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THE PATHOLOGICAL FINDINGS IN FOUR AUTOPSIED CASES OF  
ACROMEGALY WITH A DISCUSSION OF THEIR SIGNIFICANCE

By

HARVEY CUSHING AND LEO M. DAVIDOFF

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THEIR SIGNIFICANCE.\*

BY HARVEY CUSHING AND LEO M. DAVIDOFF.

(From the Surgical Clinic of the Peter Bent Brigham Hospital, Boston.)

(Received for publication, December 3, 1926.)

SUBJECT HEADINGS.

I. INTRODUCTION. ....	2
II. CLINICO-PATHOLOGICAL RECORDS OF FOUR CASES .....	6
Case I. Death from bronchopneumonia.....	6
Case II. Death from intracranial extension of tumor.....	24
Case III. Death from cardiac failure.....	43
Case IV. Death from diabetic coma.....	67
Skeletal changes in Cases II and III .....	78
III. GENERAL DISCUSSION.....	86
Comparative statistics of the four cases. ....	89
IV. THE SPLANCHNOMEGALY OF THE DISEASE.....	92
V. THE ENDOCRINE SERIES IN ACROMEGALY.....	96
The hypophysial adenoma.....	98
The thyroid.....	103
The parathyroids.....	105
The thymus.....	108
The adrenals.....	109
The pancreas.....	110
The gonads.....	114
VI. SUMMARY AND CONCLUSIONS.....	125
VII. BIBLIOGRAPHY.....	127

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\* This communication is No. V in a series of *Studies in Acromegaly*.

The authors wish to express their indebtedness to Prof. S. Burt Wolbach and his assistant Dr. Charles L. Connor of the Pathological Department for their many courtesies during the preparation of this report.



## I.

### INTRODUCTION.

Among the criteria essential to the rounding-out of a disease entity is the association with it of definite histopathological changes in a certain organ or organs. These changes, like the clinical picture, may vary within more or less wide limits depending upon the stage or severity of the disorder. But in order to be convincing and dependable they cannot well shrink beyond a certain minimum that should be present in every case.

A clearly-cut clinical syndrome, however, may exist, as is well known, in the absence of any as yet demonstrable and uniform histopathological findings. Of this, diabetes mellitus is a familiar example, the disease being easily recognized by changes in the body chemistry; and though no one can longer doubt that a functional derangement at least of the islets of Langerhans is the cause of the disorder, the pancreas in a considerable percentage of cases shows no appreciable deviation from the normal.

In acromegaly the identification of the morbid lesion to which the distinctive tissue overgrowth might be definitely assigned has been difficult, not only because of the most variable secondary symptoms characterizing the malady but still more so because of its widespread pathological manifestations. For here in marked contrast to diabetes, to continue with this example, gross alterations in many organs are both clinically and pathologically apparent.

One of us (Davidoff)<sup>27</sup> in an earlier paper has gone briefly into the history and evolution of our ideas of acromegaly, and has spoken therein of the varied conceptions of the disease and the doubts which long existed in the minds of many concerning the essential and primary rôle of the hypophysis in its etiology. It indeed has remained for the experimental pathologist rather than the histopathologist to bring dependable proof that the hormone of growth, which can alone account for acromegaly and gigantism, is secreted by the epithelial portion of the gland, and what is more, almost certainly by the chromophilic cells of that complicated structure.

From the first there were handicaps to an early solution of the problem. Among them may be mentioned: our fragmentary knowledge of the

differing function of the two portions of the pituitary body; our lack of understanding of the interrelations of the several members of what we now call the endocrine series; our obscurities with respect to the chemistry of metabolism; our defective and undependable methods of preserving and of staining hypophyseal tissues for microscopical investigation. Still another handicap has been the scarcity of tissues obtainable for study.

Acromegaly is not a very common disorder. It moreover is one which pursues a long and chronic course, so that patients are apt to drift from clinic to clinic. It consequently is unusual for them to end their days in hospitals and still more unusual for a postmortem examination to be held under the direction of those who have previously had a given case long under observation.

To be sure, of late years, fragments from a considerable number of hypophyseal adenomas in cases of acromegaly have been secured for study through operative procedures, and valuable information as to the histopathology of the primary lesion itself has been thereby secured. From the examination of such tissue-fragments obtained at operation from 35 cases in this clinic, Bailey and Davidoff<sup>4</sup> have shown, in support of Benda's original claim, that when the tissue has been properly fixed, one always finds chromophilic cells containing distinctive granules, whereas in the types of adenoma associated with non-acromegalic manifestations, the cells are invariably chromophobe in character.

We have ample grounds, therefore, to support the hyperpituitarism view of acromegaly. However, hyperpituitarism is not so simple a matter as is hyperthyroidism in which the essential lesion is restricted to the thyroid and the secondary pathological alterations of other organs are of minor consequence. In acromegaly, on the contrary, the gross secondary changes in other organs are manifold and constitute one of the amazing features of this kaleidoscopic disorder.

There exist in the literature comparatively few reports of cases of acromegaly well studied in both their clinical and pathological aspects, and it is still more uncommon for an author to have had more than the tissues from a single complete autopsy for study, so that recourse to cases published by others was necessary for comparison. The few exceptions are Fraenkel, Stadelmann and Benda (1901)<sup>39</sup> who had four cases; Cagnetto (1904 and 1907)<sup>15,16</sup> who had three (one of them incomplete);

Brooks (1898),<sup>14</sup> Ballet and Laignel-Lavastine (1905 and 1912),<sup>5,6</sup> Schultze and Fischer (1912)<sup>84\*</sup> and Kraus (1914),<sup>53</sup> each of whom had two cases.

What is more, pituitary adenomas not associated with acromegaly were apt to be included in many of the early papers on the subject which led to great confusion. This is particularly apparent in Cagnetto's papers; and in Dallemagne's report (1895)<sup>25</sup> of three presumable examples only one appears to have been actually acromegalic. But even of the accurately described cases, many were published so long ago that either the details considered essential in the light of our present knowledge of endocrine disorders are wanting, or else the autopsy was restricted to an intracranial examination so that the hypophysial lesion alone was described.

The purpose of the present communication is to put on record the clinical histories and autopsy findings of four well-studied cases. That the circumstances are unusual is shown by the fact that out of the 112 acromegalics whose clinical histories are comprised in the series studied by the senior author, only seven have come to autopsy with an unrestricted examination. Twelve cases were first observed at the Johns Hopkins Hospital and their clinical histories have elsewhere been reported<sup>23</sup> with a somewhat meagre account of two autopsies, one on an acromegalic woman following a fatal operation, and another on a case of gigantism. Two other cases from this early series of twelve, have subsequently died and the completed story is herein told. An additional pair of autopsied cases occur among the 100 acromegalics in the Brigham Hospital series which have already been analyzed by one of us<sup>28</sup> from the standpoint of their anamnesis and symptomatology. A seventh case which, like these two last mentioned, had acromegalic diabetes, died some years ago at the Lutheran Hospital in Cleveland after having been twice under observation here. A complete examination of the body was made by Dr. H. H. Pitts, and though a protocol has been sent to us we have been unable personally to examine the histological preparations and consequently have thought best to exclude the case from this report.

In spite of the unquestioned progress we have made in the past decade in our understanding of the disease, there remain many obscurities as will be apparent from these autopsy reports. No one today can have

\* These were the same two cases previously reported in 1906 in Löwenstein's thesis.

any reasonable doubt: (1) that the syndrome of acromegaly is ascribable to a dysfunction of the pituitary body whatever may be the obscure biochemical or neurological influence in the background; (2) that the pars anterior of the gland is at fault; and (3) that the substance (hormone) which provokes the overgrowth is a product of the acidophilic cells of this portion of the gland. But if we are to accept the criteria mentioned in the opening paragraph, that certain minimal histopathological changes, which are the same from case to case, must be present in a disease to make it convincing as a clinical entity, it will be seen that acromegaly remains from the standpoint of morbid anatomy almost as protean and bizarre as when it puzzled the heads of those who first began to make pathological investigations of it.

## II.

### CLINICO-PATHOLOGICAL RECORDS.

The first of these reports concerns a man who had faced his disfiguring and painful affliction with extraordinary fortitude. He had become greatly interested in the disease to which he was victim, had written an autobiographical account of his individual case, and had left instructions for an autopsy. He had submitted frequent reports to the senior author regarding the progress of his malady up to the time of his death which occurred at his home in 1921, 10 years after he first came under observation at the Johns Hopkins Hospital.\*

#### Case I.

J. H. H. Surg. No. 26068. *Typical chronic advancing hyperpituitarism of nearly 30 years' duration (1892-1921). Persistent cephalalgia. Progressive tissue overgrowth. Futile subtemporal decompression. Prolonged glandular therapy. Hemiplegia in 1915 with recovery. Death from advancing cardiovascular lesions (?) at age of 52. Chief autopsy findings: peripheral arteriosclerosis with cor bovinum; normal-sized hypophysis with central chromophile adenoma; multiple adenomata of thyroid and adrenals.*

On June 8, 1910, J. I., a teacher, 42 years of age, first came under observation on the recommendation of Dr. O. T. Osborne of New Haven, Conn., because of incapacitating headaches associated with obvious acromegaly.

As a young man he had been spare, delicate-featured and light-complexioned (cf. Fig. 1). He weighed only 140 lbs. in 1892, the year he graduated from college as valedictorian of his class, and began what was to be his sadly interrupted career as a teacher. The onset of his malady was most insidious, and occurred subsequent to his graduation. In 1896 when an operation was performed for "enlarged cervical glands," the evidences of overgrowth had become sufficiently obvious to attract the attention of his surgeon. The chief period of growth had evidently taken place before 1900, as the following figures indicate.

	Age	Height	Weight	Collar	Shoes	Hat
1892:	23	6 ft. 0 in.	140 lbs.	14½	7	6¾
1900:	32	6 ft. 2 in.	202 lbs.	17½	11	7¾

In 1898 he married, but no children were born of the union. Not until 1900 did increasing headaches first lead him to seek medical advice, and for the remainder of

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\* Cf. "The Pituitary Body and Its Disorders," 1912. Case XXX, p. 154.

his life he was never free from a persistent, sometimes intolerable, cephalalgia, recumbency affording the only measure of relief. Originally the headaches were chiefly suboccipital but they came to be described as more general in character with a bursting sensation which was greatly accentuated by a cough, sneeze or any muscular effort. They were always intensified by the erect posture and invariably relieved in a measure by a horizontal position. They were never accompanied by nausea or vomiting.

A secondary complaint was of great mental and physical inertia—of “logginess”—which became increasingly difficult to overcome as time went on. There was also a



FIG. 1. Case I. Appearance in 1892: age 23; height 6 ft.; weight 140 lbs.



FIG. 2. Appearance in 1910: age 42; height 6 ft. 2 in.; weight 200 lbs.

constant sense of heaviness and numbness—“going to sleep”—of the extremities. In addition, he had suffered greatly from shortness of breath, and on one occasion in 1896 had an attack of pseudo-angina. He was subject throughout life to tonsillitis and regarded himself as very susceptible to infections. For a number of years during the early course of the disease there were recurring attacks of corneal ulceration. His hypertrophied nasal bones caused increasing obstruction, and as time went on his greatly hypertrophied tongue impeded respiration during sleep. He also had copious night sweats and perspired over-freely at all times. There had been an early progressive decline in sexual libido with diminution in size of the testes. No abnormalities in the urine were ever recorded nor was sugar ever found.

*Physical examination* as recorded in 1910 (*cf.* Fig. 2), some 15 years at least after the disease became apparent, showed a man with a huge skeletal frame and outspoken signs of acromegalic overgrowth. The characteristic rounding of the shoulders which came in later years was not then apparent and though skeletal growth apparently continued throughout the course of the disease with progressive enlargement of the thorax and facial bones, his height never exceeded that of 6 ft. 2 in. attained in 1900.

The X-rays showed closed epiphyses with the characteristic phalangeal tufting well pronounced (Fig. 3). Röntgenography of the sella was not a highly developed procedure in 1911 but the plates showed that the fossa was not enlarged, its measured dimensions being 2.0 cm. and 1.2 cm. in depth. The clinoid processes were heavy and their tips appeared to be fused or overlapped.

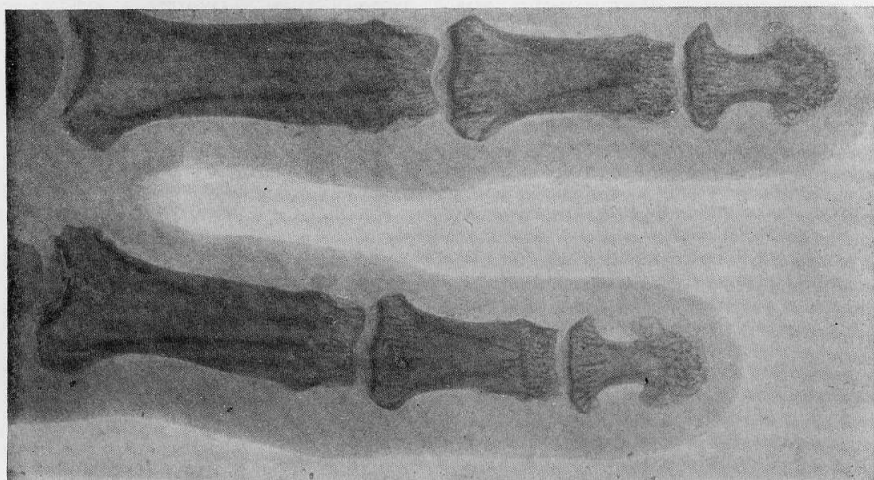


FIG. 3. Case I. X-ray of index and middle finger to show typical arrowhead terminal phalanges.

The head was large (27 cm. in the line from chin to vertex) with prominent supra-orbital ridges; the jaw showed a heavy alveolar arch, but at the time there was no mandibular prognathism nor were the teeth spaced. These changes were late in appearance and the jaws ultimately became so badly matched as to greatly interfere with mastication.

The hands had the usual spade-like appearance with deeply creased palms and a glove measurement of 27 cm. The fingers were supple despite the thickened tissues. The feet were huge (27 cm. in length and 10 cm. in breadth), the toes being much faceted by pressure of the shoes. The nails of the hands and feet showed an absence of crescents. The lips were thick, the vertical width of the exposed mucous membrane measuring 3 cm.; the tongue was so large and awkward as to impede lingual speech. The nostrils measured 4.5 cm. in breadth.

The skin was moist, soft and elastic and had the peculiar acromegalic odor from excessive secretion. The patient asserted that his complexion had darkened greatly during the course of the disease. There was a tendency toward hypertrichosis, a large hirsute patch being present over the sacral region. The panniculus was abundant, large pads of fat being present over the posterior cervical triangles. The thyroid was definitely enlarged.

*Operation:* As stated, the profound and often incapacitating headaches constituted the patient's chief complaint. In view of the relatively small sella turcica, it hardly seemed possible that they could be due to distention of the hypophysial envelopes, and under the erroneous idea that they might be caused by intracranial tension, on July 1, 1910, a right subtemporal decompression was performed. The procedure was futile. No increase of tension was disclosed and though recovery from the operation was uneventful the headaches returned in their former intensity as soon as he assumed an upright posture.

During a prolonged stay at the Johns Hopkins Hospital, the patient was studied by the methods then in vogue, tests for sugar-tolerance being employed as a measure of metabolic activity. It was found that he had a high tolerance for carbohydrates and it required the ingestion of 200 gm. of glucose to produce a transient glycosuria.

Attempts were made in those days to use the sugar test as a basis for estimating the therapeutic dosage of glandular extracts. In an effort to find what amount of anterior-lobe extract given by mouth would cause glycosuria on the ingestion of 150 gm. of lævulose, the dose of Armour and Co. tablets was run up to 100 grains *per diem*. Curiously enough considerable relief from his headaches and lethargy was experienced during the tests and he subsequently continued with this high daily dosage for several years. Certainly on the basis of an active hyperpituitarism this was distinctly contraindicated, and whether it had anything to do with the continued accession of skeletal growth cannot be told. However, it had been assumed that his great increase in weight, his subnormal temperature, etc., were indications that the acromegalism was dying out and was being replaced by a state of glandular insufficiency—a conception of the progress of acromegaly of which there is no actual proof.

These matters have been gone into here for the reason that they concern the patient's particular type of acromegaly in the course of which not only was a spontaneous glycosuria never observed, but, on the contrary, a notably high sugar-tolerance was disclosed. The fact of his having taken by mouth for many years unheard-of doses of anterior-lobe extract is also important to record. One may perhaps assume from these observations that he had a low metabolism. This must however remain conjectural, and if true it would be an exception to the usual rule. Needless to say, it was before the days of routine determinations of the basal metabolic rate.



*Subsequent History.*—During the 10 years following the futile subtemporal decompression in 1910, in spite of most persistent and often prostrating headache with increasing fatigability, he managed to hold his academic position. Meanwhile, there was unmistakable progress in his skeletal overgrowth. This was most noticeable in his face, and the lower jaw finally became so distorted that 'chewing was nigh impossible.

In 1915 he had an apoplectic stroke with partial, right-sided hemiplegia which fortunately was transient and left but a slight residual weakness. He kept on with his teaching until the fall of 1918 when it became impossible for him to concentrate longer on it. During the 2 final years there was increasing weakness and drowsiness with no cessation of headache. His mental processes were alert and he retained a healthy optimism regarding his condition to the time of his death, which occurred on April 16, 1921.

*Postmortem Examination.*—The patient's request that a complete post-mortem study of his body be made was respected. The examination was carried out soon after death, at the New Haven Hospital, by Dr. R. A. Lambert (now of the School of Tropical Medicine, San Juan, Porto Rico), to whom we are indebted not only for a highly detailed report but for several of the accompanying illustrations.

Detailed measurements of the body were taken which showed a slight though definite increase over those recorded 11 years before. A marked enlargement of the thyroid was also noted, whereas in 1910 it had been scarcely palpable. The body was X-rayed and the plates show little change from those taken in 1910, other than some advance in tufting of the terminal phalanges, the most marked change having occurred in the bones of the great toes. More important is the fact that the *sella turcica* had not altered in size, its profile measurements, *viz.*: 2.0 cm.  $\times$  1.2 cm., being the same as before; one may be reasonably assured that no increase in the size of the gland had occurred during the interval.

Though the bones were markedly hypertrophic they showed no histopathological alterations. The shaft of the humerus, for example, had a thin cortex measuring only 4 to 6 mm. with an unusually large marrow cavity easily admitting the end of the thumb. The cavity contained soft, reddish-grey marrow and no spongy bone. Histologically the tissue showed no hyperplasia of the blood-forming elements. On the contrary, the marrow cells in general were of the resting type, with rather dense deeply staining nuclei. Sections were also taken from the ribs and the sphenoid bone and neither showed evidence of marrow hyperplasia.

The essential details of the autopsy which disclosed a widespread splanchnomegaly are as follows.\*

#### THE BODY CAVITIES.

**THORAX:** Circumference 105 cm.; the anteroposterior diameter abnormally large; the ribs broad and heavy. Upon removing the sternal flap, the voluminous lungs almost completely concealed the pericardium. There were no pleuritic adhesions; each cavity contained a small amount of fluid.

**Lungs:** The larynx and trachea were very large. The right lung weighed 1650, the left 900 gm. On section they showed some oedema and congestion. The trachea and large bronchi contained muco-purulent exudate. Microscopically there proves to be a widespread desquamation of the bronchial epithelium. The alveoli contain coagulated albuminous fluid, red blood cells, and many large mononuclear phagocytes holding granular blood pigment suggestive of cardiac failure.

**Heart:** A huge organ weighing when emptied 1050 gm. with extremely coarse and firm musculature. Only a moderate amount of fat was present beneath the pericardium. The large coronary branches were patent throughout. There was relatively little dilatation of the organ, but an extraordinary degree of concentric hypertrophy which the following figures serve to emphasize:

Thickness of left ventricular wall.....	3.0 cm.
“ “ right “ “ .....	0.8 to 1.0 cm.
Left auricle.....	1.0 cm.
Length of left ventricle.....	12.0 cm.
Lower margin of aortic valve to apex.....	10.0 cm.

Histologically the muscle fibres appear to be greatly enlarged and the supporting connective tissue markedly and diffusely increased. There are occasional scarred patches in which atrophic muscle fibres are seen. The larger blood-vessels show some intimal thickening; the smaller ones are unaltered.

