved out), it is usually described as representing an "oedematous" condition of the tubero-infundibular structures.

As must have been observed by all who have studied serial sections through this region in whatever plane they happen to have been cut, this familiar "oedematous" or open appearance of the tissue is sharply confined to pars nervosa, stalk, tuber cinereum and neighbourhood of supra-optic and paraventricular nuclei. Attention, however,

does not seem to have been specifically drawn to the peculiar fact that the ependymal cells lining the lower infundibular cavity are invariably broken up by this so-called "oedema," whereas the ependyma of adjacent parts of the ventricle remains more or less intact.

The impression is inescapable from this appearance that something (the secretion in all probability) is forcing the cells apart and being extruded into the ventricle. At the tip of the infundibular cavity there may be no trace whatsoever of the ependymal lining (*cf.* Fig. 17) and patches of it begin to appear only as one passes upward (*cf.* Fig. 18). Not infrequently one sees the more or less intact ependyma lifted into a bleb that has the appearance of rupturing into the ventricle (*cf.* Figs. 19-20), after which a new cuticular layer of cells reforms. Even when the lining of the infundibular cavity is found to be reasonably intact, should the cells happen to be cut lengthwise in the direction of their long tails, the cell bodies here and there seem to be irregularly separated, as though mechanically forced apart. This broken-up appearance of the tubero-infundibular ependyma must have been observed by many and likely enough been ascribed to an artifact from some fault in tissue fixation or section cutting.

Posterior Lobe Basophilia in Disease: Moderate degrees of basophilic infiltration of the pars nervosa have often been described with no suggestion made, or at least no emphasis laid, on the possibility that it represented a physiological activation of the neurohypophysis. And while it is not the purpose of this communication to do more than point out what are looked upon as histological indications of posterior lobe activity, the reasons for bringing the matter up anew at this time may briefly be given.

A long known polyglandular disorder has been shown to be caused by an actively secreting basophilic adenoma of the pars distalis. In the study by serial sections of the pituitary body and interbrain of a fatal case of this disorder (as told in another place⁶), a most extensive infiltration of basophilic elements from the pars intermedia was disclosed. Since the clinical disorder, among other symptoms, is characterized by hypertension, glycosuria and adiposity, which suggest a posterior rather than anterior lobe effect, it was assumed that the cellular invasion of the pars nervosa might well have been the causative factor in these symptoms and might therefore represent a physiological hyperactivation of the posterior lobe.

Aware that Anselmino and his co-workers¹ had found in the blood of patients suffering from the hypertensive toxæmias of pregnancy (eclampsia) a substance giving the reactions of posterior lobe extracts, also that Irvine Page (personal communication) had found a similar or the same substance in the blood of certain patients with so-called essential hypertension, as opportunity has arisen studies have been made of the glands secured from a few fatal examples of these two disorders.

These glands have shown, in somewhat less degree, the same massive basophilia of the pars nervosa seen in the aforementioned polyglandular disorder. It is assumed, therefore, that the process in all probability *does* indicate an hyperactivation of the posterior lobe and consequently represents the pathological basis of these hypertensive maladies. It is perhaps not overventuresome to predict that in some of these hypertensive states the posterior lobe principle may prove to be detectable in the fluid of the third ventricle as well as in the blood stream.

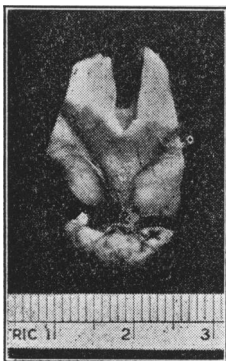


FIG. 1. The original block of tissue (natural size).

Illustrative Material: The accompanying photograph (Fig. 1) shows the original block of tissue from a fatal case of essential hypertension.* It is viewed from behind and shows the small, somewhat cupped, gland with prominent posterior lobe, the stalk and tuber being distinctly "juicy" in appearance. After fixation in formalin the entire block was cut serially from below upward on the horizontal plane in 8 micron sections, every tenth section having been stained with haematoxylin and eosin† and numbered accordingly.

* For this particular specimen I am indebted to Dr. George Hass of the pathological department of the Peter Bent Brigham Hospital.

† The preferential method (1) of fixing, (2) of cutting and (3) of staining the pituitary body naturally differs with what may be the object of the study. Da Costa,⁵ for example, states that the hyaline bodies are better preserved in small tissue fragments fixed in Flemming's solution, with which we have had no experience. For our particular purposes it is undesirable that the gland should be cut in parts before fixation, as is commonly done. Hence, owing to its greater penetrability, formalin has distinct advantages over Regaud's, Zenker's or Kolatchew's fluid.

For our purposes also, serial sections in the horizontal plane prove to be preferable to coronal or sagittal sections as they give better topographical orientation, particularly should the block include the tuberal region as well. (Continued on opposite page.)

Photomicrographs of certain selected sections from this single case will suffice, it is hoped, to bring out the principal points relating to posterior lobe activity, which it is the purpose of this communication to reemphasize. For orientation all sections should be regarded as being seen from above, the anterior structures lying at the top of the print, the posterior structures at the bottom. Figures 2 to 12 have been chosen for the purpose of tracing on these horizontal sections the "hypophysio-portal" circulation from pars anterior to tuber cinereum. Figures 13 to 20 serve to show the formation (from the inwandering basophilic elements of the pars intermedia) of the secretory product and its upward passage through pars nervosa and stalk toward the ventricle. The legends facing these illustrations (to be found at the end of the text) will render it superfluous to redescribe them here.

SUMMARY

In all the recent attention paid to the pituitary body and its functions, the posterior lobe has been much neglected because of the greater temporary interest in the hormones of the pars anterior and the newly discovered activities of the interbrain. It nevertheless has an active principle or principles capable among other properties (1) of raising blood pressure, (2) of contracting smooth muscle, (3) of causing hyperglycaemia, (4) of expanding cutaneous melanophores, and (5) of diminishing renal secretion.

Its secretory product is unmistakably derived from the investing pars intermedia, whose cells become basophilic when ripened. Doubtless under nervous impulses from hypothalamic nuclei these cells, by a form of holocrine secretion, are cast off, invade the pars nervosa and become transformed into "hyaline bodies," which as Herring first showed in lower animals make their way through the loose neural spaces of pars nervosa in the direction of the infundibular cavity. They may, in favourable preparations from the cat and

Simple haematoxylin and eosin stains give perfectly satisfactory cellular differentiation when the solutions are properly used. While many stains, like Mann's eosin-methyl blue and Mallory's aniline-blue orange G, give a more brilliant colour contrast, this is often at the expense of a clear picture of the cellular morphology. The specific stains for the granules, such as Bailey's acid-violet eosin or ethyl-violet orange G, after Regaud fixation, or Severinghaus' acid-fuchsin methyl-green acid-violet stain after Kolatchew fixation, for the reasons given are inapplicable to the serial study of a large block of tissue.

dog, even be seen to extrude themselves into the ventricle between the ependymal cells.