**ABDOMEN:** The subcutaneous fat was relatively slight in amount over both the chest and abdomen. The abdominal panniculus measured 2 cm. in thickness. The pectoral and rectus muscles were of normal red color, but very coarse in texture. The peritoneum was smooth, shiny and without fluid accumulation. The liver just reached the margin of the ribs in the mid-axillary line. The spleen lay well up under the diaphragm. The fat of the omentum and mesentery, like that of the subcutaneous tissue, was relatively slight in amount. The intestines were distended; the stomach extremely large.

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\* In the protocols of all four of the cases the gross appearance and histological findings for the individual organs of the three major cavities will be recorded in conjunction, and presented for convenience from case to case in the same order; whereas the ductless-gland findings will be separately assembled at the end of each protocol. Necessarily the original accounts have been much abbreviated.

*Liver:* Weighed 3150 gm. and measured  $36 \times 22 \times 8$  cm. Aside from its large size, the organ showed nothing abnormal on fresh section. Microscopically there is a dilatation of the sinuses throughout the lobules with atrophy and pigmentation of the cells nearest the efferent veins suggesting slight chronic passive congestion. There are occasional foci of fat-filled liver cells, but no necrosis and no connective-tissue increase. The individual cells and lobules do not appear to be enlarged.

*Spleen:* Weighed 535 gm. and measured  $18 \times 12 \times 5$  cm. The surface was smooth and the tissue firm. On section it showed a dark red background studded with grey Malpighian bodies of unusually large size. At one pole, however, there was an indefinite triangular area considerably lighter in color and firmer than the rest suggesting an area of ischemic necrosis.

Histologically the lymph follicles prove to be of ordinary size and normal cell content. There is a large amount of blood in the sinuses and many large mononuclear cells. The connective-tissue framework is not increased. The striking feature of the section is the extreme thickening and hyalinization of the arterial walls. Every vessel, other than the capillaries, seems affected, and the lumina are reduced to minute openings or entirely occluded. Presumably the infarct-like area noted on fresh section was the result of such a vascular occlusion.

*Kidneys:* Both were very large. The right weighed 478 gm. and measured  $17.5 \times 9 \times 8.5$  cm.; the left 375 gm. and measured  $17.5 \times 8 \times 6$  cm. The capsule stripped freely leaving a smooth surface. On section the cortex had an average measurement of about 1 cm. The markings were regular; the glomeruli could be easily made out. (The bladder and prostate showed no abnormalities.)

Histologically the glomeruli prove to be large; the tubules, particularly the convoluted, are definitely dilated. The epithelium is little altered. Here and there in the cortex occur a number of typical arteriosclerotic scars infiltrated by mononuclear cells and showing atrophic tubules and hyalinized glomeruli. The vascular changes, however, are not striking and the walls of many of the larger vessels are of normal thickness. One can only account for the great enlargement of the organs either by an increase in the number of cells or by an enlargement of the tubules.

**ALIMENTARY CANAL:** The tongue was markedly hypertrophied, measuring 11 cm. in length, 7.5 cm. in breadth, and 3.5 cm. in thickness. While the hypertrophy appeared to be largely muscular, there was marked thickening of the mucosa. In the posterior third, the normal rugæ were thrown up into coarse, fleshy polypoid structures, with a flattened surface. Anteriorly the papillæ were coarse and bristling, particularly in the medial furrow. The faucial tonsils for an acromegalic were surprisingly small.

Histologically the lingual papillæ prove to be strikingly hypertrophic (Fig. 4), and there is a diffuse, though not marked, lymphoid cell infiltration of the submucosa. The musculature is unchanged except for a moderate enlargement of the fibres. The tonsils show marked involution with only isolated foci of lymphoid cells.

*Esophagus:* Apparently normal except for its large size and thick muscular coat which measured about 6 cm. on section. Histologically the fibres appear to be hypertrophic. There is no hyperplasia of the lymphoid tissue.

*Stomach:* An enormous organ, the greater curvature of which measured 70 cm. in length and the lesser 30 cm. It contained 900 cc. of semi-fluid material with much undigested food. The mucosa showed moderate postmortem digestion. Histologically the acidophilic cells seem unusually numerous.

*Intestines:* The length of the entire small intestines including the duodenum measured 34 ft. (average normal: 22 ft.); large intestine  $8\frac{1}{2}$  ft. (average normal: 5 ft.). The muscular coat, particularly of the colon, was conspicuously thick. The lymphatic tissue was not hyperplastic. Histologically there is nothing noteworthy.



FIG. 4. Case I. Hypertrophied papillæ of tongue ( $\times 43$ ).

*HEAD:* The scalp was fully 1 cm. in thickness and considerable difficulty was encountered in everting it. The bones of the skull, particularly the frontal, were greatly thickened in places, showing an average measurement along the saw-line of 2 cm. The increase appeared to be confined to the inner table and rough hyperostoses extended over practically the entire inner surface of the frontal bones. The occipital bone was thinner, averaging approximately 1 cm. The groove of the longitudinal sinus was conspicuous, being both broad and deep. The sella as shown by the X-rays, was not appreciably enlarged.

*Brain:* Weighed 1525 gm.; possibly not disproportionate to the patient's size, as the average normal weight for an adult male is given as 1359 (Warthin). The sur-

face showed nothing remarkable aside from the enlargement of the basilar vessels, particularly of the internal carotids, which had a moderate degree of patchy sclerosis (Fig. 5). The infundibular stalk was normal. (For the hypophysis *cf.* below.)

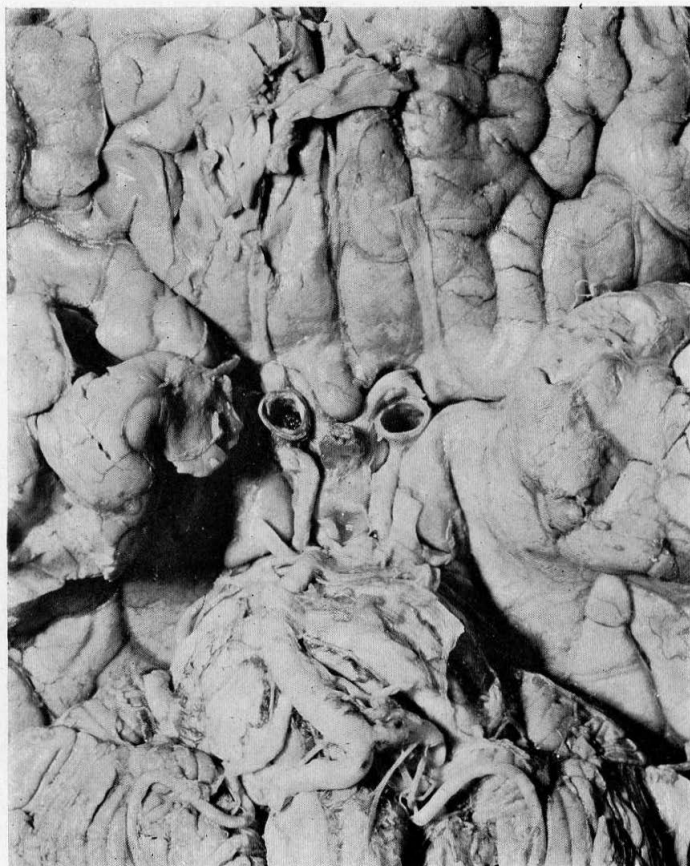


FIG. 5. Case I. Base of brain. Note large size of carotids, tortuosity of basilar artery, hypophyseal stalk and undeformed chiasm. (Natural size.)

The only definite pathological finding disclosed on sectioning the cerebrum was a small cyst in the left temporal lobe near the lenticular nucleus, evidently the end stage of an old vascular occlusion, doubtless accounting for the recorded hemiplegia. The small cerebral arterioles show extensive thickening of the intima.

## THE ENDOCRINE SERIES.

*Hypophysis:* The infundibular stalk, as described above, was normal in appearance and there was nothing noteworthy about the superior capsule of the gland which was not bulging. The gland with adjacent structures was removed *en bloc*.

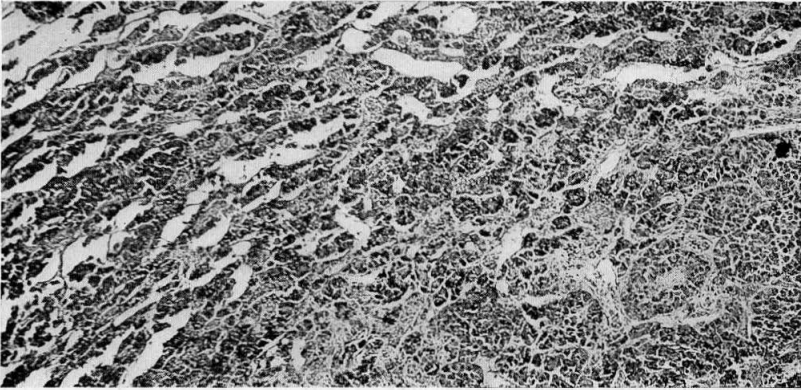


FIG. 6.

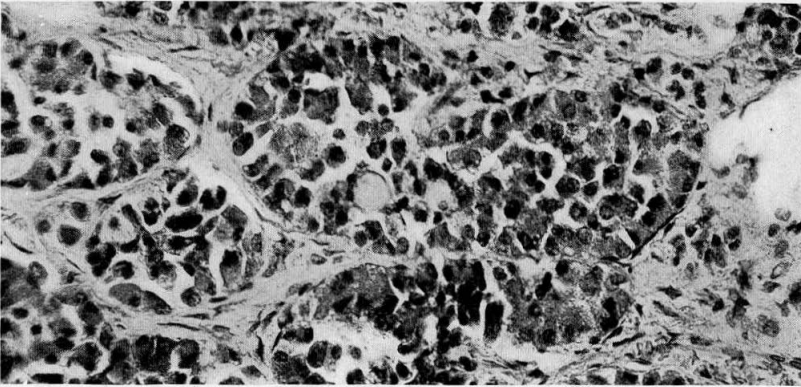


FIG. 7.

FIGS. 6 and 7. Case I. Showing flattened anterior lobe of hypophysis. Stain H. and E. Upper,  $\times 80$ ; lower,  $\times 300$ .

Upon exposing the sella from below, the floor was found to be in large part absorbed, leaving the anterior lobe covered only by thin dura and mucous membrane. The outline of the gland was distinct and appeared to be of normal or even subnormal size.



**Microscopical appearance.** Unfortunately for our present purposes the gland with its enveloping sella and adjacent structures was decalcified before being embedded and cut in serial sections. However, the posterior lobe is found to be composed of normal-looking neuroglia tissue. In the pars intermedia there are a few dilated acini filled with colloid which may be considered normal.

The pars anterior on the other hand presents a varied picture. In its central and upper portion the structure is nearest normal (Figs. 6 and 7). The stroma (*cf.* Fig. 10) is moderate in amount, possibly a little increased in places, the cells being arranged in irregular acini or in larger cylindroid masses, more or less surrounded by

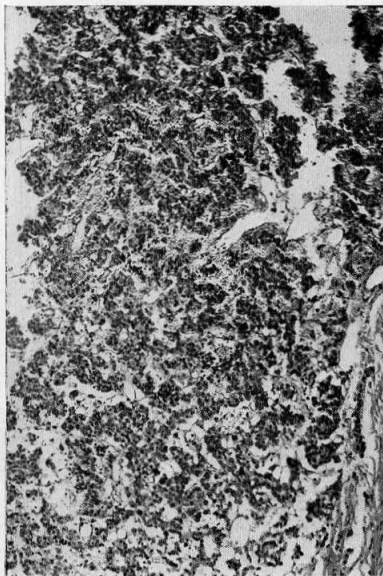


FIG. 8.

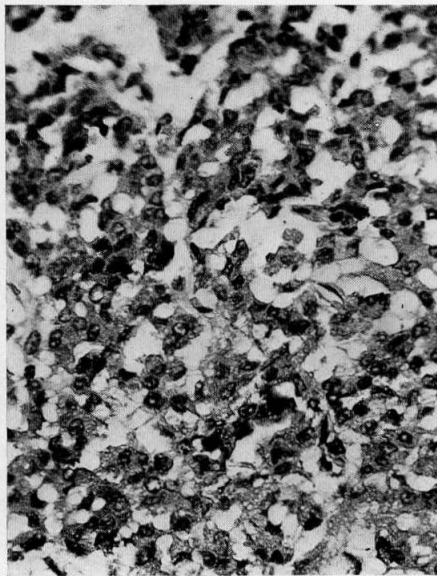


FIG. 9.

FIGS. 8 and 9. Case I. Showing hypophysial adenoma. Stain H. and E. Left,  $\times 80$ ; right,  $\times 300$ .

dilated blood sinuses. Owing to the friability of the tissue, after decalcification, special stains for alpha granules are somewhat unsatisfactory. Toward the centre the cells are mostly of the acidophilic type; toward the periphery neutrophilic cells predominate. No definite basophiles are seen. Toward the interior portion of the gland, the histological picture changes markedly (Figs. 8 and 9) although the transition is not sharp. The stroma here (*cf.* Fig. 11) is little more than a delicate reticulum. The parenchymal cells are loosely arranged with little or no tendency to acinus formation. The general appearance suggests proliferative activity. The capsule of the gland appears to be infiltrated here and there by nests of cells which in places have broken through to the outside.

The nuclei of the cells are large, irregular in size and pale-staining. Occasionally a multinucleated cell is seen. The cytoplasm which is moderate in amount tends to take the eosin stain, and with ethyl violet it becomes heavily impregnated though, because of the poor fixation, the alpha granules are indistinct. None of the cells are basophilic, however. Perdrau stains (Fig. 11) show a greater abundance of spider web-like stroma than is seen in the usual acromegalic adenoma. All told, however, the process appears to be distinctly inactive and had not the patient been known to have acromegaly, the abnormalities described herein might easily have escaped notice.

The *pineal body* measured  $1 \times 0.5 \times 5$  cm., was uniform grey on section, and quite normal in appearance.

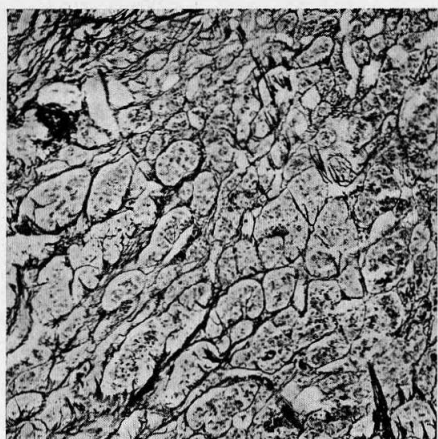


FIG. 10.

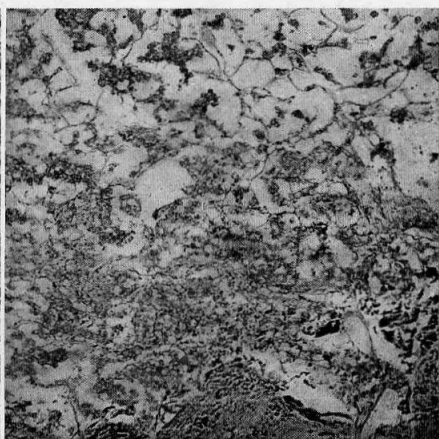


FIG. 11.

FIGS. 10 and 11. Case I. Perdrau stain for connective tissue: left section, through flattened anterior lobe; right, through the centre of the adenoma ( $\times 80$ ).

The *thyroid* was markedly and somewhat symmetrically enlarged. It weighed 310 gm. Each lobe measured approximately  $10 \times 5 \times 3.5$  cm.; the isthmus, which was practically the same size as the lobes, had a tumor-like enlargement which filled the suprasternal notch. The cut surface of the gland showed small, circumscribed, colloid, adenomatous nodules separated by coarse fibrous septa (Fig. 12), with here and there small foci of calcification. Some of the nodules were broken down into cysts containing a dirty brownish fluid. The largest of these single adenomas was in the isthmus and measured 3.5 cm. in diameter.

Histologically (Fig. 13) the follicles vary greatly in size. Some are really macroscopic cysts; others are minute but in nearly all there is abundant deep-staining colloid. There is in general a single layer of lining cells, cuboidal in form. A great



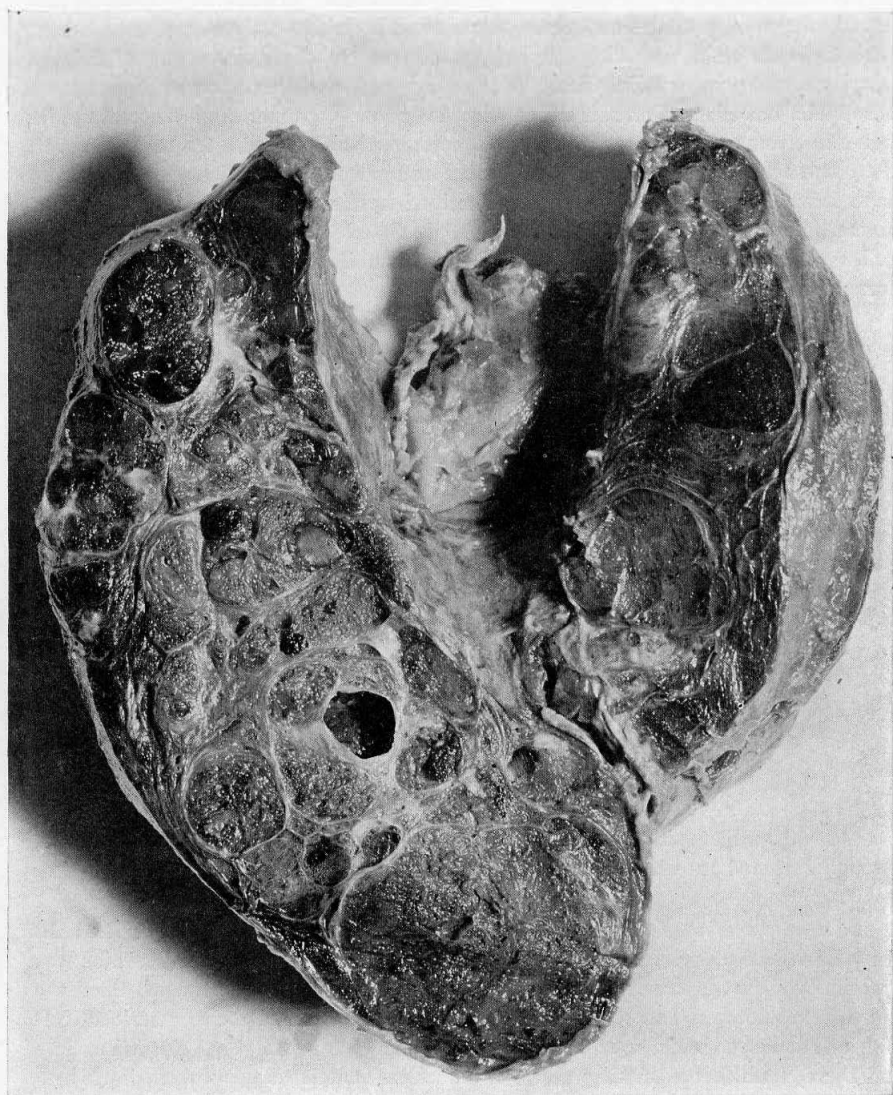


FIG. 12. Case I. Section through left lobe of thyroid (natural size) to show the colloid adenomatous goitre.

increase in the connective-tissue framework is noticeable. Nowhere does the tissue show evidence of hyperplasia.

*Parathyroids:* Four were found showing great variability in size and general appearance. The largest measured  $1 \times 0.8 \times 0.5$  cm. and was opaque yellowish-grey in color. Two others though smaller were similar in appearance. The fourth was almost spherical and deep red.

Microscopically the four glands show practically the same picture, except for varying degrees of vascularity. There is considerable adipose tissue ("fatty replacement") in the largest one. The parenchymal cells show the usual irregular arrange-

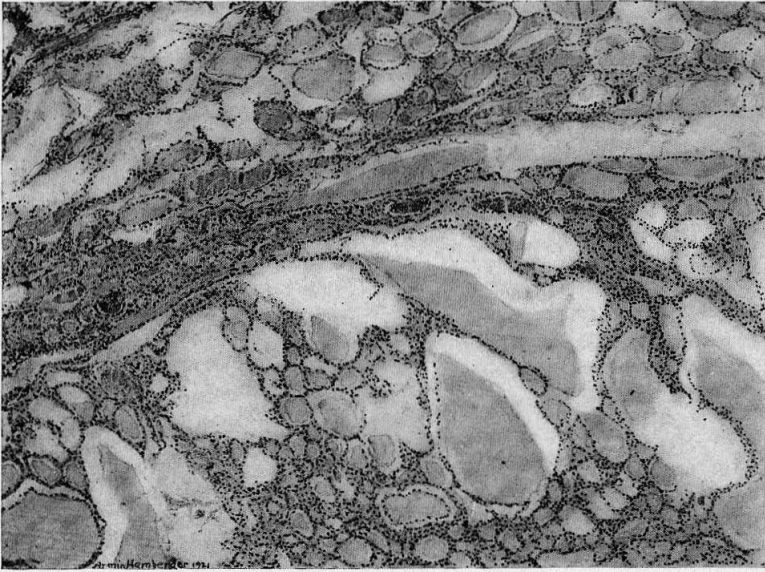


FIG. 13. Case I. Section of thyroid showing adenoma below and normal thyroid above ( $\times 40$ ).

ment of anastomosing strands some of which form lobules with lumina, between which there is more than the usual amount of stroma. The cells are mostly neutrophilic with pale vacuolated cytoplasm. Here and there patches of typical acidophilic cells are seen while in other places there are a number of cells which are definitely basophilic and show a tendency to a reticular arrangement. The general appearance suggests proliferative activity (Figs. 14 and 15), but there is no great deviation from the normal.

*Thymus:* On first opening the thorax considerable thymic parenchyma was seen in the flat mass of the fat and areolar tissue which covered the base of the pericardium. The entire pad measured approximately  $16 \times 6 \times 1.5$  cm. On section, tiny grey foci

of glandular tissue were seen. Histologically the relative amount of parenchyma to fat is considerably more than is normally found in the adult thymus. There is nothing unusual about the microscopic picture. Hassall's corpuscles though small are fairly numerous; the remaining cells are mostly of the usual lymphoid type (Fig. 16).

*Adrenals:* Both were large, firm and nodular; their combined weight was 43 gm. The cut surface was studded with multiple adenomatous nodules of yellowish cortical tissue which so altered the normal architecture that the usual medullary and cortical relations were present only in a few places. The medullary tissue appeared to be reduced in amount.

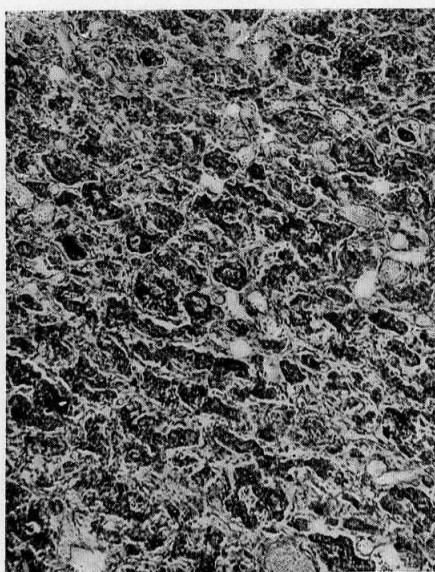


FIG. 14.

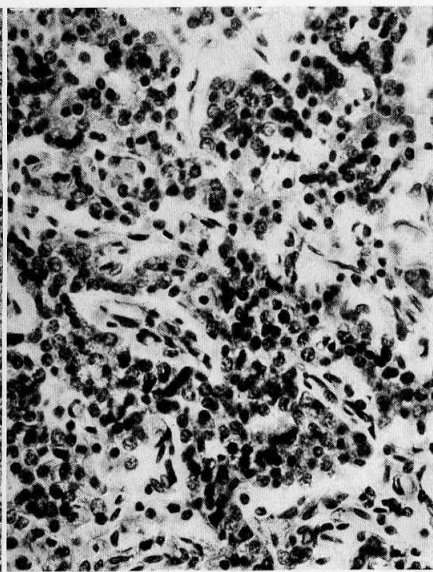


FIG. 15.

FIGS. 14 and 15. Case I. Parathyroid tissue. Stain H. and E. Left,  $\times 80$ ; right,  $\times 300$ .

Histologically the normal architecture of the gland is hardly recognizable owing to the multitude of adenomata of all sizes scattered through the tissue (Fig. 17). They are all composed of cortical cells and there is very little to be seen of the normal tissue which they replace. The cells of the cortical tissue itself are so highly vacuolated that little but the nuclei in a cobweb of fatty tissue is to be seen. The cells of the adenomata are more compact and dense; their cytoplasm takes a heavy eosinophilic stain. In the greater part of the gland no medulla is seen, but when any is found, and there are occasional areas of fair size, the cells are quite normal-looking.

*Pancreas:* Weighed 225 gm. and was of normal appearance and consistency. On

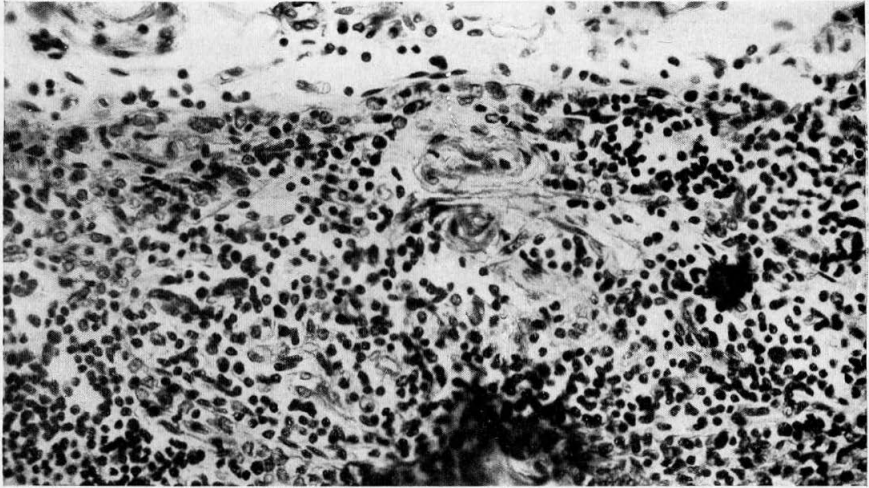


FIG. 16. Case I. Section from thymus. Stain H. and E.  $\times 300$ .

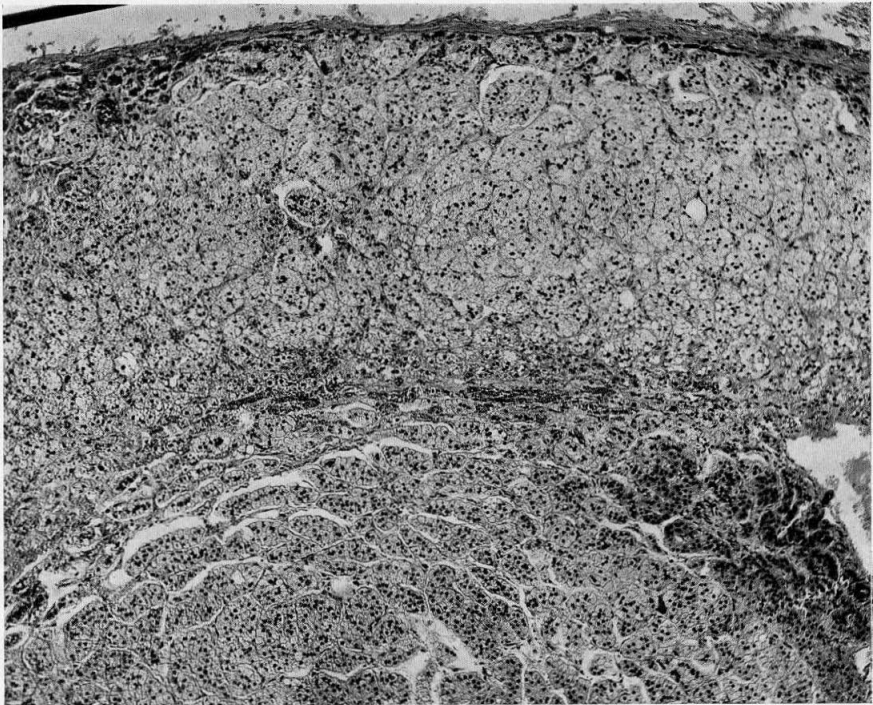


FIG. 17. Case I. Showing adrenal cortex with subjacent adenoma. Stain H. and E.  $\times 80$ .

section the lobulation was rather coarse and consequently very distinct. There was no gross evidence of fibrosis or other pathological change, apart from the general enlargement.

Histologically the changes are relatively insignificant. There are a few small fibrous patches and occasional groups of mononuclear cells. Some of the smaller arteries



FIG. 18.

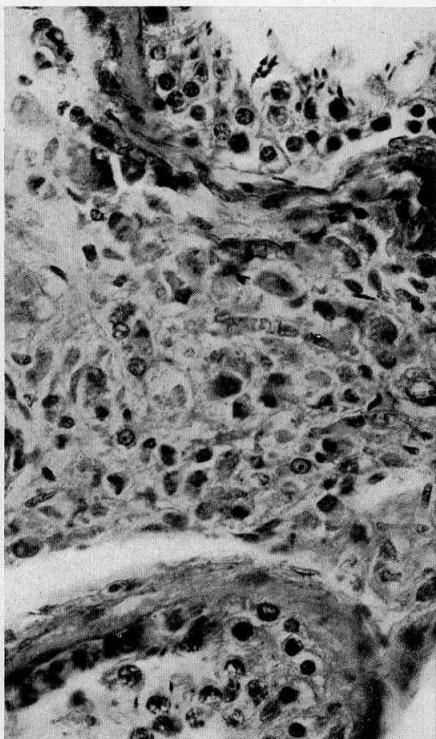


FIG. 19.

FIGS. 18 and 19. Case I. To show excess of interstitial cells of testes beneath albuginea, also heads of spermatozoa in tubules. Stain H. and E. Left,  $\times 80$ ; right,  $\times 300$ .

show thickened walls. The islands of Langerhans are few in number and small, but the cells (*cf.* Fig. 93) appear to be normal in all respects and show no hyalinization or fibrosis.

*Testicles:* Weighed 36 and 38 gm. respectively. On section the parenchyma had the usual ochre-yellow color and the tubules could be strung out readily. Histologically the tubules are found to be well preserved and to show imperfect spermatogenesis (Fig. 18). The interstitial cells in certain areas are markedly increased in



number (Fig. 19). The individual cells are apparently enlarged and are occasionally multinuclear. Their cytoplasm stains deeply with eosin.

*Anatomical diagnosis: Acromegaly with typical skeletal changes and visceral splanchnomegaly. Small hypophysis with chromophile adenoma. Cardiac hypertrophy. Generalized peripheral arteriosclerosis with multiple infarcts of brain, spleen and kidneys. Multiple adenomata of adrenals and of thyroid. Terminal bronchopneumonia.*

*Summary and Comment.*—In this patient the disease was slowly progressive for nearly 30 years; he became increasingly incapacitated and died at the age of 52, apparently with a terminal bronchopneumonia. A prolonged treatment extending over many years with anterior-lobe extract in large doses gives rise to some speculation on its possible effect on the malady. The dominant complaint throughout was of persistent cephalalgia moderately relieved by recumbency. Nevertheless, *there was no evidence of enlargement of the pituitary fossa on X-ray examination during life, and at autopsy the gland was found to be of normal size.*

The autopsy showed in addition to the general splanchnomegaly of unusual degree, a persistent thymus, a large colloid goitre, enlarged parathyroids, hypertrophy of the pancreas and greatly hypertrophied adrenals due to an adenomatosis of the cortical substance. To any one of these markedly changed glands an observer might in the 1880's have ascribed the malady with greater seeming probability than to the normal-sized hypophysis.

One is inclined to ascribe the long duration of the malady to the small size of the adenoma, for many victims of the disease die from intracranial symptoms caused by an extension of the tumor beyond the sella. Yet there have been cases in which the disease has lasted longer. Sternberg for example records one of nearly 50 years' duration; Gauckler and Roussy's<sup>41</sup> patient who lived to be 83 had symptoms for 38 years, the tumor having become cystic.

What makes this Case I of paramount interest is the fact that the pituitary body was not enlarged. Certainly if Marie and Marinesco<sup>67</sup> had chanced to encounter such an example of acromegaly at autopsy instead of one in which the hypophysis was unmistakably enlarged they would have had ample grounds to oppose the view of Minkowski<sup>69</sup> and others who were inclining towards the hypophysial origin of the disease. The much more obviously involved adrenals might easily have been held responsible if indeed a primary disorder of any one of the

ductless glands were in those days to be considered at all as etiologically concerned in the disease. Yet a normal-sized gland has been occasionally found in bodies outspokenly acromegalic. Israel's much-quoted though incompletely recorded case (1901)<sup>59</sup> may be recalled; also that of Bleibtreu (1905),<sup>10</sup> probably a case of gigantism in which a degenerative process of hæmorrhagic character was found replacing the hypophysis, a fact which led him to enter the lists as a champion of the hypofunction theory of acromegaly. In the same year (1905)<sup>58</sup> Dean Lewis described another case with a macroscopically normal gland of which, however, it was stated that "the great increase of highly functioning chromophile cells, their irregular disposition and the lessened amount of stroma, are indicative of excessive function." In 1906, Widal, Roy and Froin<sup>94</sup> reported a case in which the gland was actually atrophied and contained a small cyst, but otherwise showed nothing they regarded as abnormal. And one may recall, too, the case described by Petrén (1907)<sup>77</sup> over which a controversy arose: for with a normal-appearing hypophysis a coincidental syringomyelia was found which naturally led him to the view that the disease was primarily neurogenic.

Unfortunately in our own case the process through which the hypophysis had been put for the purpose of decalcifying its bony envelope made the tissue unfit for special stains for granules, and the gland might well enough be regarded as normal. Nevertheless, with ethyl violet the protoplasm shows the coloration distinctive of the alpha granule cells even though the isolated granules are not clearly demonstrable. Moreover, in view of our present-day knowledge of the disease and belief in its unquestioned dependence upon the acidophilic elements of the pars anterior, one may feel assured from the appearance of the slides that there is an acidophilic adenoma or local hyperplasia of acidophilic elements in the centre of the pars anterior.

### *Case II.*

The following case likewise first came under the senior author's observation at the Johns Hopkins Hospital and the clinical history up to 1912 has already been recorded.\* This, too, was an example of outspoken acromegaly, but in contrast to the foregoing there was an enor-

\* Cf. "The Pituitary Body and Its Disorders," 1912. Case I, p. 30.

mous hypophysial adenoma which had extended widely into the intracranial chamber and was the indirect cause of death. Because of this complication the course of the malady was cut short. Like the first case, this patient was also observed before the days of routine metabolism determinations. Rightly or wrongly it was then regarded as an example of hyperpituitarism which had passed over into the stage of glandular insufficiency.

P. B. B. H. Surg. No. 1784. *Acromegalic gigantism of unusual degree. Onset at an early age. Pronounced neighborhood symptoms. Sellar decompression (1910) with temporary improvement. Adiposity with high sugar-tolerance. Secondary operation attempted (1915) with fatality, at age of 40. Chief autopsy findings: widespread splachnometegaly; eosinophilic adenoma with huge intracranial extension; colloid goitre; testicular atrophy.*

On Dec. 8, 1910, M. Van W., a farmer, single, aged 35, first came under observation at the Johns Hopkins Hospital (Surg. No. 27045) having been referred by Dr. H. G. Marxmiller of Los Angeles for advancing blindness with acromegaly.

He was the eldest of 6 children, and at birth weighed somewhere between 10-12 lbs. His father was 6 ft. tall and weighed over 190 lbs., and the mother was said to have strikingly massive features.

So far as could be learned no unusual symptoms occurred until the age of 13, when he began to grow with unusual rapidity. At the age of 19 his height was 6 ft. 4 in. and his weight 200 lbs. He was described as having been at the time a physically powerful, intelligent and alert young man with a somewhat uncontrolled libido. At the age of 23 (1898) he had a severe illness, the outstanding symptoms of which were polyuria and persistent multiple furunculosis. A photograph taken at the age of 25 shows no evidence of acromegaly.

At 27 years of age (1902) it is stated that he took on a second period of growth, and he soon began to suffer from intense frontal headaches and pains in the arms and legs. The headaches were often relieved after a profuse muco-hæmorrhagic discharge from the nose. He was told at the time that he had acromegaly. Ere long he began to have trouble with his vision; he had periods of diplopia and bitemporal blindness.

By 1907 (ætl. 32) his excessive overgrowth had become crippling. He meanwhile had lost his former vigor, had become weak, drowsy, easily fatigued and impotent. Glycosuria had never been observed but there had been polyuria and extreme polyphagia, with a particular appetite for sweets. In the course of the next 3 years he had become practically blind and had increased greatly in weight.

In spite of a progressive bowing of the spine his height from 1904 to 1910 had increased 2 in. The headaches from which he had previously suffered had by this time largely disappeared.

When he first came under observation in 1910 he was described as a veritable Gargantua. Photographs (Figs. 20 and 21) do scant justice to his extraordinary appear-



ance. His height was 6 ft. 6 in. (198 cm.); his weight 269 lbs. (122 kg.). The cranial circumference was 64 cm.; the frontal sinuses were enormous. The neck measure over the greatly enlarged larynx was 42.5 cm. The tongue was huge, though it hardly filled the cavernous mouth. The ears measured 8 cm. in length; the nostrils 5.5 cm. in breadth. The lips and tonsils were greatly hypertrophied. There was marked deformity with tilting and protrusion of lower mandible. The huge thorax

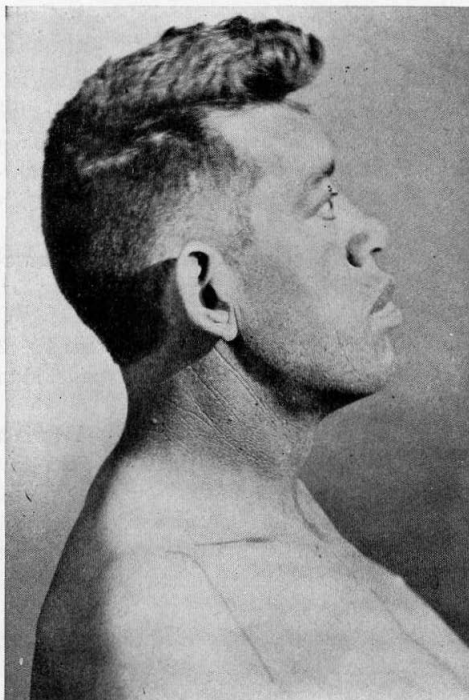


FIG. 20.

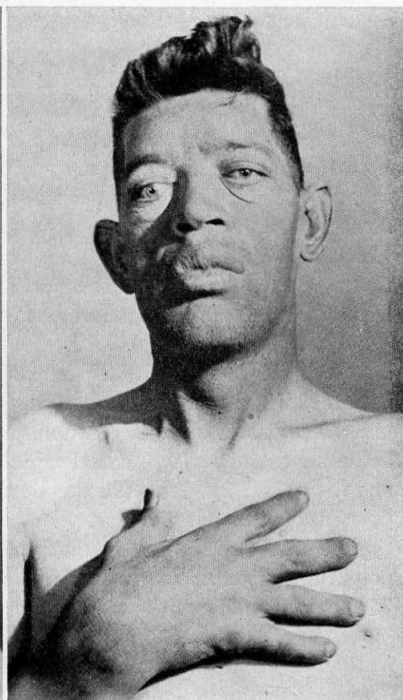


FIG. 21.

FIGS. 20 and 21. Case II. Acromegalic gigantism.

measured 112 cm. in circumference and there was a marked prominence of the xiphoid. The arms and legs were long but dwarfed by their huge extremities.

The hands were enormous, with a glove measurement of 30.5 cm. The middle finger was 12 cm. in length with a circumference at the proximal joint of 10 cm. The fingers nevertheless were supple from the extreme muscular hypotonicity. The feet also were colossal (Fig. 22) and measured 31.5 cm. in length. The circumference over the metatarso-phalangeal joint was 36 cm.; of the big toe alone 13 cm.