In certain conditions of disease characterized notably by hypertension, but also by other symptoms suggestive of known physiological effects of posterior lobe extracts, the normal cellular activity of the pars intermedia becomes greatly exaggerated. This is shown by a marked hyperplasia of the basophilic elements that penetrate far into the lobe. Under these circumstances not only is the visible secretory product (hyalin) greatly increased in amount over what is customarily seen in supposedly normal glands, but the cuticular ependyma of the lower third ventricle has a highly broken up appearance.

An extreme degree of cellular hyperactivation of the posterior lobe was first observed in the pituitary body of a fatal case of what is known as pituitary basophilism associated with a basophilic adenoma of the pars distalis. Since then a similar condition has also been found in cases of eclampsia and of so-called essential hypertension. In both of these latter states there has been found in the blood stream a substance indistinguishable in its effects from posterior lobe extract, but not detectable in the blood under normal conditions.

The conclusion is drawn that the infiltrative basophilia of the pars nervosa is an expression of functional hyperactivation of the posterior lobe and may be taken to represent the pathological basis of these hypertensive disorders. What particular form of neurohumoral stimulus primarily incites the neurohypophysial basophilia remains to be determined.

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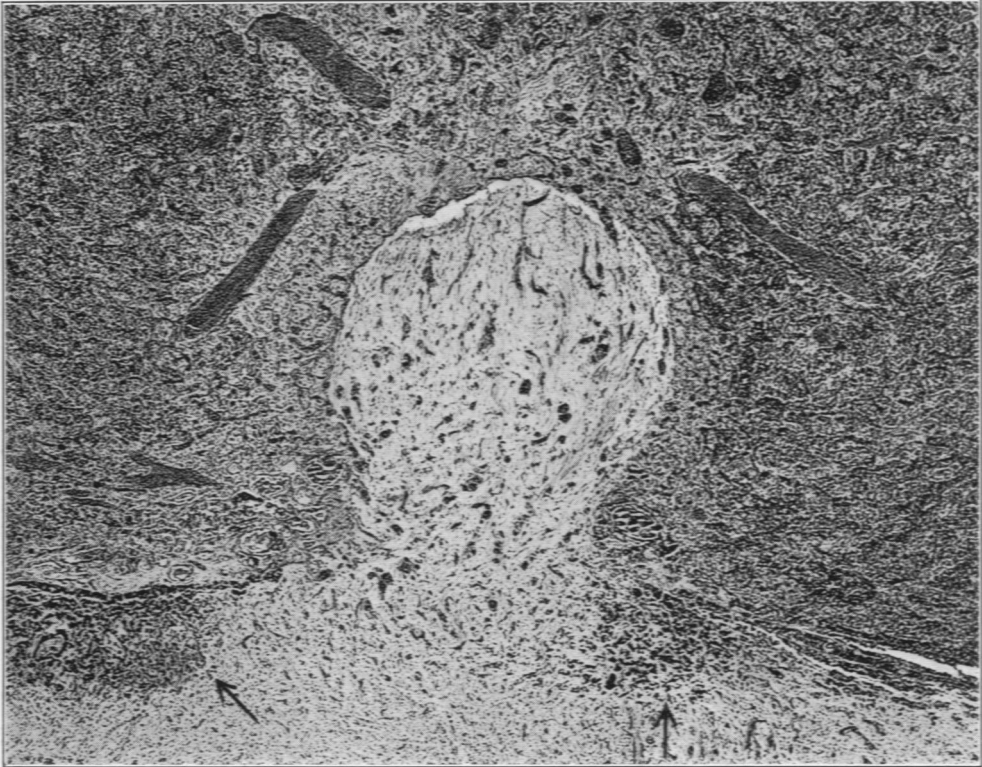
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DESCRIPTION OF PLATES

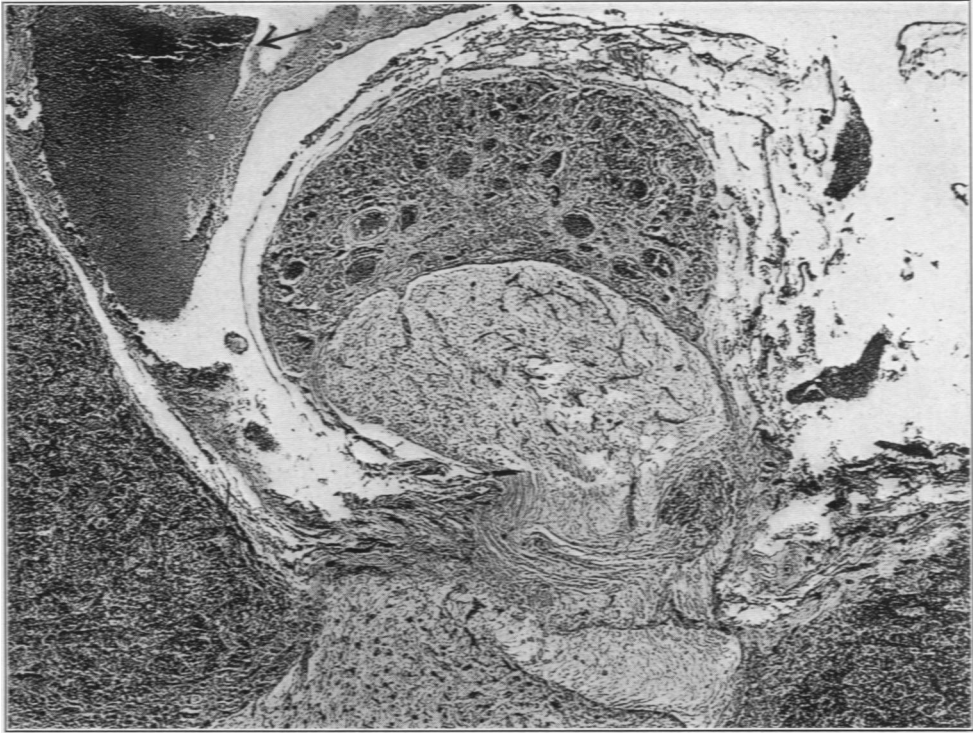
PLATE 75

FIG. 2. (Section No. 40: mag. $\times 30$.) This section transects the upper part of the gland where chiefly acidophilic elements abound. Three large collecting sinusoids can be seen in the pars anterior (above) passing in the general direction of the root of the stalk which appears in the centre of the field. Even at this high level the infiltration of the pars nervosa by basophilic elements (arrows) from pars intermedia is abundant (*cf.* Fig. 13).

FIG. 3. (Section No. 52: mag. $\times 30$.) This section passes through the base of the emerging free stalk and shows the anteriorly placed situation of the pars tuberalis through which pass the large ascending "hypophysio-portal" venous trunks. At the upper left (arrow) lies a small subarachnoid clot from an agonal extravasation. Numerous, minute, capillary haemorrhages are present throughout the pars nervosa, not visible at this low magnification.



2



3

Cushing

Posterior Pituitary Activity

PLATE 76

FIG. 4. (Section No. 61: mag. $\times 30$.) At this level the stalk is entirely free and beginning to be completely enveloped by the cuff of pars tuberalis. This still holds the many ascending portal trunks, which, as Popa and Fielding have shown, are without cross anastomoses.

FIG. 5. (Section No. 85: mag. $\times 30$.) This shows the tendency for the cuff of pars tuberalis to swing toward the sides and back of the stalk as the tuberal enlargement is approached.

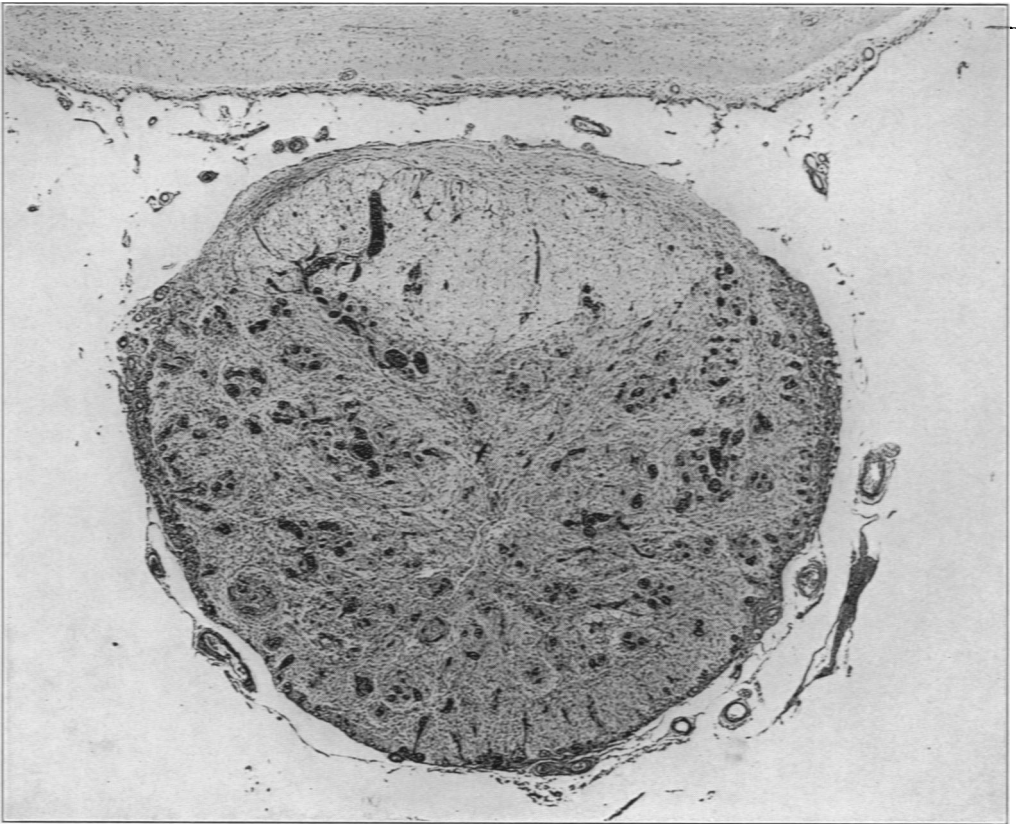
FIG. 6. (Section No. 115: mag. $\times 30$.) Here the stalk is enlarging into the tuber at the near proximity to the chiasm shown in the upper part of the field. The "hypophysio-portal" vessels are beginning to leave the cuff of pars tuberalis to plunge into the nervous tissue, forming glomerulus-like tufts (the "secondary capillary net" of Popa and Fielding) enveloped by comparatively dense glial sheaths (*cf.* Fig. 12).



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5



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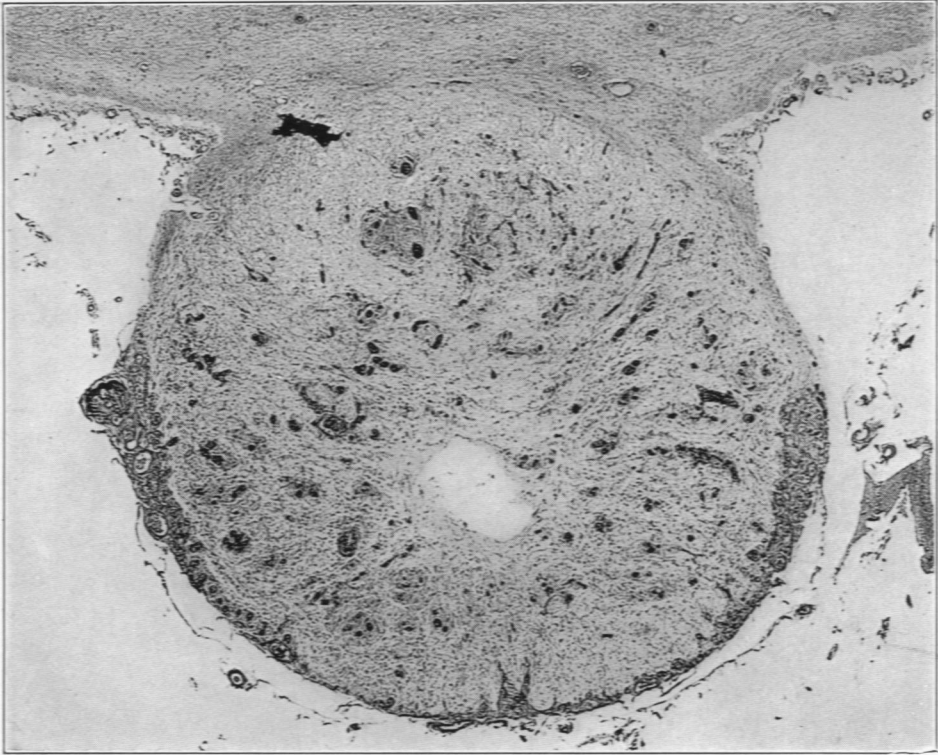
Cushing