The skin was remarkably smooth, velvety, elastic and hairless. He had an abundant head of hair but practically no beard, and a pubic hairs of feminine distribu-

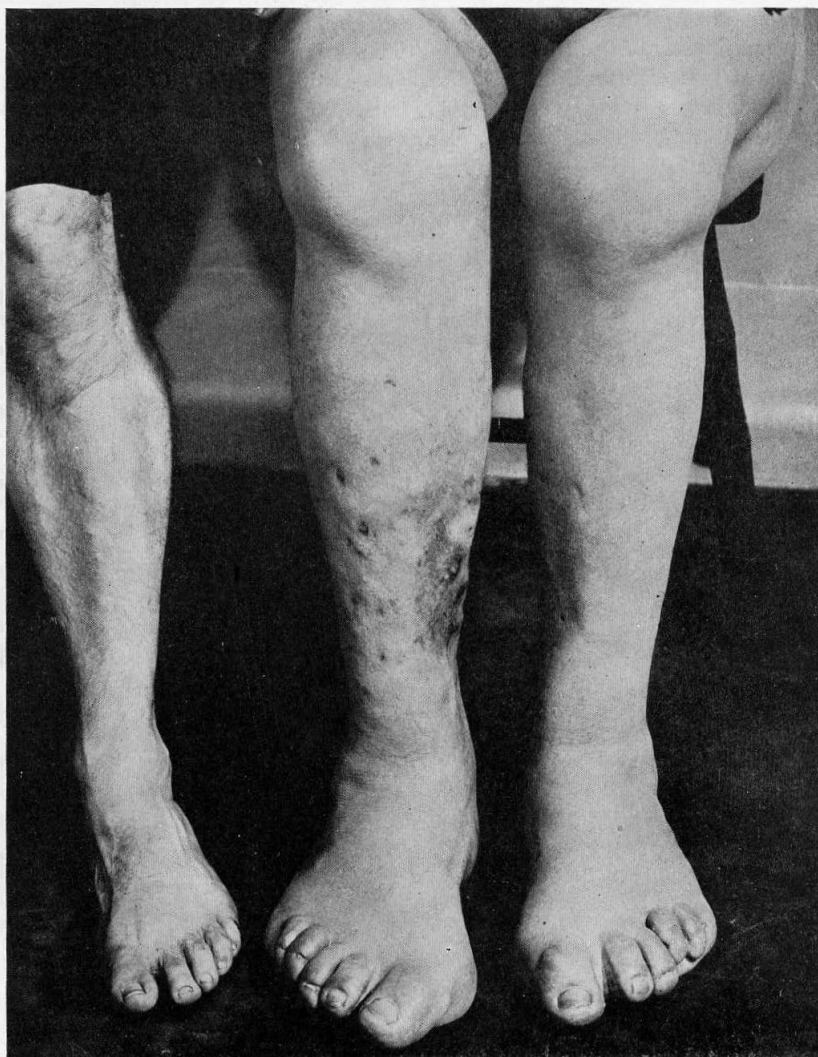


FIG. 22. Case II. Patient's lower extremities compared with that of a normal man.

tion. There was considerable boggy œdema of face and extremities which varied in degree from time to time. The panniculus was over-abundant. The testes were soft and atrophied.

Though prone to drowsiness, when aroused he proved to be intelligent, responsive and co-operative.

The examination of the abdominal and thoracic organs was negative aside from a moderate degree of arteriosclerosis with some cardiac hypertrophy. The systolic blood-pressure was extremely low, varying from 75 to 100 mm. of Hg. The temperature was constantly subnormal, the pulse usually below 70.

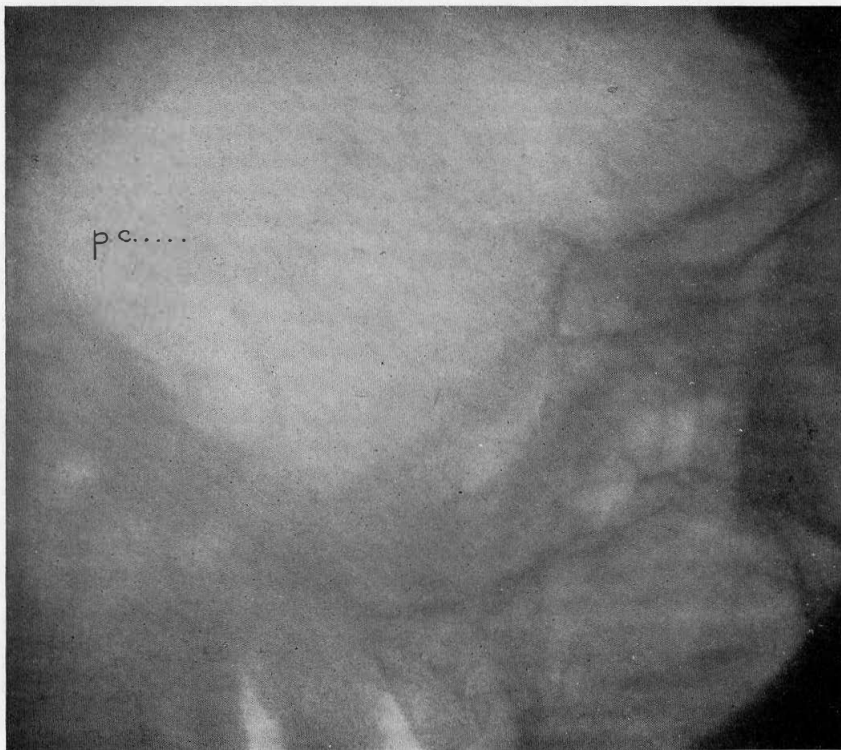


FIG. 23. Case II. Lateral view of greatly distended sella with hypertrophied and posteriorly tilted dorsum. p. c. points to top of posterior clinoid process.

The *localizing evidences of tumor* were pronounced. The cranial X-ray (Fig. 23) showed a hugely ballooned sella, 4 cm. in its anteroposterior diameter, 3 cm. in depth, and with a heavy, hypertrophied and posteriorly tilted dorsum sellæ. There was primary optic atrophy with practical blindness and a divergent squint. It was not realized at the time how great had been the intracranial extension of the growth and consequently a transphenoidal operation was performed (*Dec. 17, 1910*) in the hope of relieving pressure against the chiasm. There was slight improvement in vision and marked relief from headaches which lasted for nearly 3 years.

Fragments of the tumor which had been removed were described as showing (Fig. 24): "masses of chromophobe cells separated by greatly dilated sinusoidal spaces, giving an appearance which would suggest a telangiectatic round-celled sarcoma, did one not know the source of the tissue. There are large non-cellular areas which bear the faintly acid-staining properties of hyalin, and a few small acini containing colloid. No eosinophilic cells seen. The nuclei of the cells are small and stain deeply. There is possibly some increase in the interstitial tissue."

He had been found to have a very high alimentary tolerance for glucose which was estimated to be something over 300 gm., consequently glandular therapy by mouth was instituted and persisted in for a long period—a futile procedure as is now better

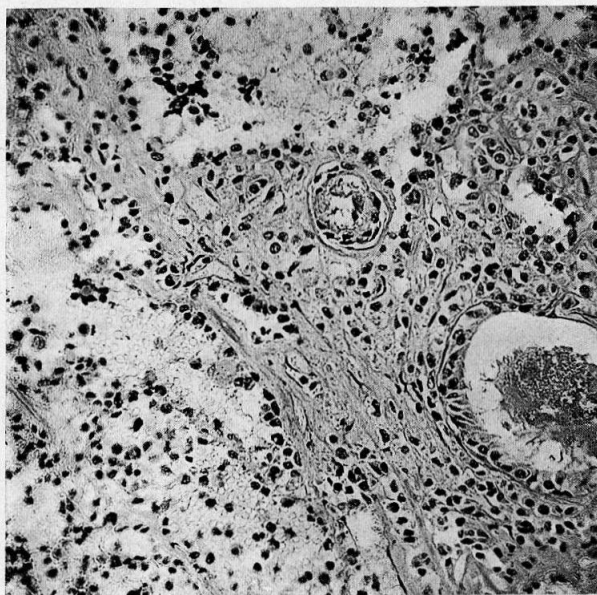


FIG. 24. Case II. Section of tissues from first operation. Chromophile adenoma with colloid cysts and increase in connective tissue ( $\times 190$ ).

known. There was a progressive advance in his acromegalism. His weight continued to increase and on May 1, 1911, reached its highest recorded point of 281 lbs.

On Sept. 16, 1914, he entered the Brigham Hospital owing to a progressive advance in symptoms. In the interval he had become much crippled by bony exostoses about the joints so that he was no longer able to stand erect (Fig. 25). The spine was greatly bowed and rigid. A considerable increase in the enlargement of the features and in the boggiess and looseness of the cutaneous and subcutaneous tissues had taken place. Some fibromata mollusca had appeared over the back and chest and a small

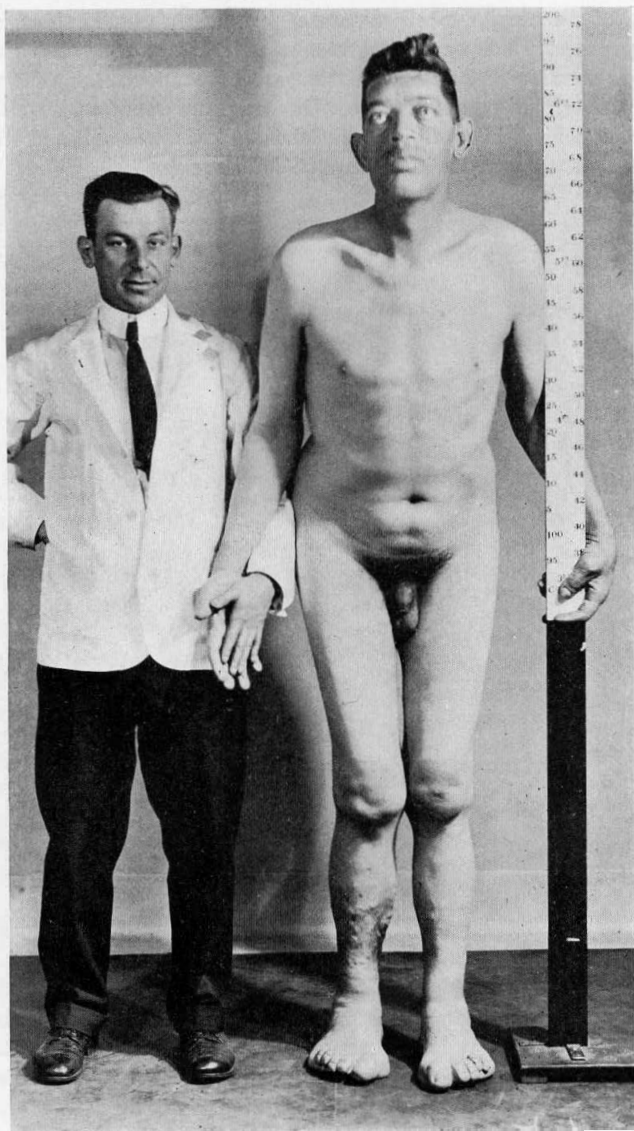


FIG. 25. Case II. To show patient's stature, acral enlargements and crippled posture in 1914, compared with a man of average stature.

lipoma was present below the scapula. The scalp had become markedly hypertrophic (Fig. 26) with the deep corrugations sometimes seen in the disease. There was occasional vomiting. His temperature tended to be subnormal and he suffered greatly from the cold. Blood and urine examinations were normal. There was no glycosuria at the time nor had glycosuria ever been observed.

The headaches which had been in abeyance for nearly 3 years had set in again and became intolerable, with occasional vomiting suggesting intracranial pressure.

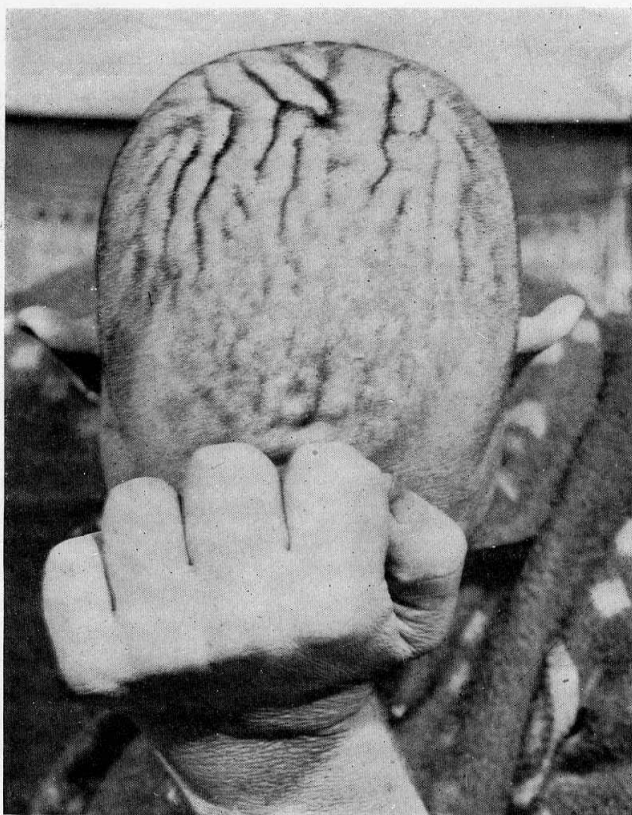


FIG. 26. Case II. To show the 'bull-dog' scalp of advanced acromegaly.

(No choked disc of course could develop under the circumstances, owing to blocking of the optic nerve sheaths.) His discomforts were measurably relieved by recumbency and there was considerable somnolence. In the hope that a subtemporal decompression might lessen his cephalalgia the measure was carried out on *Sept. 24, 1914*, with no subjective benefit whatsoever. The operation disclosed no increase of tension and subsequently when he was erect the decompression area remained sunken.



He was kept under observation in the hospital for the ensuing 5 months. Headache persisted with bouts of projectile vomiting. He had visual hallucinations and some weakness of the right side became apparent. On the appeal of his family, in the vain hope that an adenomatous cyst might be encountered and some measure of relief afforded by emptying it, a second transphenoidal operation (*Feb. 15, 1915*) was undertaken. Owing to the hypertrophic bony conditions it was found impossible even to expose the lesion by this route sufficiently well to accomplish anything on this second session. He gained his release by death the following day.

*Postmortem Examination.*—Permission was granted for an unrestricted autopsy with removal of the skeleton. The examination was made 10 hours after death by Dr. Warren Sisson, resident pathologist to the hospital at the time. From his copious records the following notes have been culled. The general appearance of the body has been sufficiently described in the clinical notes.

#### THE BODY CAVITIES.

**THORAX:** On opening the huge thorax with its greatly hypertrophied ribs the serous surfaces were found to be normal.

**Lungs:** These were strikingly voluminous in appearance. The right weighed 990 gm., the left 940. They showed on section no evidence of acute infection. Histologically they show distortion and widening of all the alveoli with some increase in peribronchial connective tissue.

**Heart:** The organ weighed 480 gm. but seemed small considering the size of the chest. The musculature was flaccid but of normal appearance. The tricuspid orifice measured 15 cm. in circumference; the mitral 11.5 cm.; aorta at valves 8 cm.; valves all normal. The coronary orifices and arteries showed no evident change. The aorta and large blood-vessels appeared normal except for isolated, opaque, yellowish areas on the intima seldom more than 1 cm. in diameter.

Histologically the cardiac muscle in some areas shows extreme fragmentation but is otherwise normal. There proves to be considerable thickening of the aorta and blood-vessels with proliferation of the intima and narrowing of the lumen in places.

**ABDOMEN:** The subcutaneous and omental fat was coarse, deep yellow and considerable in amount. The serous surfaces were smooth and the cavity without contained fluid.

**Liver:** Markedly enlarged; weight 3380 gm. Fresh section showed the lobules to be indistinct but apparently somewhat hypertrophic. The biliary system was negative except for a greatly distended gall-bladder with normal mucous membrane. Histologically the liver shows diffuse fatty changes with very slight increase in the connective tissue of the periportal spaces and slight lymphocytic infiltration. There is no evidence here of endothelial proliferation of the vessel walls.

**Spleen:** Weighed 385 gm. The capsule was thin and wrinkled. On fresh section

the organ was soft and pulpy; the follicles not prominent. Histologically there are evidences of congestion. The Malpighian bodies are prominent and show large accumulations of phagocytic endothelial cells associated with a few germinal-centre cells. The engorged vessels show definite thickening of their walls.

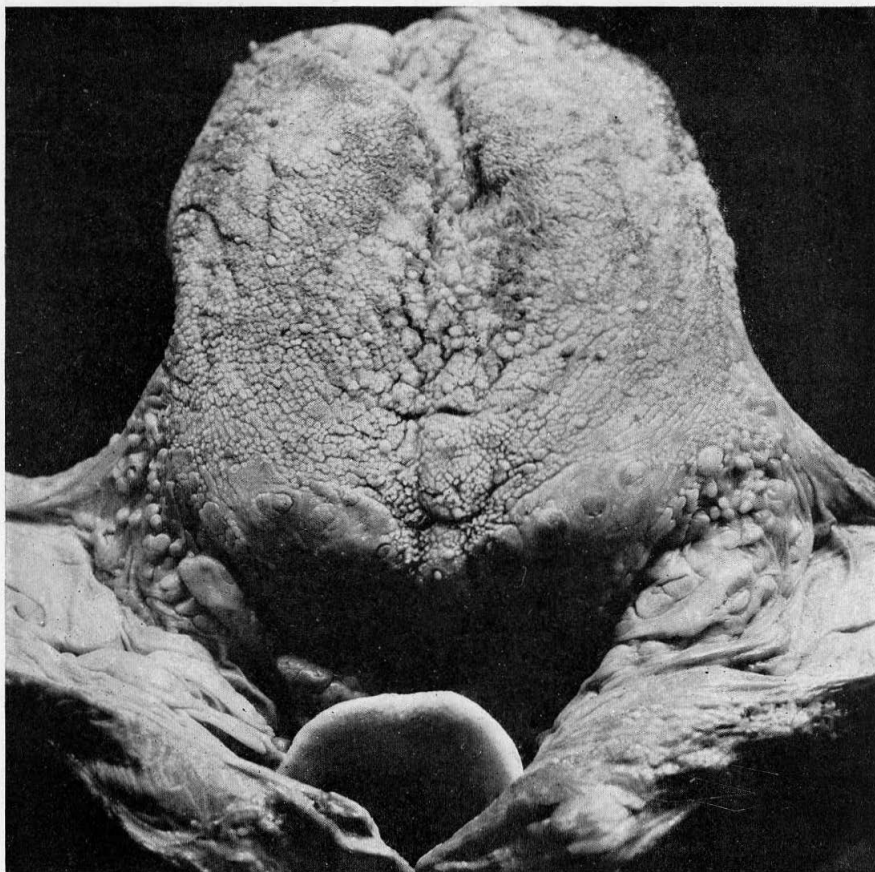


FIG. 27. Case II. Hypertrophic tongue, much shrunk by fixation. (Natural size.)

*Kidneys:* Both were considerably enlarged; the left weighed 280 gm., the right 285 gm. The surface of each was smooth, capsule not adherent. On section all parts of the organ appeared to be somewhat enlarged and equally so. The bladder was markedly dilated with no accentuation of trabeculations. The prostate showed some general enlargement. Histologically these organs are all essentially normal.



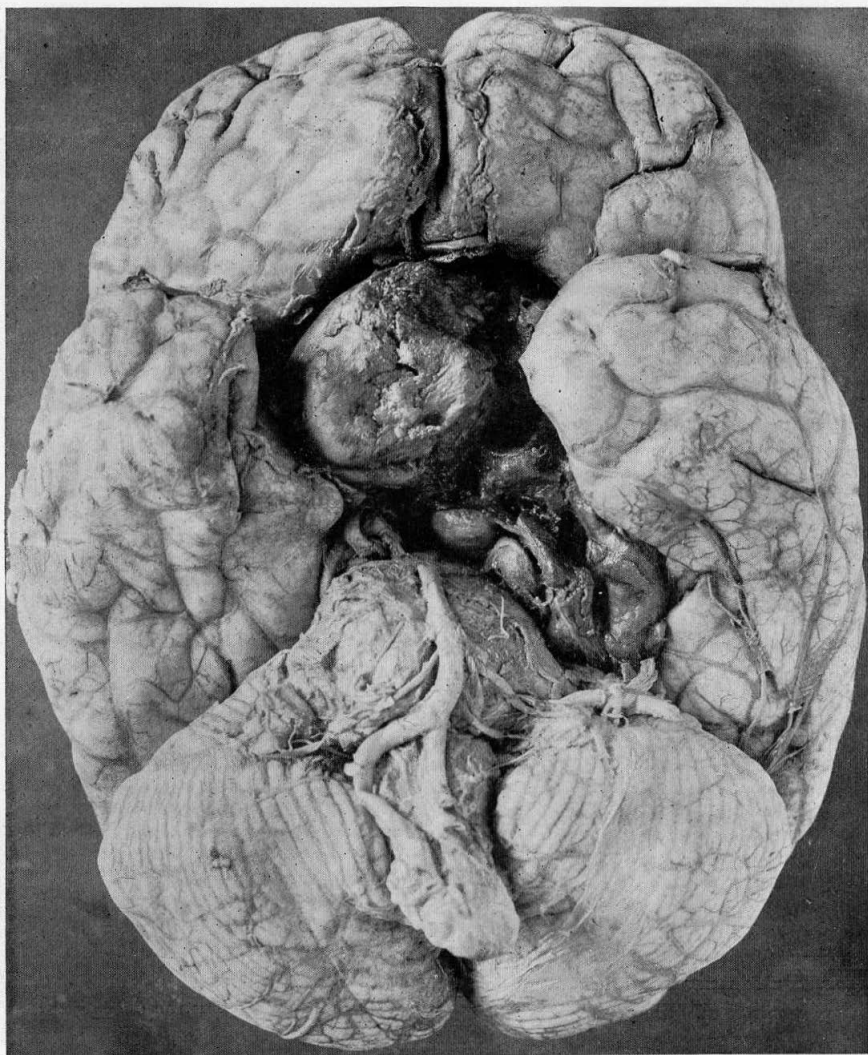


FIG. 28. Case II. Base of brain showing wide intracranial extension of pituitary tumor.