Posterior Pituitary Activity

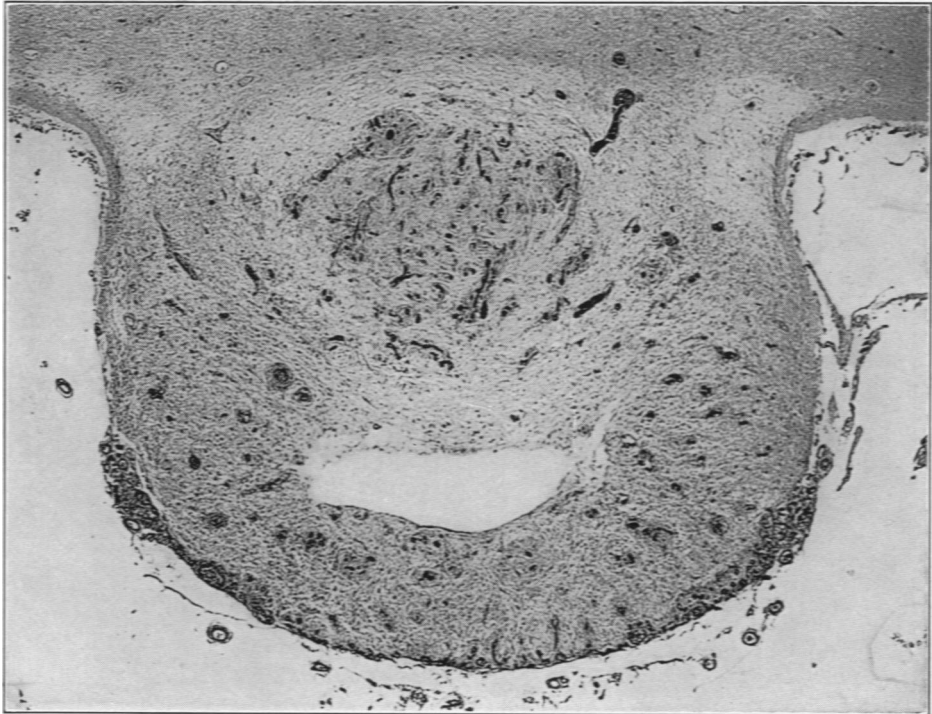
PLATE 77

FIG. 7. (Section No. 124: mag. $\times 30$.) Here the tuber cinereum is fused with the posterior margin of the chiasm, narrow residuals of the pars tuberalis being still evident on its posterior and lateral surface. The tip of the infundibular cavity with its disrupted ependyma (*cf.* Fig. 17) is apparent in the lower centre of the field.

FIG. 8. (Section No. 133: mag. $\times 30$.) The terminal capillary bed of "hypophysio-portal" vessels has here largely swung around to lie anterior to the infundibular cavity. The cuticular ependyma of the ventricle is still missing on the anterior side, but posteriorly the cavity begins to show an intact ependymal lining. Traces of the tuberal cuff are still discernible on the posterolateral surface of the tuber.



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8

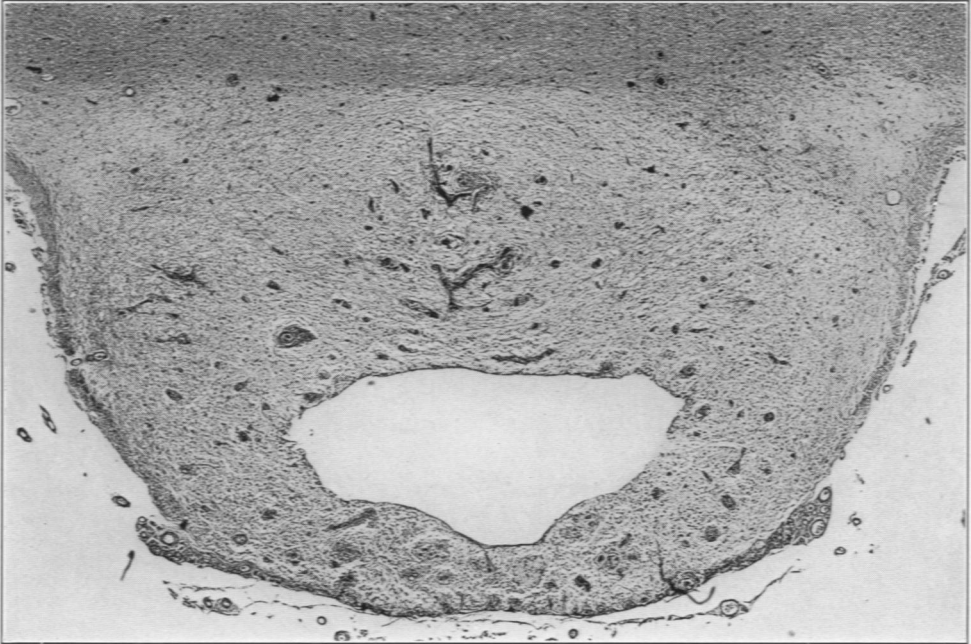
Cushing

Posterior Pituitary Activity

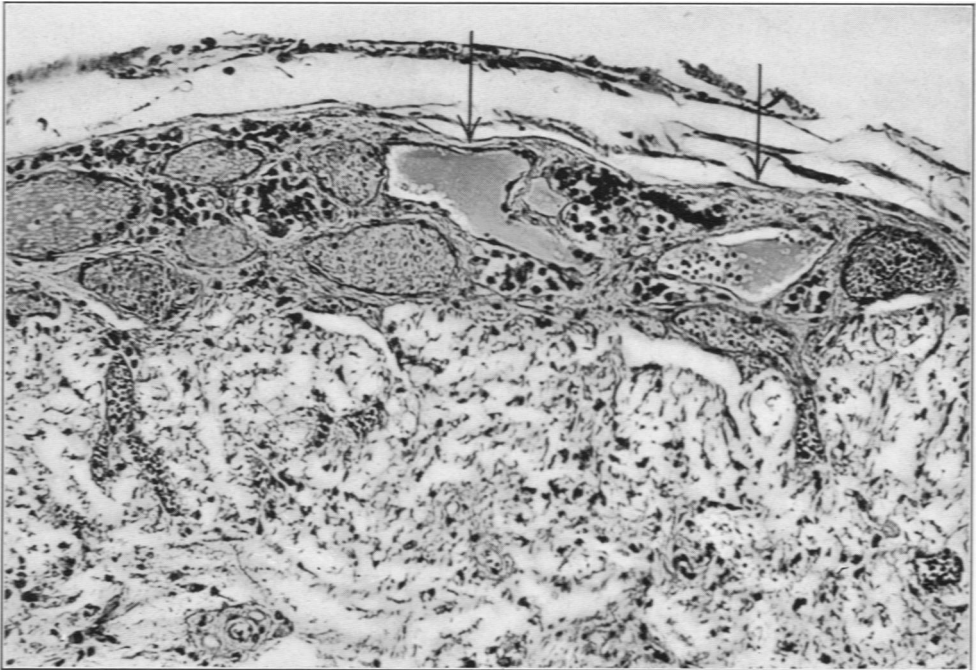
PLATE 78

FIG. 9. (Section No. 142: mag. $\times 30$.) The tuber cinereum here is flattened out against the posterior surface of the chiasm. The loose texture of the tuberal tissue is clearly distinguished by its light shade even at this low power. The cuticular ependyma of the widening cavity is fairly intact, except at its lateral angles. Traces of the terminal capillary plexus of the portal system surrounded by its glial sleeve are still to be seen between ventricle and chiasm.

FIG. 10. Showing (mag. $\times 175$) homogeneous and refractile masses of colloid (?) in two of the ascending hypophysio-portal vessels of upper stalk (arrows). From a case of "pituitary basophilism" due to an adenoma. Colloidal masses in this case are also to be seen in the capillaries of the pars nervosa.



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10

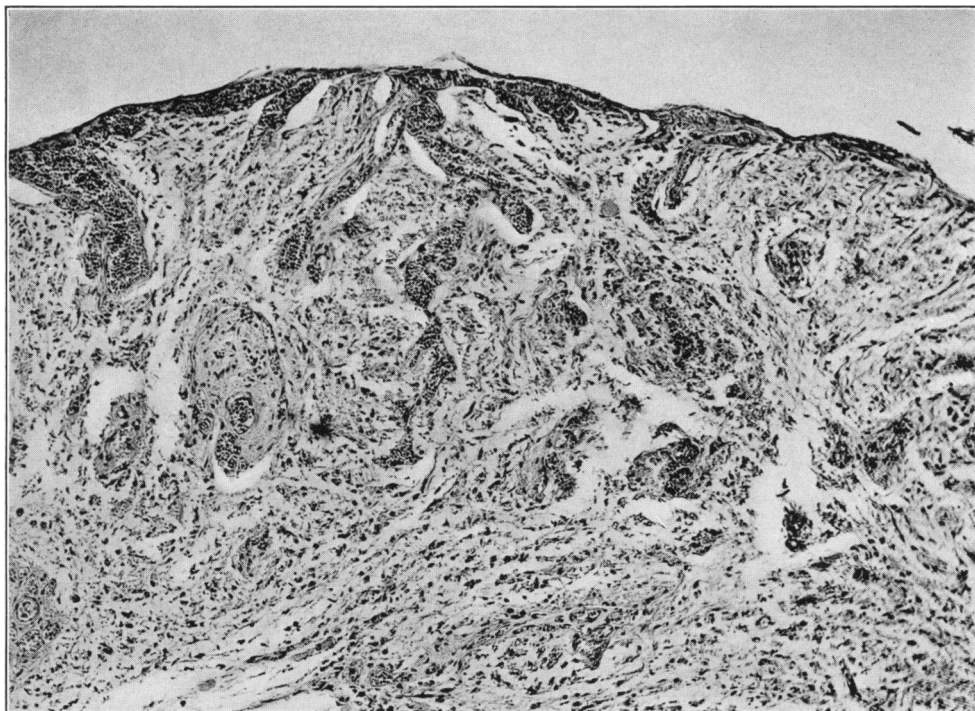
Cushing

Posterior Pituitary Activity

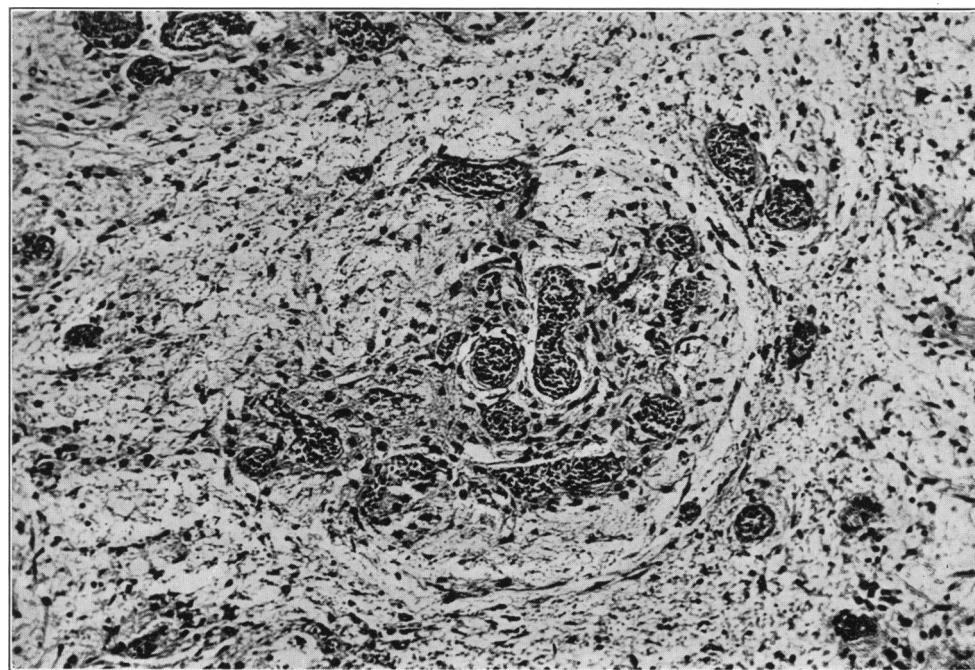
PLATE 79

FIG. 11. Showing (mag. $\times 100$) at level of tuberal enlargement of upper stalk how the large ascending portal trunks break up into smaller vessels which leave the residual of the pars tuberalis to plunge into the tuberal tissue forming the secondary capillary net.

FIG. 12. (Section No. 119; mag. $\times 150$.) A glomerulus-like tuft of capillary vessels with glial sheath characteristic of the vessels composing the secondary net.