ALIMENTARY CANAL: The tongue was enormous (Fig. 27), measuring 11.3 cm. in length, 6.7 cm. in breadth. The mucosa was thickened and roughened with hypertrophic papillæ. Though the lingual tonsils were markedly hyperplastic, the faucial

tonsils were not especially large. The right parotid weighed 35 gm.; the submaxillary glands, combined, 22 gm.; the sublingual, combined, 10 gm.

*Æsophagus, stomach and intestines:* Showed nothing rotatable other than a marked hyperplasia of the lymph follicles in the lower æsophagus, in the cardiac end of the stomach, in the ileum and cæcum. The follicles were less evident in the intestines and the Peyer's patches were not discernible. The small intestine measured  $34\frac{1}{2}$  ft. in length (*cf.* Case I). The valvulæ appeared somewhat enlarged but normal in appearance. The appendix was 11 cm. long, normal otherwise. The large intestine measured 9 ft. in length. The cæcum was greatly dilated.

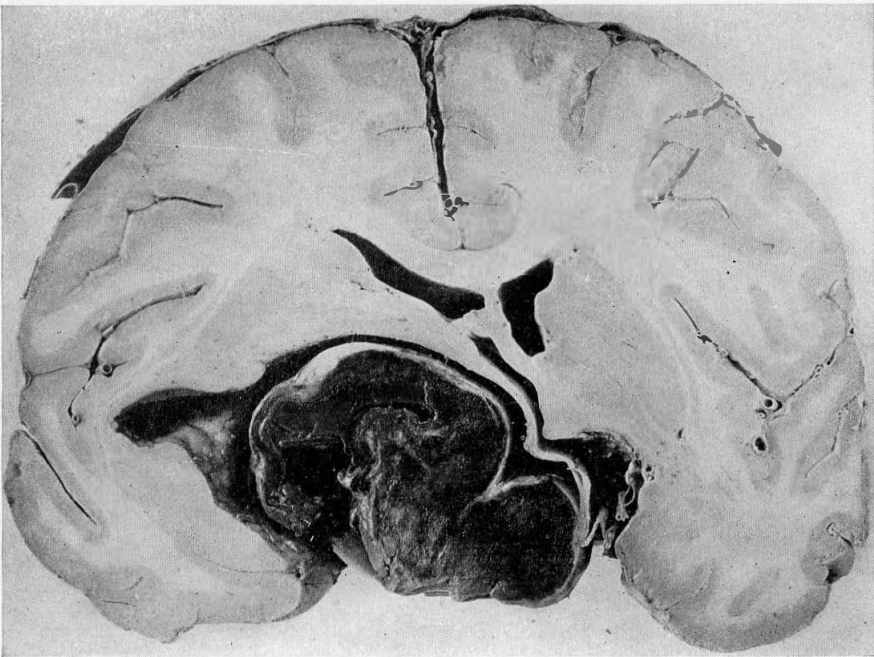


FIG. 29. Case II. Coronal section through central mass of the hæmorrhagic adenoma showing from behind the displacement of the IIIrd ventricle and chiasm to the right. (Reduced.)

Histologically the solitary follicles seen in the cardiac and pyloric ends of the stomach consist of lymphoid tissue in which large phagocytic cells have practically replaced the germinal-centre cells. This peculiar appearance is also present in the numerous lymph follicles occurring in the ileum. The same is true to an even more marked degree in the cæcum where the great size of the follicles is striking. In the transverse colon a similar picture is again presented. These peculiar endothelial phagocytes in the centres of the nodules stain heavily with eosin and often contain

many nuclear fragments. Beyond this point in the colon only an occasional follicle is found with the above characteristics.

*Lymph nodes:* All the lymph nodes, but especially the cervical, omental, bronchial, mediastinal, mesenteric and gastrohepatic, showed definite enlargement. On cross-section all these glands appeared somewhat firm but otherwise normal. Histologically all the nodes sectioned show a replacement of germinal centres by the large phagocytic cells described in the follicles of the intestines.

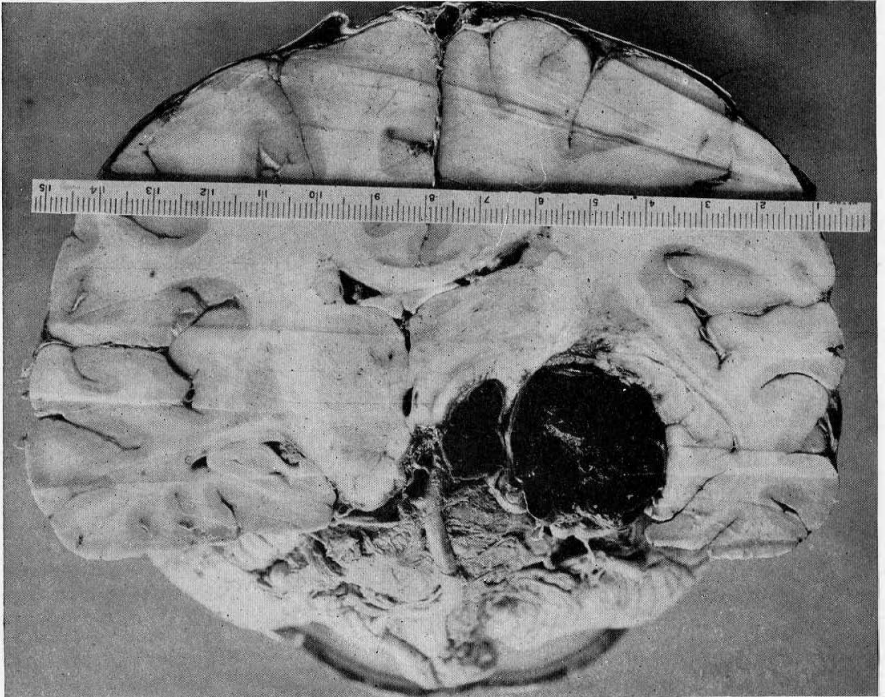


FIG. 30. Case II. Coronal section to show from in front the posterior extension of the adenoma under the left temporal lobe. (Reduced.)

**HEAD:** The marked thickness of the scalp which was thrown into rugæ has been noted. (For the skull *cf.* the description of the skeletons to follow.) The *brain* as usual was fixed before removal by carotid injection with 10 per cent formalin. On the inferior surface was seen (Fig. 28) a roundish dark-colored tumor mass filling the interpeduncular space. From this an extension passed out under the left temporal lobe and projected through the incisura tentorii nearly to the cerebellopontile angle, one nodule actually indenting the pons. The central mass of the tumor occupied a hugely dilated sella turcica, the base of which was completely absorbed; the enlarged

dorsum sellæ was pushed backward and was intact. The lower portion of the tumor showed some lacerations from the recent operation. The tumor was extracerebral and when lifted out of its bed the greatly flattened optic chiasm could be seen pushed off about 2 cm. to the right of the midline with consequent lateral displacement of the chiasmal cross-roads. The Willisian vessels were likewise greatly distorted by the growth.

A coronal section (Fig. 29), taken 2 cm. back of the tips of the temporal lobes, passed through the centre of the main tumor mass which has a uniform blackish-red color on section. It shows that the growth lay principally on the left side, and pushed the tuber, the IIIrd ventricle and the optic chiasm far over to the right.

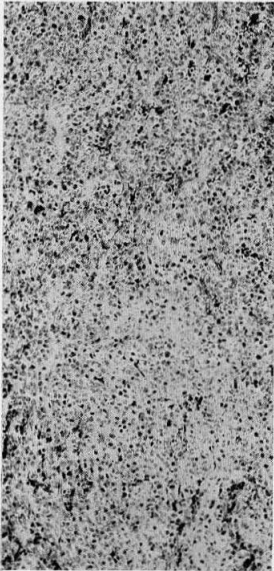


FIG. 31.

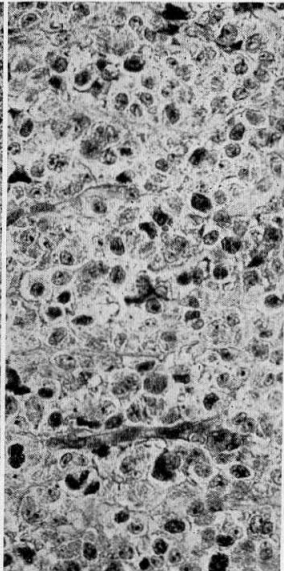


FIG. 32.

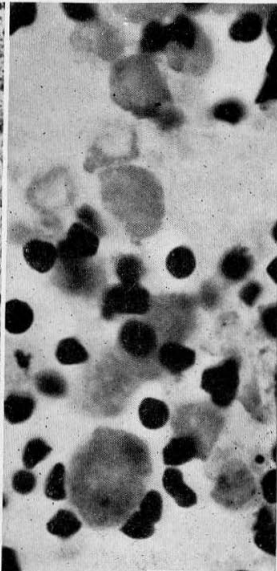


FIG. 33.

FIGS. 31-33. Case II. Showing the adenoma (struma) composed of a structureless mass of cells. Left, H. and E. stain,  $\times 80$ . Centre, H. and E. stain,  $\times 300$ . Right, ethyl violet orange G,  $\times 850$ , showing cells with alpha granules.

A second coronal section taken 2 cm. farther back shows (Fig. 30) the posterior extension of the tumor which distorts the left temporal lobe and lies in proximity to the pons.

#### THE ENDOCRINE SERIES.

*The hypophysial tumor:* The appearance of the adenoma as fragmentarily removed at the first operation in 1910 has been described. It had an alveolar arrangement, contained small cysts, and a considerable amount of connective tissue. The frag-

ments taken at the second operation and put in Zenker's solution show a much more solid collection of cells in a structureless mass (Figs. 31-33). The tumor as disclosed postmortem proves to be the seat of a uniform extravasation of blood, probably associated with the final attempt at its partial surgical removal.

Several blocks were taken from the tumor for study and though marginally there are some zones of fairly intact adenoma, for the most part the lesion is too heavily infiltrated with blood for satisfactory study. Scattered here and there throughout

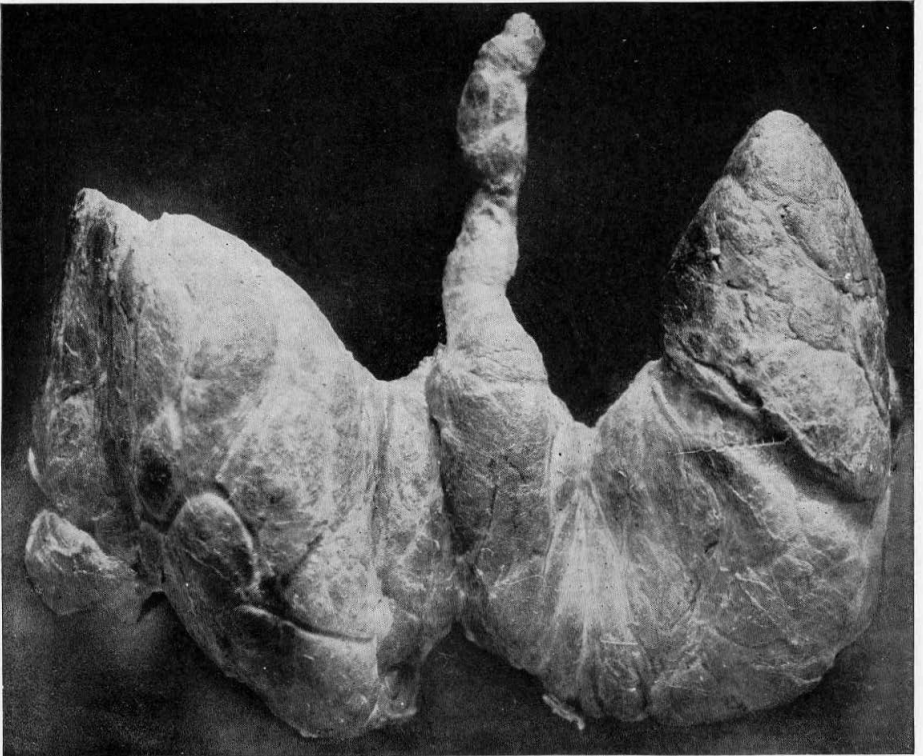


FIG. 34. Case II. To show configuration and size of the thyroid. (Nat. size.)

the clot are irregular-shaped cells, singly and in clusters, which are evidently of tumor parenchyma broken up by the extravasation. Stained by ordinary methods the nuclei are sharply defined, two or three often occurring in a single cell. With special stains the cytoplasm of the large cells is found to be filled with fine dust-like alpha granules (Fig. 33), the nuclei remaining unstained. The lesion is unmistakably a chromophilic adenoma wholly replacing the original gland of which no traces are apparent; nor can the posterior lobe and its stalk be identified.

*Thyroid:* The gland was large, weighing 105.2 gm. It had a median thyreo-glossal extension (Fig. 34). It was firm in consistency, pink in color and presented a lobulated surface. On section it showed a homogeneous, glistening surface with small cyst-like formations representing the lobules which are light brownish-pink in color and separated by fine greyish trabeculae—the appearance of a colloid goitre.

Histologically (Fig. 35) the tissue shows for the most part alveoli of irregular size and shape, lined with low cuboidal epithelium and having an excess of colloid. There are however a few small areas in which the alveoli are essentially normal in size and



FIG. 35. Case II. Histological appearance of the thyroid ( $\times 80$ ).

have higher cuboidal cells. There is an excess of stroma in certain fields. No areas of hyperplasia are seen. There are a few small aggregations of round cells which, however, do not resemble the lymphoid nodules associated with hyperthyroidism.

*Parathyroids:* Two small nodular masses thought to be parathyroids attached to the outer aspect of each lateral lobe were removed but not identified subsequently as parathyroid tissue.



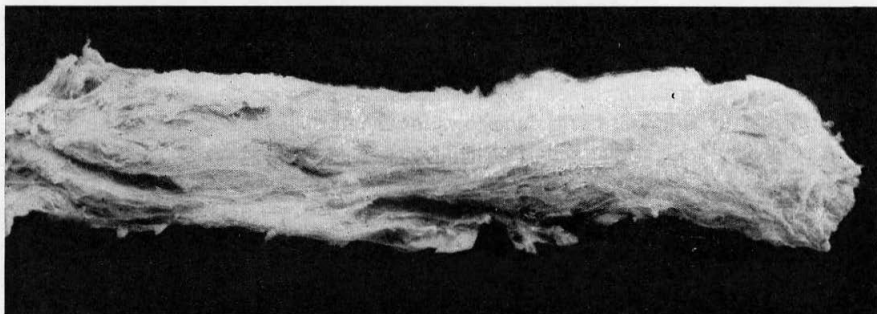


FIG. 36. Case II. The thymus. (Natural size.)

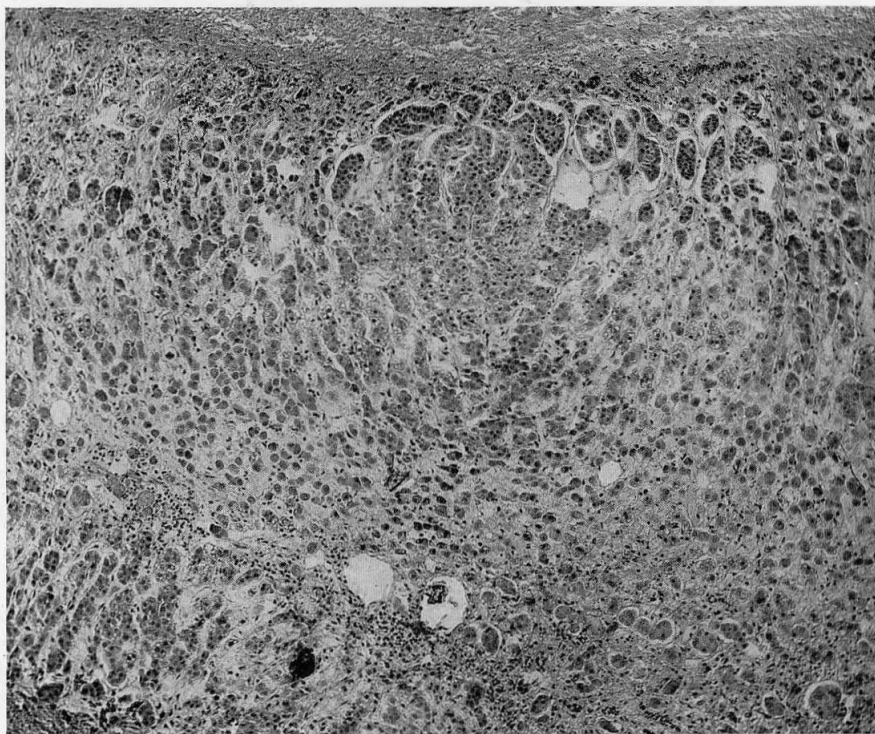


FIG. 37. Case II. Showing wide adrenal cortex with tendency to adenomatous formation. Stain H. and E. ( $\times 80$ ).



*Thymus:* When freed from most of the adherent fat and connective tissue it weighed 8.2 gm. It was pinkish in color and somewhat lobulated, but estimating 17.5 gm. as the average weight for the patient's age the organ was small (Fig. 36). Histologically one finds, dispersed through the fat, foci of lymphoid tissue very atrophic in appearance. No definite follicular arrangement can be made out. Occasionally a hyalinized Hassall body is seen.

*Adrenals:* They were of normal shape and appearance but of unusual size: the right weighed 20 gm., the left 23 gm. On section the relation between cortex and medulla appeared to be normal. Histologically they show a considerable thickening of the capsule, a well-defined cortex and highly vascularized medulla. No definite adenomatous bodies are seen, but there are areas suggesting their formation (Fig. 37).

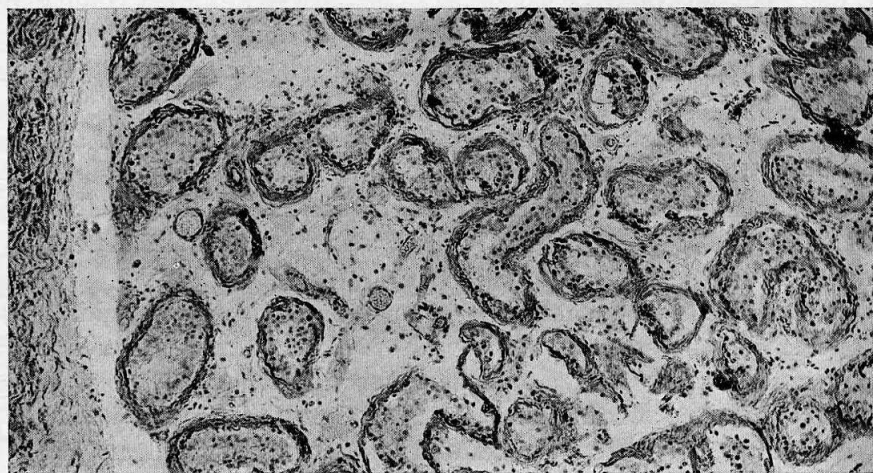


FIG. 38. Case II. Showing section of testes. H. and E. stain ( $\times 80$ ).

*Pancreas:* Weighed 83 gm.; normal in consistency and homogeneous in appearance on section. Histologically, aside from an increase in the interstitial connective tissue especially about the ducts, the alveoli and islands of Langerhans appear normal in all respects (cf. Fig. 94).