11



12

Cushing

Posterior Pituitary Activity

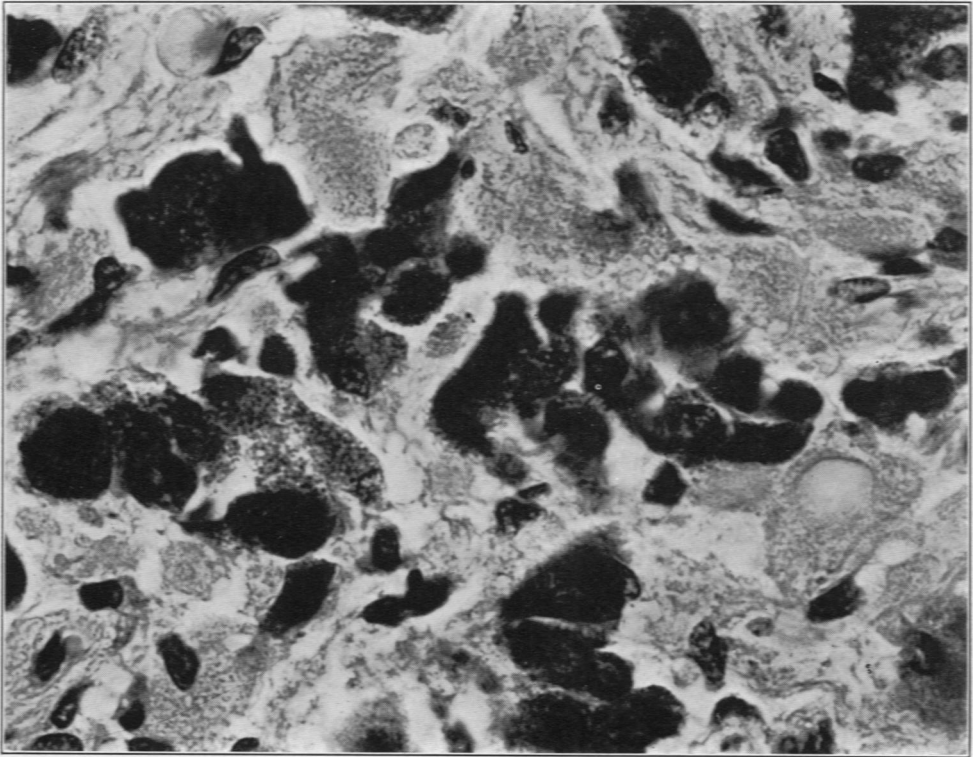
PLATE 80

FIG. 13. (Section No. 34: mag. $\times 80$.) This section passes approximately through the centre of the gland and transects the body of the posterior lobe. It shows the character of the basophilic invasion of the pars nervosa by pars intermedia cells. This invasion occurs in varying degrees of depth from almost the entire juxtaneural epithelial surface.

FIG. 14. Showing (mag. $\times 850$) the masses of secretory holocrine product lying between the tongues of invading and fully ripened basophilic elements. The cast-off cells are still highly granular in appearance but have largely lost their tinctorial affinity to haematoxylin (they stain a reddish brown with Mallory's phosphotungstic acid haematoxylin). In the granular protoplasmic mass of many of the discharged cells the trace of the greatly swollen nucleus is often discernible (*cf.* Fig. 15).



13



14

Cushing

Posterior Pituitary Activity

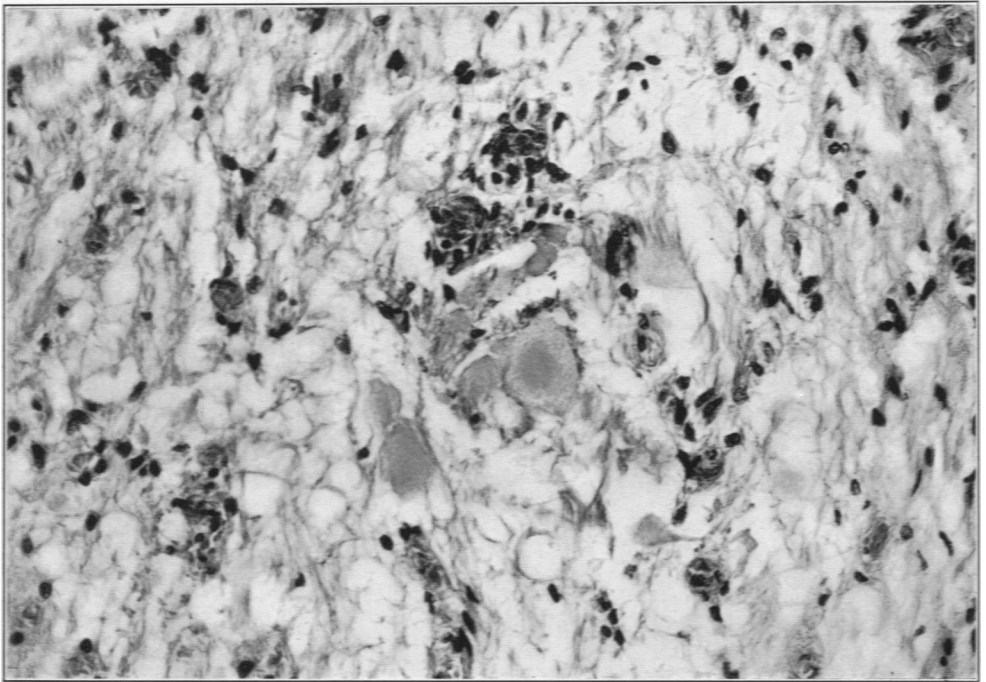
PLATE 81

FIG. 15. To show masses of cast-off holocrine secretion making their way upward through the interstices of the pars nervosa. Ghosts of swollen nuclei still discernible in the secretory masses which become increasingly homogeneous (hyalinized) in their passage through the lobe (mag. $\times 850$).

FIG. 16. Occasional hyaline masses are even to be found trapped in the loose tissue spaces of the tuber. It is assumed from the appearance of the tuberal tissue that the open mesh was once full of the secretory product that has been dissolved out in the process of fixation (mag. $\times 300$).



15



16

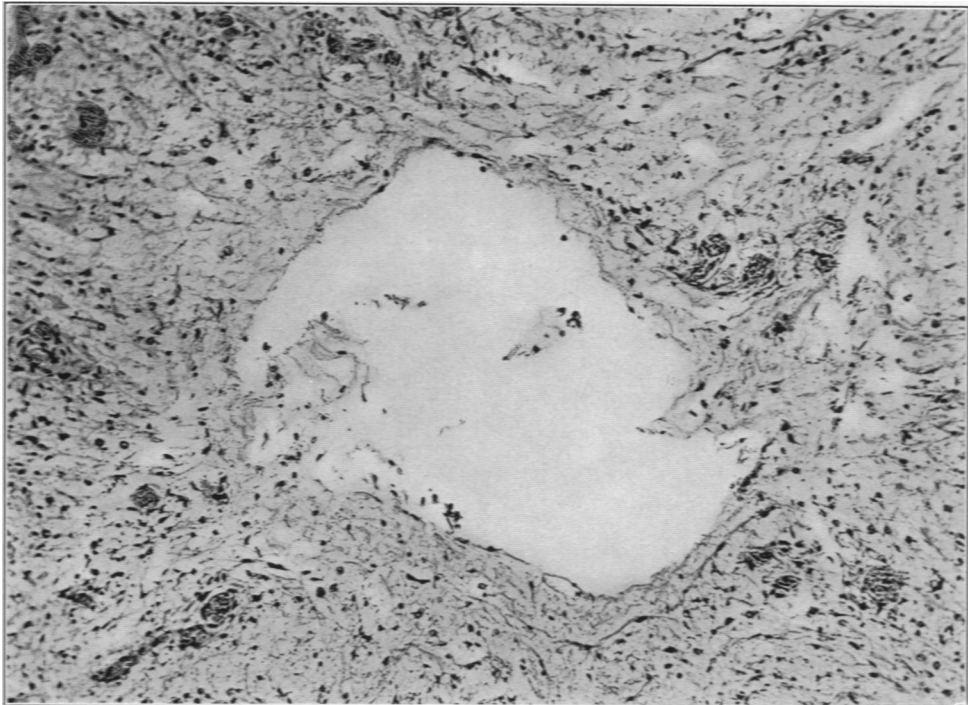
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Posterior Pituitary Activity

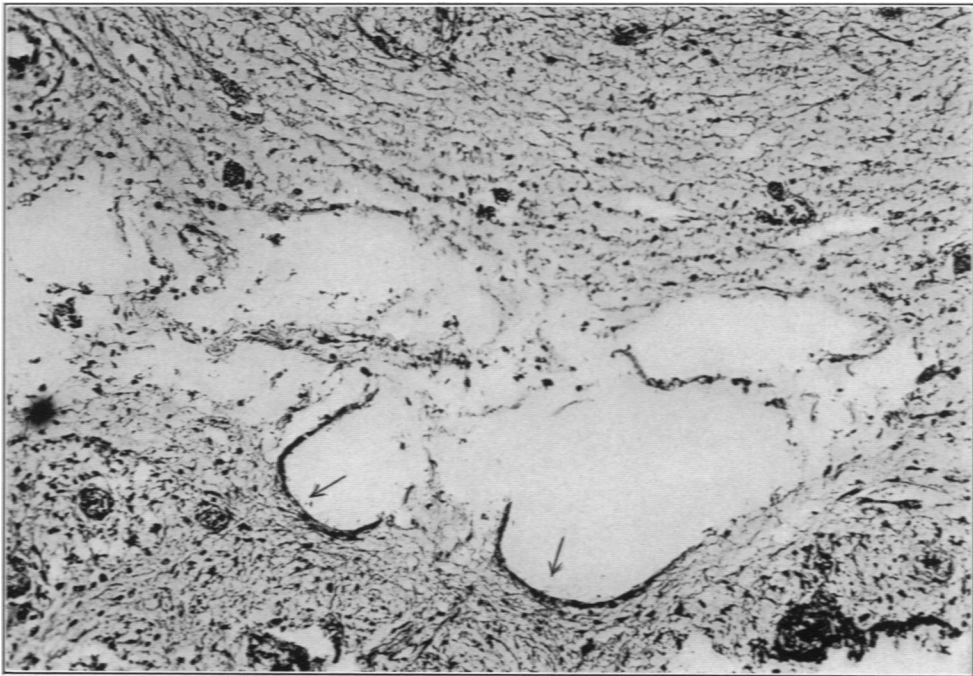
PLATE 82

FIG. 17. (Section No. 124: mag. $\times 125$.) To show at higher magnification a cross-section of the tip of the infundibular cavity (*cf.* Fig. 7). Note the broken-up appearance of the ependymal lining which is invariably present in this region. No cuticular layer is here discernible.

FIG. 18. (Section No. 131: mag. $\times 125$.) To show tip of infundibular cavity slightly higher up than in Fig. 17 (above). Here two loops of intact cuticular ependyma (arrows) are present with an intervening break in the lining. Otherwise one would hardly know that the open spaces represent the ventricular cavity.