*Testes:* Though soft and atrophic they were of about normal size, weighing 13 and 10 gm. The tissue on section strung normally on teasing. They were light brown in color and showed trabeculae of varying width. The epididymes appeared normal. Histologically the testes show (Fig. 38) marked atrophy. The tubules show a badly preserved and irregularly disposed layer of cells consisting of spermatocytes but no recognizable sustentacular cells and formed spermatozoa. The interstitial tissue is

abundant and oedematous and there is a practical absence of cells of Leydig. The seminal vesicles and epididymes have normal epithelium but there is a marked increase of interstitial tissue.

*Anatomical diagnosis: Acromegaly with typical skeletal changes and generalized splanchnomegaly, the heart and blood-vessels being spared. A large hypophysial adenoma of chromophilic type extending beyond the confines of the sella. Colloid adenomatous goitre. Hypertrophy of adrenals. Persistent thymus. Atrophy of testes.*

*Summary and Comment.*—We were dealing here with an acromegalic giant who came from a family of strikingly large people and who began to show signs of a pathological increase in growth in his second decade, earlier than the average age of onset for acromegaly. This, according to our analysis of 100 cases, usually occurs in the third decade, averaging 26.9 years, corresponding with the age at which he had his second recognized wave of overgrowth.

He showed on examination the ocular and radiological signs of a large hypophysial tumor, accompanied by a low pulse, low blood-pressure and marked mental apathy. He had obtained some relief from a sellar decompression, but 5 years later returned with evidences of an intracranial extension of the tumor.

At this time headache had again become the dominant complaint. It however was unassociated with evidence of intracranial tension and (as was also true of Case I) a subtemporal decompression failed to give the slightest relief, nor was any intracranial tension disclosed in spite of the large tumor subsequently found. He died after a second and futile transphenoidal operation.

Pathologically, aside from the skeletal and tissue overgrowth characterizing all cases of acromegaly, there was a disproportional splanchnomegaly affecting chiefly the lungs, liver, kidneys and intestines. In contrast to Case I, however, the heart was not disproportionately enlarged nor were there comparable changes in the peripheral blood-vessels.

On the part of the ductless glands, instead of a small hypophysis, as in Case I, concealing a possibly chromophilic adenoma, the adenoma was huge and had extended widely into the intracranial chamber. The remaining endocrine organs moreover were not extensively modified.

There was, to be sure, a large colloid goitre and over-large adrenals were present; but the pancreas and thymus were both within normal limits. In contrast to Case I, in which the malady had been of even longer duration, the testes proved to be markedly atrophic.

### *Case III.*

This third case, though less striking an example of acromegaly than the two preceding ones, was physically of quite a different type, being a man of average normal stature. One may assume that the period of overgrowth had started in after complete closure of the epiphyses. The especially notable features of the case lie: (1) in the postmortem disclosure of an extremely large intracranial extension of the adenoma though there had been no impairment of vision, no change in the eye-grounds, and surprisingly few intracranial symptoms; (2) in the adenomatous condition of other endocrine glands; and (3) in the fact that the patient had pituitary diabetes from which he had apparently recovered.

P. B. B. H. Surg. No. 61. *Typical acromegaly of circa 15 years' duration (1899-1914) with diabetes. An enlarged sella without headaches or chiasmal involvement. Transphenoidal operation (1913) with temporary improvement. Bilateral excision of superior cervical sympathetic ganglia with subsequent disappearance of glycosuria. Readmission a year later with death from cardiac failure at the age of 35 years. Chief autopsy findings: general splanchnomegaly; cardiac hypertrophy with chronic passive congestion; huge intracranial extension of a chromophilic adenoma; hypertrophy of thymus; adenomata of thyroid, parathyroids, pancreas (acinar) and adrenals; testicular atrophy.*

On April 15, 1913, G. B. S., a Canadian fisherman, married, and 34 years of age, was admitted on the recommendation of Dr. B. S. Bishop of Freeport, Digby County, Nova Scotia, with the diagnosis of acromegaly and complicating diabetes.

The family history was essentially negative. None of the patient's male relatives were men of unusual stature. As a child he had diphtheria and otitis media without subsequent ill effects. Since 13 years of age he had earned his living at hard labor and had worked up until a few weeks before his admission to the hospital. He had been married for 5 years; there were no children of the union; he soon after became impotent.

The present illness seems to have begun insidiously; so far as could be told at about 1899, when he was 20 years of age. He began at about that time to increase in size and soon found that his hands and feet had become so large that he had trouble fitting himself with shoes and winter gloves. Coincidental with this period of overgrowth there was a marked increase in appetite, though he had always been a most hearty eater. What his weight may previously have been is not certain, but he stated that

he had gained 50 lbs. in the course of 2 years and at one time in 1908 had weighed 220 lbs.

He was not a particularly observant individual as shown by the fact that though his mandibular prognathism was a most striking feature of his case, he seemed to be only hazily aware of the fact and had no idea when his jaw had begun to be undershot.

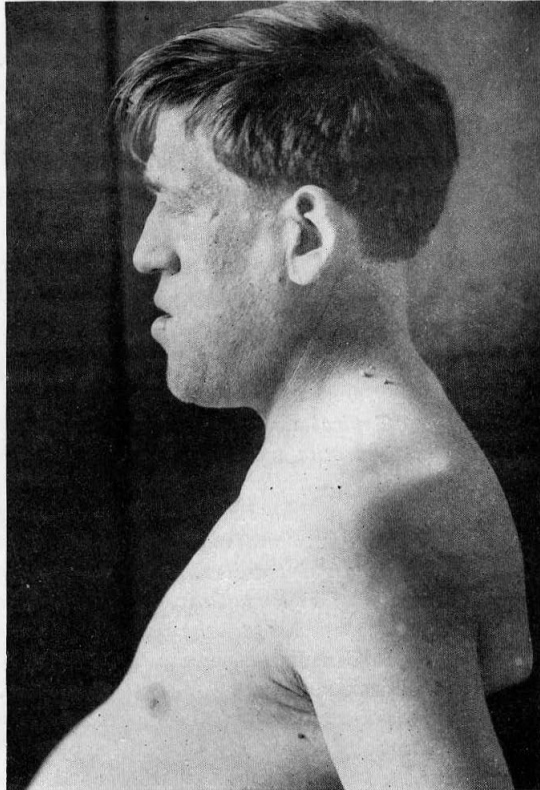


FIG. 39. Case III. To show the acromegalic prognathism, the coarsened features and skin, with moderate adiposity.

As time went on, he came to be troubled greatly by excessive sweating both day and night, and by paræsthesias of his hands and feet. But for the most part, for a period of 10 years when his malady must have been progressive, he seems to have paid little attention to it nor to have been in any appreciable way incapacitated thereby. Not until about 1910 did he begin to have a tendency to drowsiness and first to notice an increase in his output of urine. (The presence of sugar was not detected till 3 years later.)

During the years from 1910 to 1913, some dispositional changes had been noted by his friends and relatives. He became irritable and increasingly forgetful. Throughout his life he had had occasional headaches and of late they had been a little more troublesome, coming on every 2 or 3 weeks, usually in the morning and usually relieved by vomiting. On the whole, they were never particularly pronounced. For the past year he had been subject to peculiar attacks suggesting uncinate seizures, associated with a peculiar subjective odor, a vague dreamy state, and there was a history of occasional nocturnal attacks in which he had become unconscious.

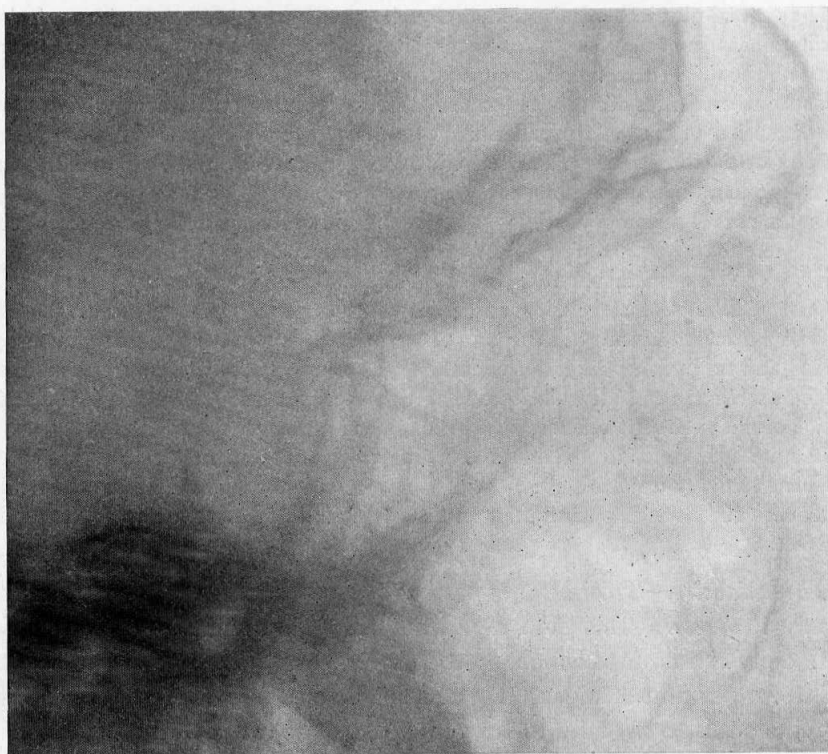


FIG. 40. Case III. To show the moderately enlarged and deepened sella.

*Physical examination:* To be brief, this showed at the time of his admission a distractable, drowsy and irritable acromegalic of 5 ft. 8 in. in height, weighing 178 lbs. There was considerable adiposity. The skin was smooth, moist, with a few areas of pigmentation and numerous fibromata mollusca scattered over the shoulders and back (*cf.* Fig. 39). The hair though abundant on the head was scanty over the pubes and practically absent on the rest of the body. He shaved infrequently.

The *skeletal changes* were pronounced. The thorax for a man of his height was huge and barrel-shaped. The head was massive with extremely marked prognathism, the lower teeth projecting 2 cm. beyond the upper. The teeth were all widely spaced. The X-rays of the skull showed (Fig. 40) a markedly enlarged and deepened sella turcica measuring 2.5 cm. in its anteroposterior direction and 2.2 cm. vertically. The frontal sinuses were moderately hypertrophied. Films of the hands and the feet showed only moderate tufting of the terminal phalanges though the extremities were greatly enlarged. The length of the hand from the radius to the tip of the middle finger was 22.5 cm. The radial and other epiphyses were closed.

The general physical examination disclosed a greatly enlarged heart with auricular fibrillation as shown by electrocardiographic tracings. The systolic blood-pressure was 140, the differential blood-count negative.

The local evidences of a pituitary adenoma were curiously inconspicuous aside from the distension of the sella mentioned above. The eyegrounds showed no trace of atrophy or papillœdema. The fields of vision were normal. The neurological examination in all other respects was negative.

On the part of the other ductless glands the thyroid was not definitely palpable; both testes were markedly atrophic. The urine was found to contain *circa* 4 per cent of sugar. The basal metabolic rate was estimated to be +83 per cent.\*

On April 29, 1913, under ether anæsthesia, a transphenoidal operation was carried out with no particular difficulty. The floor of the sella was found to be almost completely eroded and on incising the dural capsule of the gland, soft adenomatous tissue extruded itself and a considerable amount of it was scooped away. Histological examination of this tissue showed the usual eosinophilic adenoma.

In spite of his uncontrollable diabetes and his cardiac lesion the patient made an excellent recovery from this operation. He expressed subjective relief from his mild headaches and noticed a diminution in the soggy and doughy swelling of his hands and feet.

*The Diabetes.*—During the patient's prolonged hospital sojourn of nearly 10 weeks at this time, detailed studies were made of his glycosuria with daily estimations which, on the first days of admission, showed from 4.5 to 5.0 per cent of sugar. On a carbohydrate-free diet, it was possible to reduce this to *circa* 1.0 to 1.5 per cent, but he was a refractory patient and his excessive appetite was difficult to control. The urine never became sugar-free nor did the operation on the gland serve to appreciably modify the high percentage usually present.

\* It should be noted that these observations, calculated in terms of the respiratory quotient, were made by Dr. Boothby in the early days of these determinations. Though repeated in this case with approximately the same reading the figures perhaps may not be dependable. It is safe to say, however, that the basal metabolic rate was considerably above normal.

It was at this time that some experimental studies were being made by Weed, Cushing and Jacobson on the autonomic control of the hypophysis and its relation to the metabolism of the carbohydrates.<sup>93</sup> These studies had appeared to show that impulses passed by way of the superior cervical sympathetic to the hypophysis with the resultant discharge of a 'hormone' with glycogenolytic properties, and it was on the basis of these experimental studies that finally in the case of this patient on *May 19, 1913*, a bilateral superior cervical sympathectomy was performed. At the time the operation was done, he had been on a carbohydrate-free diet and his urine the morning of operation showed 1.0 per cent of sugar. The first specimen immediately after the operation showed a jump to 4 per cent and a second sample to 4.5 per cent just as in the laboratory experiments, with a prompt fall again to its previous reading of 1.0 per cent. Whatever the ultimate effect of the procedure may have been, it certainly was not immediately corrective of the diabetic condition; for when dietary restrictions had been removed and he was allowed to satisfy himself with an abundance of carbohydrates, the glycosuria again rose to 4.5-5.0 per cent, where it was at the time of his discharge on *June 5, 1913*. Unfortunately there is no record of a subsequent urine examination till 8 months later.

The patient returned to his home and during the course of the next few months wrote hopefully about himself in spite of the continuance of his occasional convulsive attacks. He stated that he was feeling much stronger and had even returned to work; also that his ravenous appetite had diminished. Early in 1914 he began to suffer from shortness of breath and from oedema of the extremities which prevented him from getting about. Dr. Bishop who had continued to have his case in charge found to his surprise on examining him in February that *the glycosuria had disappeared*. This negative finding was repeated. ●wing however to his increasing oedema and associated cardiac distress the man was advised to return for further study.

*Mar. 13, 1914.* Readmission to Brigham Hospital. The 3 days' journey had proved a great trial and the patient when admitted was very cyanotic, dyspnoic, orthopnoic and irrational.

The heart showed a marked enlargement with dulness from the mid-sternal line to 15 cm. on the left and 7 cm. on the right. The pulse was almost imperceptible at the wrist, irregular and of extremely low tension. The lower edge of the liver was 11 cm.



below the costal margin, there was dulness in the flanks suggesting fluid. There was generalized anasarca with œdema chiefly marked in the lower extremities and scrotum. During the night of admission the respiration became greatly impaired and assumed a Cheyne-Stokes type of rhythm. He died within 12 hours after his admission.

A single catheter specimen of urine had been obtained. It showed a trace of albumen and the sediment of chronic passive congestion. It was free from acetone, diacetic and contained no sugar. Though there was an atypical reaction to Nylander, the Fehling's test was negative.

*Postmortem Examination.*—Permission was received for an unrestricted autopsy with removal of the skeleton. The examination was made by Prof. W. T. Councilman on *Mar. 14, 1914*, five hours after death. The long and detailed report will herein be rearranged and considerably condensed. Three things are particularly to be emphasized: (1) the cardiovascular changes and their consequences; (2) the evidences of overgrowth; (3) the polyglandular adenomata.

The description of the body has been sufficiently covered. Aside from the general anasarca, stress was laid on the great enlargement of the hands and feet, particularly of the fingers and toes, and of the lower jaw. The subcutaneous fat, which over the abdomen was 3.5 cm. in thickness and over the thorax 2 cm., was of a distinct yellowish color and was separated into distinct lobules by thick œdematous bands of connective tissue. In the right inguinal region was a lobulated lipoma weighing 150 gm., its color contrasting sharply with the color of the adjacent panniculus.

#### THE BODY CAVITIES.

**THORAX:** Described as huge and barrel-shaped. The pleural cavities contained considerable fluid and there were a few old adhesions. The *lungs* (not weighed) showed congestion and emphysema but were otherwise practically negative in their gross and microscopic appearance.

**Heart:** The enormously enlarged organ (Fig. 41) when emptied of blood weighed 1000 gm. with the aorta attached. The fat in the auriculo-ventricular grooves showed minute ecchymoses. All the cavities were greatly dilated with widened valvular orifices. The right auricle was described as being the size of a large fist; the tricuspid and mitral orifices easily admitted three fingers. The right ventricular wall was 1 cm. in thickness, the left 2.4 cm. The valves were delicate, translucent and without abnormality.

Microscopically the cardiac muscle shows hypertrophy but no pathological change. There was no sclerosis of the coronary arteries nor was the aorta or large arterial

branches altered in the slightest. The small vessels throughout the body showed no arteriosclerosis.

**ABDOMEN:** The peritoneal cavity contained *circa* 1000 cc. of clear, slightly yellow fluid. The *liver* was very large, weighing 2480 gm. Its surface was intensely dark red and slightly irregular. On fresh section it showed the usual nutmeg appearance of chronic congestion of long standing. Histologically there is a moderate degree of central necrosis with congestion. The cells do not appear enlarged nor do the lobules seem hypertrophic.

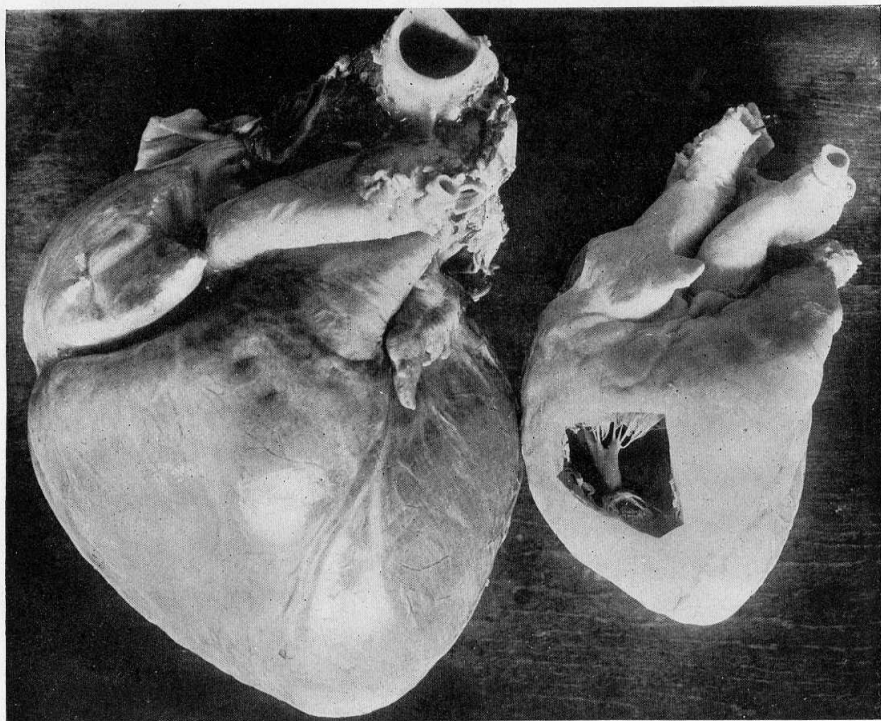


FIG. 41. Case III. Patient's heart (left) weighing 1000 gm. contrasted with a normal 340-gm. organ.

The *spleen* (not weighed) was hyperæmic, firm, and also presented the picture of marked passive congestion. The follicles were prominent though not enlarged. Histologically the follicles are seen to be composed chiefly of cells of the germinal-centre type. The reticulum is thickened; there are in the pulp a few large basophilic mononuclear cells, comparatively few polymorphonuclear leucocytes, no nucleated reds.

The *kidneys* were large and intensely hyperæmic but without hæmorrhages. The left weighed 340 gm., the right 310 gm. The capsule was smooth and not adherent.

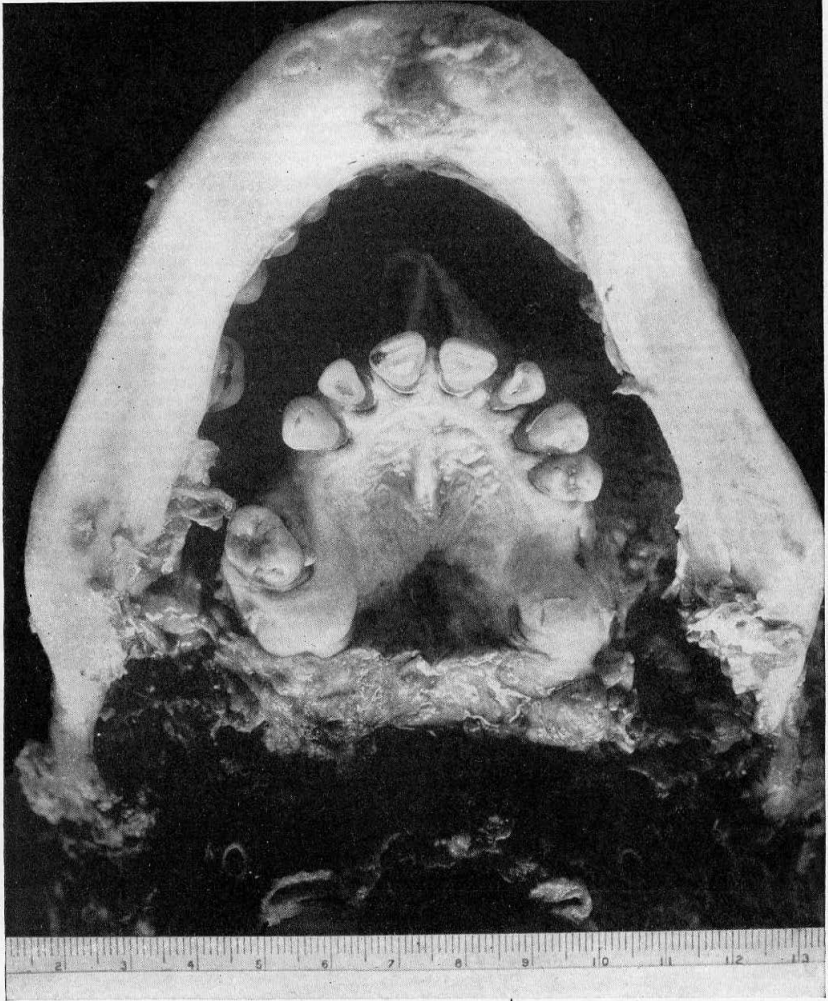


FIG. 42. Case III. Maxillæ before disarticulation, showing the extreme overdevelopment of the mandibular arch and the spaced teeth. (Natural size.)

All parts of the kidney on fresh section appeared to be symmetrically enlarged. The cortex measured 8 mm.

Histologically they show marked congestion and œdema. The loops of Henle

contain swollen cells with glycogen and vacuolization resembling those seen in cases of diabetes. The glomeruli are distinctly enlarged and their capillaries engorged. They average  $250\mu$  in diameter whereas those in another adult kidney of passive congestion average only  $200\mu$ . All the tubules are large, the convoluted average  $90\mu$  in diameter as compared with a normal of  $70\mu$ . The very large size of the kidney therefore may be ascribed partly to an hypertrophy of all its components, partly to congestion and œdema.

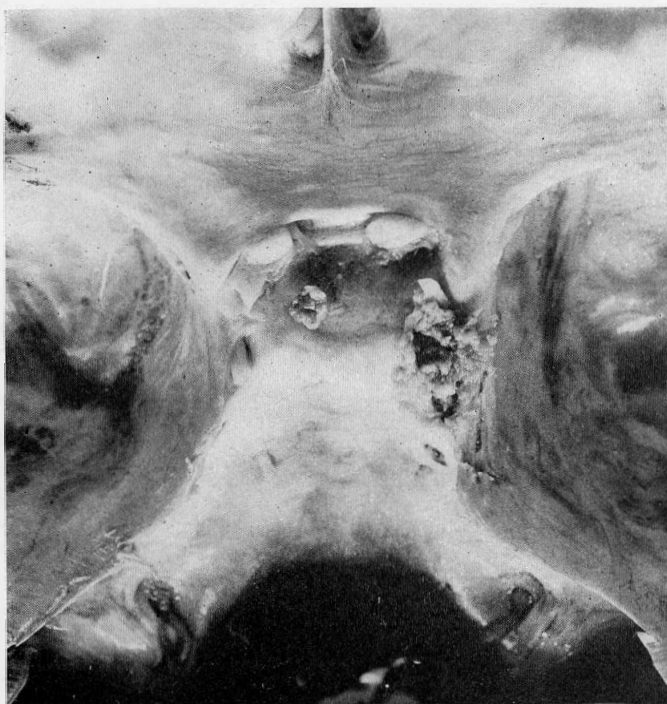


FIG. 43. Case III. Showing (natural size) the pituitary diaphragm pierced by the infundibular stalk. To the right is the broken neck of the intracranial extension of the adenoma.

**ALIMENTARY CANAL:** The tongue was huge, measuring 7 cm. in breadth by 12 cm. in length. The circumvallate papillæ were prominent and all the glands and follicles enlarged. On section there was found thickening of the epidermis with hypertrophy of the glands. Histologically the epidermis proves to be greatly thickened and the subepidermal tissue œdematous but the muscle fibres themselves are not apparently hypertrophied. The lingual glands are all enlarged and their alveoli dilated with coagulated mucus.

The *tonsils* were greatly hypertrophied, one of them measuring 5 cm. in its longest diameter. On section they show large sinuses and hyperplastic follicles with particularly well-marked germinal centres. The pharyngeal follicles were also greatly hypertrophied.

The *lymph nodes* throughout the body were all enlarged in varying degrees, some measuring  $2 \times 3$  cm., those in the abdomen were pale and those in the thorax hyper-

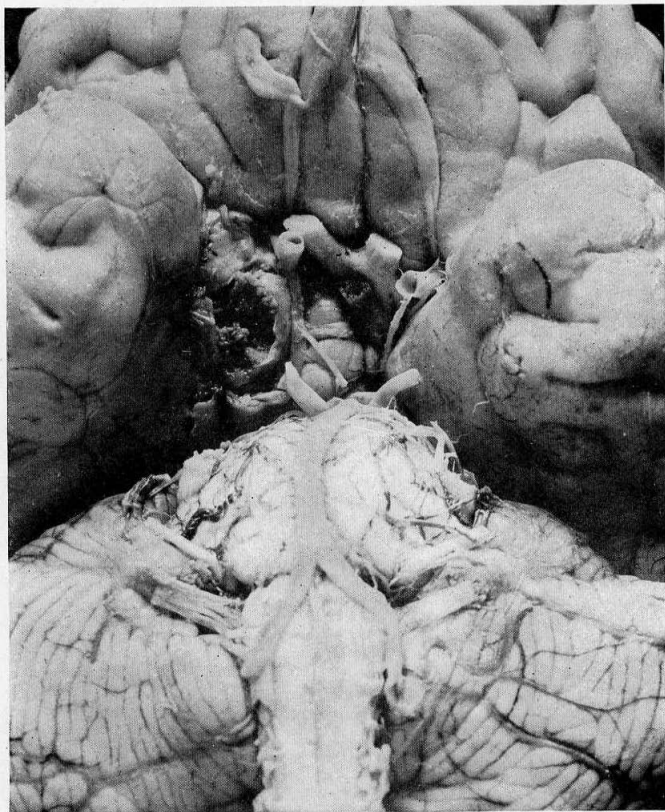


FIG. 44. Case III. To show the interpeduncular space with the distorted chiasm and the broken neck of the tumor. (Cf. Fig. 43.)

æmic. They show no distinctive histological change. The *solitary follicles* of the intestines, particularly those in the ileum, were also enlarged. In one area, immediately beneath the muscularis mucosæ, small islands of glandular tissue were found similar in character to Lieberkühn's crypts.

The *œsophagus*, *stomach* and *intestines* showed no gross abnormality aside from venous stasis and œdema.

HEAD: (For skull *cf.* discussion of skeletal changes.) The unusual ease with which the tissues stripped from the bone was noted. The calvarium was remarkable for its thinness wherein it differed from the usual acromegalic skull. There were a few frontal endostoses, and the greatest thickness was 6 mm. The Pacchionian digitations were marked and one or two of them actually perforated the skull. Most notable was the extreme degree of prognathism (Fig. 42); the upper jaw measured 5 cm. across from molar to molar; the lower 8 cm. across.

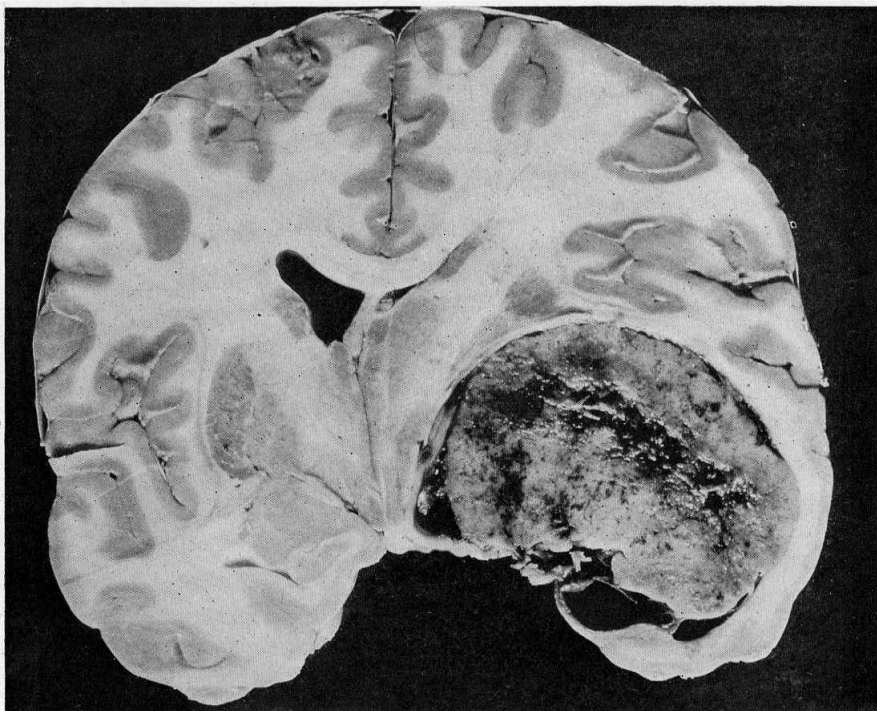


FIG. 45. Case III. Coronal section of brain showing large unsuspected and symptomless intracranial extension of hypophysial adenoma into right temporal region. (Reduced.)

*Brain:* The organ was 'fixed' as customary with formalin *in situ*. During its removal a normal though succulent hypophysial stalk was encountered and divided. It projected through the interclinoidal diaphragm which was not protruding. However, to the right side of the sella the neck of a tumor extending into the temporal lobe was disclosed and torn across (Fig. 43). The brain was small and of normal configuration. In the right temporal lobe a definite flattening of the convolutions was apparent.



On the base of the brain (Fig. 44) was seen a tumor mass which, as described, was connected by a narrow neck with the intrasellar portion of the lesion. The growth had crowded the optic chiasm and infundibular stalk to the left. It also indented the right temporal lobe and had evidently pressed against and greatly deformed the region of the uncus, doubtless accounting for the patient's seizures during life.

A coronal section just posterior to the pituitary stalk and through the mammillary body disclosed a huge and entirely unexpected intracranial extension of the lesion (Fig. 45). The mass which lay almost wholly in the right temporal lobe measured  $6.3 \times 5$  cm. in diameter. It was nowhere attached and had pushed the pia-arachnoid ahead of it. It was denser in consistency than the usual struma and showed con-

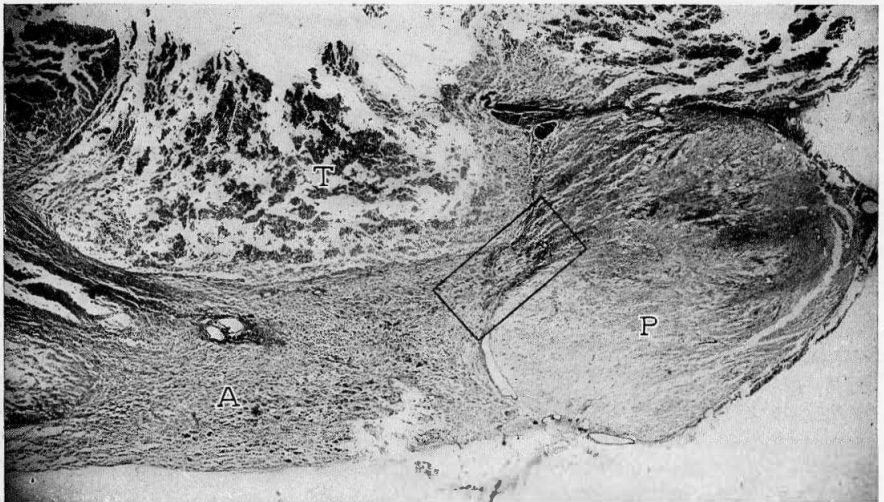


FIG. 46. Case III. Section through the intrasellar tissues showing (A) anterior lobe; (P) posterior lobe; (T) tumor. For blocked-out area, see Fig. 47. Stain, iron hematoxylin ( $\times 8$ ).

siderable degeneration in its central portion. It had collapsed the right ventricle. A histological examination of the compressed cerebral tissue adjacent to the tumor shows a slight gliosis. Sections from other parts of the brain and spinal cord were negative.

*The hypophysis and the intrasellar portion of the adenoma:* A longitudinal section through the contents of the sella turcica disclosed a flattened hypophysis, measuring  $1\frac{1}{2}$  cm. in length and about 0.3 cm. in thickness. The posterior lobe was clearly visible and it was histologically identified. Compressing the flattened anterior lobe was the intrasellar portion of the adenomatous mass so well demarcated that its outline was unmistakable. The growth had broken through the dural envelope of the gland on the right side and had completely enveloped the right internal carotid artery in its progress into the cranial chamber.



*Microscopic examination:* A longitudinal section through the intrasellar mass (Figs. 46 and 47) shows distinctly the pars nervosa, the compressed pars anterior and the origin of the adenoma. The pars nervosa is invaded by large numbers of anterior-lobe cells. Most of them show distinct beta granulations but there are also alpha cells in small numbers. The dividing line between the two lobes is distinctly shown by the cleft (*cf.* Fig. 46) which is not, however, lined by epithelium but simply by connective tissue.

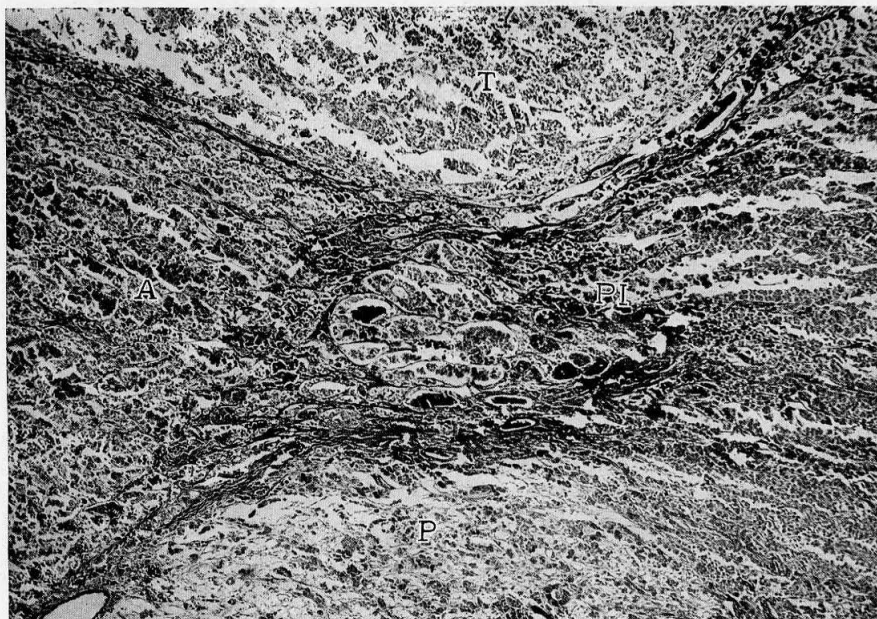


FIG. 47. Case III. Enlargement of squared area in Fig. 46 showing junction of (A) anterior lobe; (P) posterior lobe; (T) tumor; (PI) pars intermedia. Stain, iron hematoxylin ( $\times 45$ ).

The anterior lobe consists of cells in a well-marked connective-tissue network, permeated by thin-walled blood-vessels. Flattening of the gland causes the strands to run parallel through the greater length of the specimen. The two types of cells appear to be present in approximately equal numbers throughout the anterior lobe. If anything, alpha cells predominate.

The adenoma itself is extremely cellular (Figs. 48 and 49), the cells following no definite architectural arrangement. Small capillaries run through it at rare intervals, although a few larger sinuses are also present. The cells of the tumor have large, vesicular nuclei with scanty chromatin, each nucleus having a large, heavily staining nucleolus. The cytoplasm of the cells is fairly abundant, and some of them contain

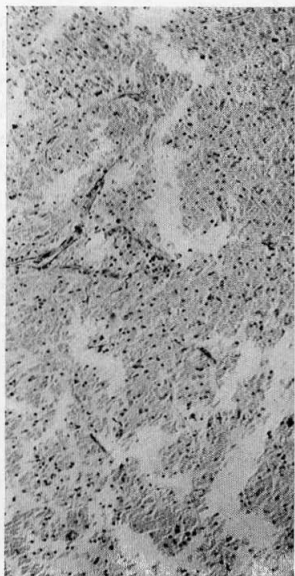


FIG. 48.

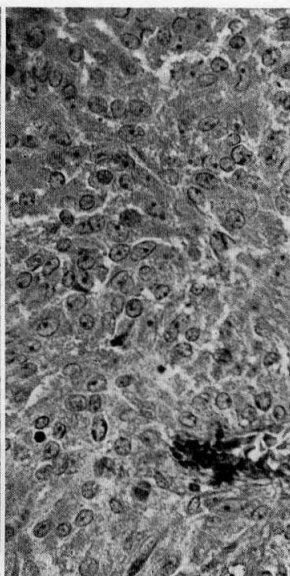


FIG. 49.

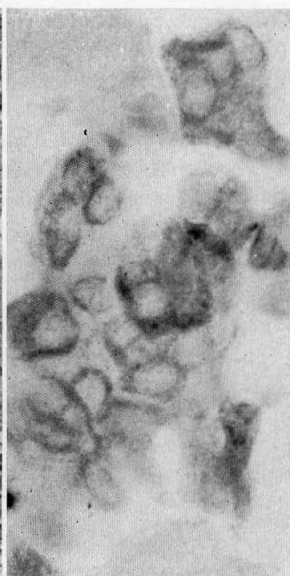


FIG. 50.

FIGS. 48-50. Case III. Showing hypophyseal adenoma in structureless masses. Left, acid violet eosin,  $\times 80$ ; centre, acid violet eosin,  $\times 300$ ; right, ethyl violet eosin,  $\times 850$ , showing alpha granules in cytoplasm.

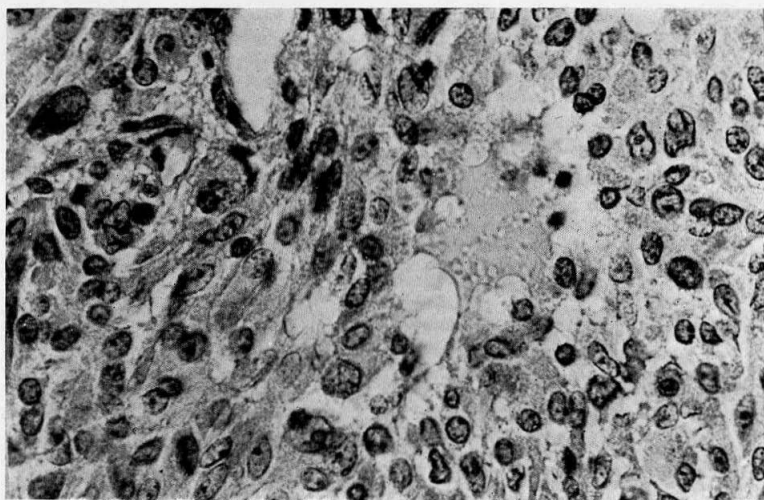


FIG. 51. Case III. Section from the large intracranial tumor mass showing hyalin. H. and E. stain ( $\times 600$ ).

very definite alpha granules (Fig. 50). Beta granulations are seen only in some of the cells in the compressed anterior lobe. The intracranial extension of the growth has essentially the same histological characteristics (Fig. 51).

#### THE OTHER DUCTLESS GLANDS.

*Pineal:* The gland presented a normal appearance in gross and this the microscope confirms. There are a small number of psammoma bodies, and a considerable degree of calcareous degeneration distributed irregularly, but chiefly in the course of the vessels.



FIG. 52.

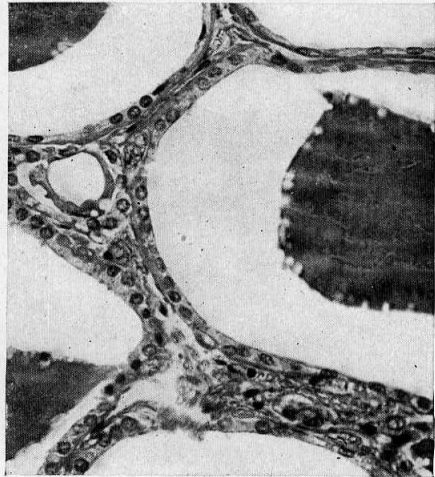


FIG. 53.