17



18

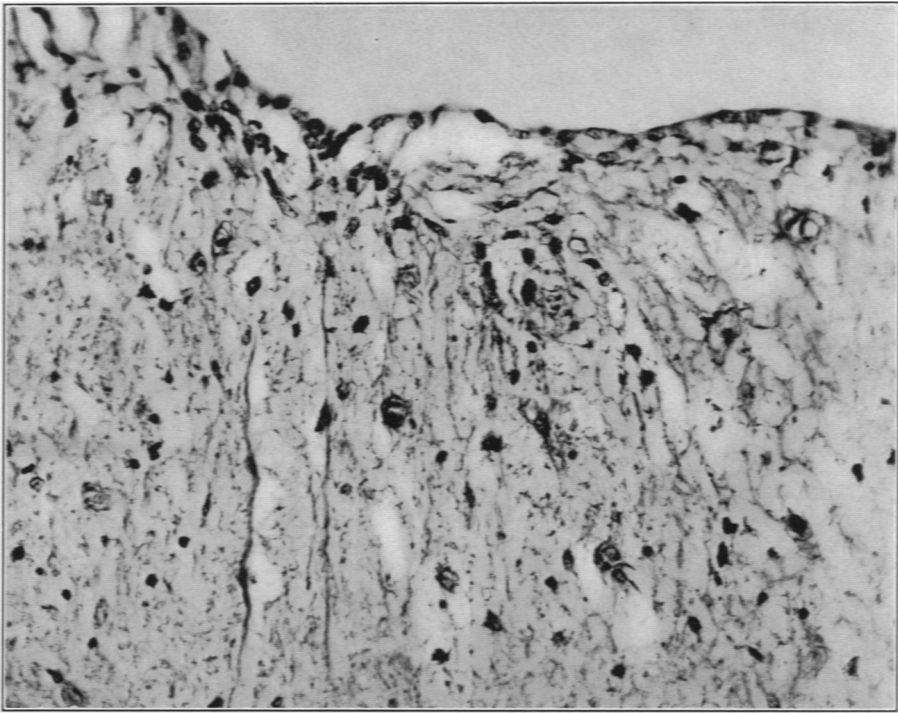
Cushing

Posterior Pituitary Activity

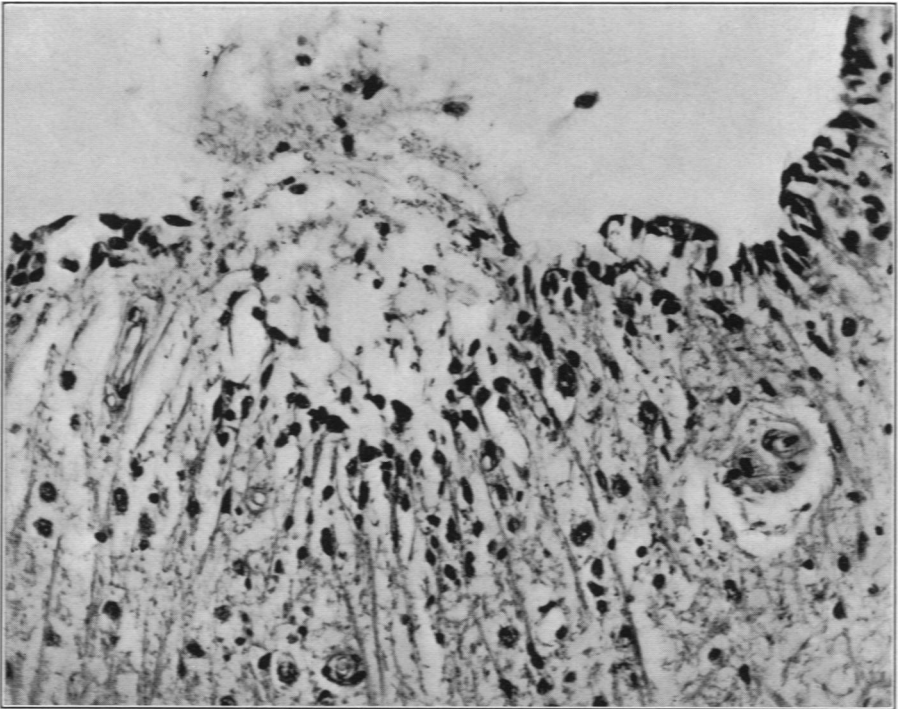
PLATE 83

FIG. 19. (Section No. 151: mag. $\times 300$.) To show a characteristic bleb forming under the still intact cuticle. As these subependymal blebs form, bulge into the ventricle and rupture, a new line of ependymal cells reforms below the protrusion and comes to take the place of the original surface layer.

FIG. 20. A more highly advanced stage (mag. $\times 300$) of what is shown in Fig. 19, indicating the rupture and escape of something (presumably secretion) into the ventricle. Note the tendency of new ependymal bodies to reassemble on the neural side of the bleb.



19



20

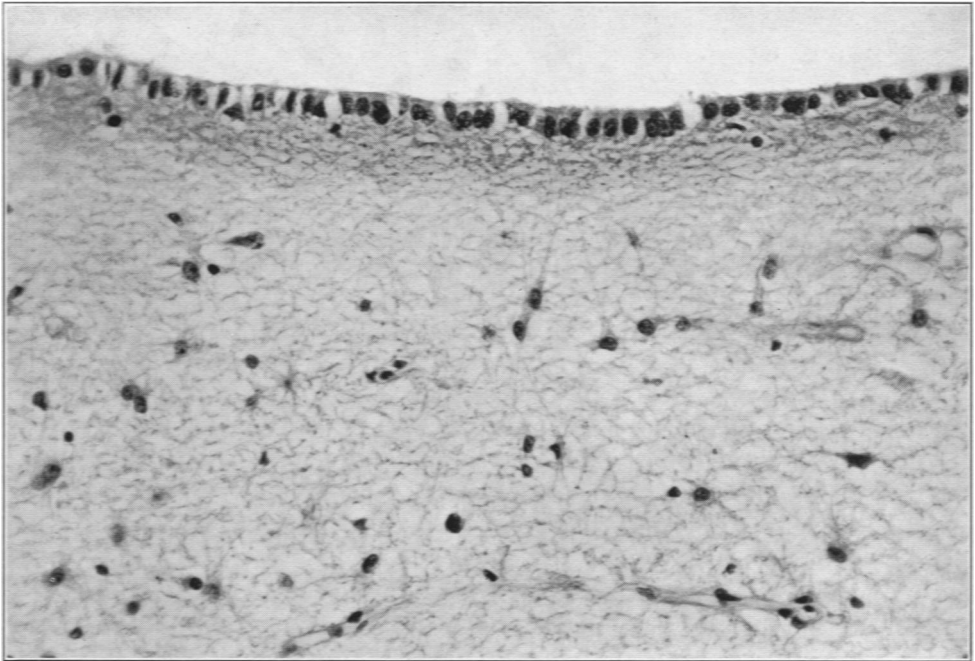
Cushing

Posterior Pituitary Activity

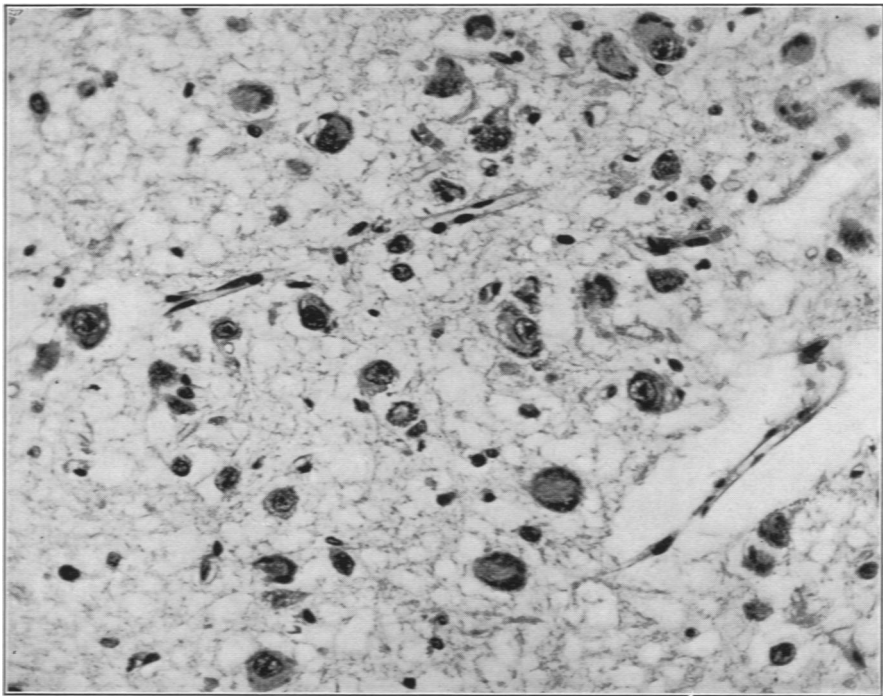
PLATE 84

FIG. 21. In contrast with Figs. 19 and 20, here is shown (mag. \times 300) the fairly intact ependymal lining of the lateral and dorsal aspects of the anterior third ventricle. That this view is taken from the tuberal region is shown by the characteristic open network of the subependymal tissue.

FIG. 22. Here is shown (mag. \times 300) the loose (oedematous) character of the tissue in the region of both paraventricular and supra-optic nuclei, presumably opened out by stimulatory secretion. The adjacent neural tissue elsewhere is normally compact.



21



22

Cushing

Posterior Pituitary Activity