FIGS. 52 and 53. Case III. Colloid goitre. Left, H. and E. stain ( $\times 80$ ); right,  $\times 300$ .

*Thyroid:* Distinctly and symmetrically enlarged, weighing 100 gm. Each lobe measured  $7.5 \times 6 \times 3$  cm. The external surface was grossly lobulated. On fresh section the surface appeared greyish, soft and elastic, with small lobules held together by evident strands of connective tissue. There were no definite areas of hyperplasia. The general picture was that of a colloid gland.

Histologically the tissue shows a typical colloid goitre (Figs. 52 and 53). The follicles are large and irregular containing granular colloid material staining deeply with eosin. The character of the epithelium is essentially the same in the various-sized alveoli. The cells are of the low flat-cuboidal type. Many sections were cut and there is no evidence anywhere of hyperplasia.

In the search for the lower parathyroids, a nodule about 1 cm. in diameter which had a slight yellowish color suggesting parathyroid tissue was found embedded in the

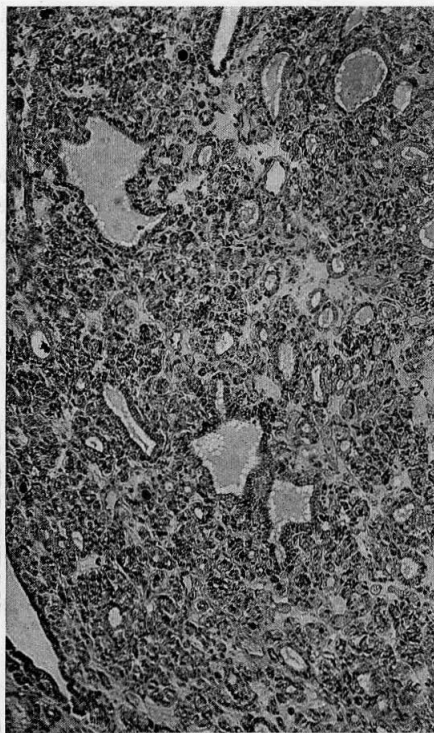


FIG. 54.



FIG. 55.

FIGS. 54 and 55. Case III. A peculiar and isolated thyroid adenoma. Stain, H. and E. Left,  $\times 80$ ; right,  $\times 300$ .

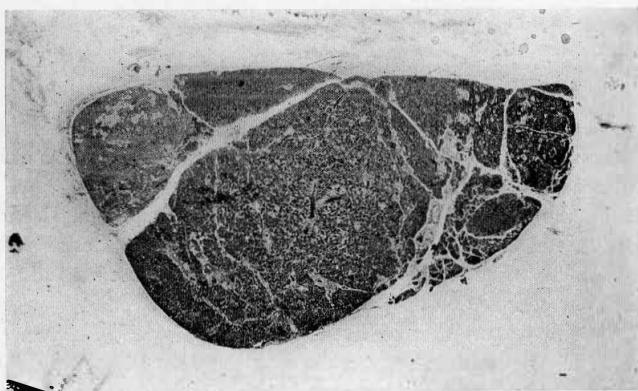


FIG. 56. Case III. Showing adenoma of the smaller parathyroid,  $\times 13$ . The tumor is represented by the central mass.

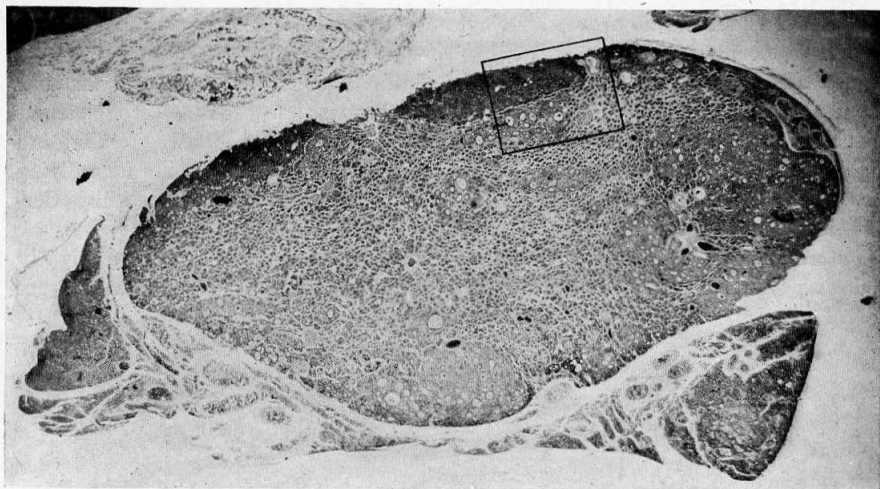


FIG. 57. Case III. Showing large adenoma of parathyroid ( $\times 12$ ). The fragments at the ends show normal parathyroid tissue. The heavy stained marginal strip is strongly eosinophilic.

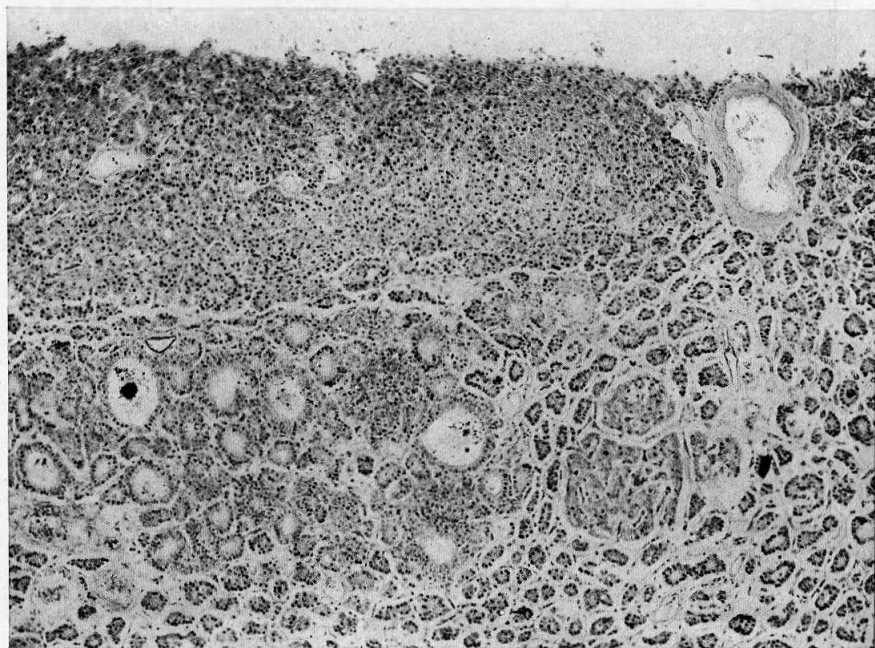


FIG. 58. Case III. Squared area from Fig. 57, to show the closely packed and highly eosinophilic marginal area in comparison with the subjacent acinar tissue. H. and E. stain ( $\times 80$ ).



side of the gland. This proves histologically to be a discrete thyroid adenoma of unusual appearance (Figs. 54 and 55). Though there is some colloid present it is scanty compared to that in the rest of the gland. The alveoli vary greatly in size, the smaller ones being so closely packed that the tissue is almost solid. Into the larger ones rounded papillæ project, the epithelium throughout being slightly granular and high. Cells of irregular shape much smaller than the epithelial cells are found lying between them. Some of the smaller alveoli are largely composed of these cells. Certain fields are reminiscent of foetal adenoma.

*Parathyroids:* Only the two upper ones were identified. Both were a slightly yellowish color. The smaller (Fig. 56) measured 4 mm. in its long diameter, the larger (Fig. 57) 9 mm.

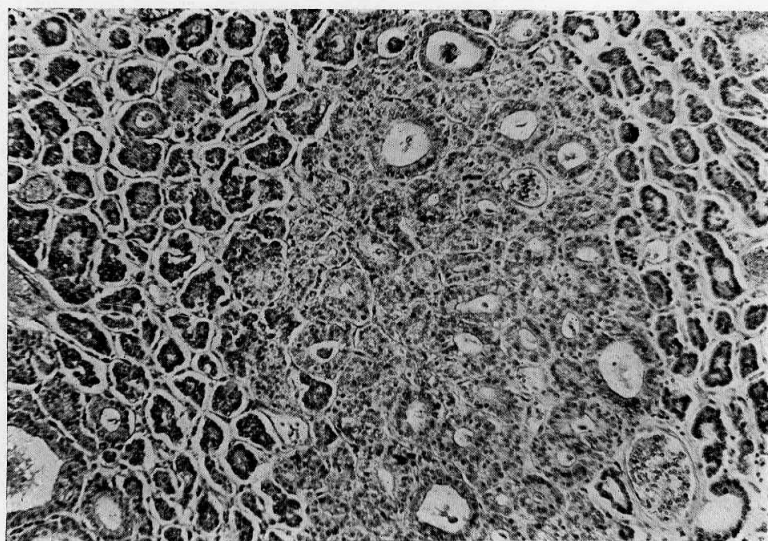


FIG. 59. Case III. From centre of parathyroid adenoma showing compact area of glandular tissue suggesting hyperplastic thyroid.

Microscopically both glands show what is apparently a central adenoma which in the large gland comprises its chief portion though it is partly surrounded by the normal parathyroid tissue. The histological appearances of the two adenomas are very similar. On the margin of the larger tumor (Fig. 57) can be seen a zone of heavily stained and closely packed eosinophilic cells. Within the cell clusters small lumina are occasionally found. The nuclei are small and homogeneous. The main mass of the tumor, anatomically continuous but clearly demarcated by its difference in character (Fig. 58), consists of epithelial tissue arranged in alveoli with brightly staining, vesicular, closely packed nuclei. The cells are small, faintly eosinophilic and granular. Among these are masses of cells strongly eosinophilic, resembling those of

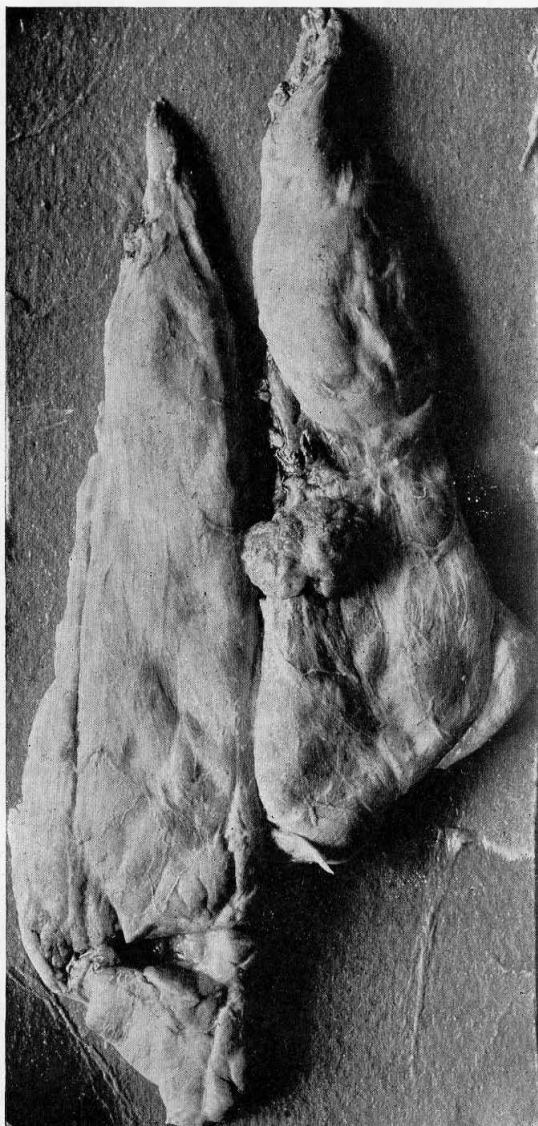


FIG. 60. Case III. Showing the bilobar hypertrophic thymus weighing 78 gm. (Natural size.)



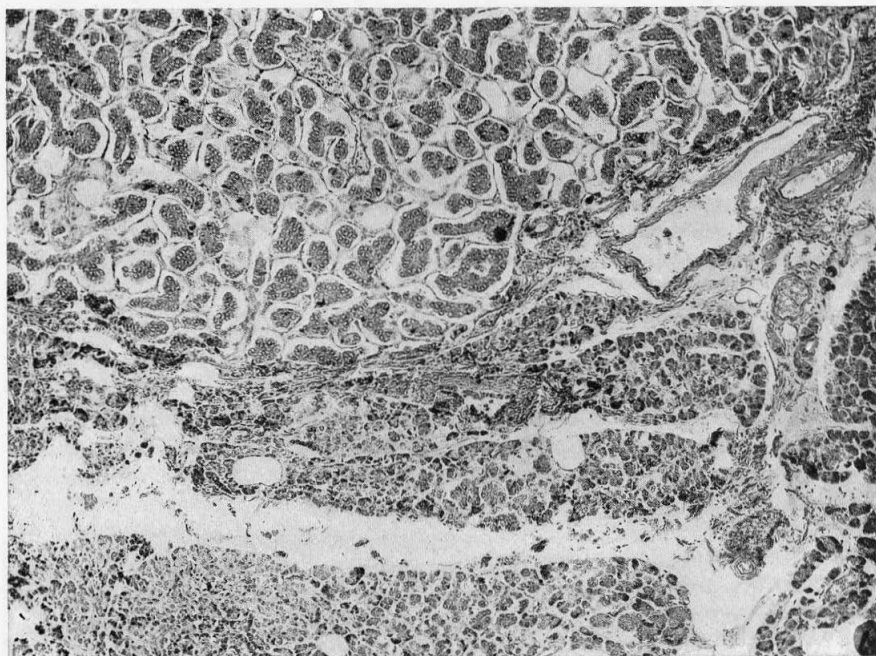


FIG. 64. Case III. Showing margin of acinar adenoma of pancreas with normal pancreatic tissue below. Stain H. and E. ( $\times 80$ ).



FIG. 65. Case III. Testis. (Natural size.)

tumor nodule 1 cm. in diameter was disclosed. This proves microscopically to be an adenoma of acinar origin (Fig. 64). The organ shows a considerable interlobular infiltration with fat but is apparently normal. The islets show no fibrous, hyaline or hydropic change, and were it not for their unusually large size and possible increase in number would pass as normal in all respects (*cf.* Fig. 95).

*Genitalia:* The scrotum was markedly cedematous. The *testes* were very small and measured only  $2.5 \times 2$  cm. (Fig. 65). The epididymis also was atrophic and the ducts were not visible. The prostate was very small and the seminal vesicles showed an obliteration of the greater portion of their cavities. The fluid present in what remains of the lumina contained no spermatozoa.

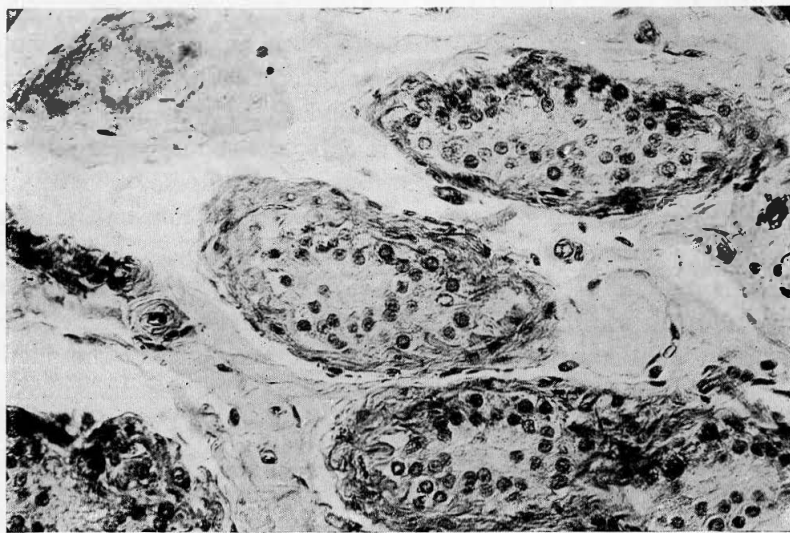


FIG. 66. Case III. Section of atrophic and cedematous testis. H. and E. stain ( $\times 300$ ).

Histologically the testes prove to be atrophic and cedematous. The tubules contain indifferent epithelial cells with no spermatogenesis. The interstitial connective tissue is in excess and appears to be largely hyalinized. No cells of Leydig can be definitely recognized (Fig. 66).

*Anatomical diagnosis:* (1) *Acromegaly with typical skeletal changes and splanchnomegaly; macroglossia, hypertrophy of thymus, tonsils and lymphatic apparatus; lipoma of thigh, etc.*

(2) *Eosinophilic adenoma of hypophysis with large extrasellar extension; colloid goitre with adenomata; acinar adenoma of pancreas; adenomata of parathyroids and adrenals; testicular atrophy.*

(3) *Marked hypertrophy and dilatation of heart with passive congestion of lungs, liver, spleen, kidneys and general anasarca.*

*Summary and Comment.*—The foregoing is an example of how kaleidoscopic acromegaly may be. Here was a man presumably quite healthy until the age of 20 when his acromegaly began to be apparent. Fourteen years later when he first came under observation he had severe diabetes mellitus and cardiac hypertrophy. Though there was no clinical evidence of chiasmal deformation his headaches were sufficiently severe to justify a decompression of the distended sella with partial removal of the adenoma. He experienced some subjective relief in spite of the fact that there must have been at the time a large and unsuspected intracranial extension of the lesion.

In the hope of modifying his diabetes, both superior cervical ganglia were removed. Whether influenced by this procedure or not, he at all events ultimately became sugar-free though at no time had he adhered to a restricted diet. Eventually he re-entered the hospital with general anasarca from a wholly decompensated heart and died shortly after. The autopsy showed extreme chronic passive congestion but nothing to account for his enormous myocardial hypertrophy.

The hypophysial lesion, though a typical chromophilic adenoma, is quite out of the ordinary in size and situation, and there had never been any perimetric disturbances of vision. The remainder of the ductless-gland series presented a striking array of pathological changes chiefly of an adenomatous nature except in the case of the testes which were atrophic, with spermatogenous and interstitial elements lacking.

Attention may also be drawn to the generalized hyperplasia of the lymphatic apparatus and particularly to the huge thymus. In this connection one naturally recalls the early autopsy report by Fritsche and Klebs,<sup>40</sup> antedating Marie's baptism of acromegaly; in their case the thymus was also so disproportionately involved that they were impelled to ascribe the patient's giant-growth to a functional disturbance in which the thymus played an essential rôle.

The cause of the enormous cardiac hypertrophy in the absence of any histopathological evidence of cardiovascular disease remains unexplained. In this respect the condition was in marked contrast to Case I, in which there was an advanced and widespread peripheral arteriosclerosis, to account, in part at least, for the cardiac enlargement.

Of particular interest is the fact that the hypophysis itself, though compressed by the relatively small intrasellar portion of the adenoma, re-

mains normal in its appearance, all three subdivisions of the gland being easily recognizable. One may recall the much-quoted case described by Erdheim<sup>32</sup> in which, with a normal hypophysis, an eosinophilic adenoma was found projecting into the sphenoidal cells—a case which has always been regarded as such an important one in its bearing on the etiology of acromegaly so far as the hypersecretion theory is concerned. Apparently in both Erdheim's case and the present one under discussion the adenoma was in such a situation as to break through the glandular envelopes and to extend outward without seriously compromising the hypophysis itself. Had the growth long remained within the confines of the sella, as it usually does, the hypophysis might have been destroyed almost beyond trace.

#### Case IV.

This, the last of these cases, concerns a woman of small stature with advanced acromegaly which had begun fairly late in life. She too, like the preceding case, had coincidental diabetes which, however, came on abruptly and had a different ending, for she died in coma in the days before insulin.

P. B. B. H. Surg. No. 3234. *Advancing acromegaly of circa 21 years' (1895–1916) duration in a woman who after a transphenoidal operation with improvement (1915) developed diabetes in the late course of the disease, became comatose and died at 52 years of age. Chief postmortem findings: pituitary adenoma (chromophilic); colloid thyroid; adrenal adenoma; sclerosis of ovaries; pancreas histologically normal.*

On July 14, 1915, Mrs. E. A. W., aged 51, first entered the hospital on the advice of Dr. M. C. Smith of Lynn, Mass., with the major complaint of headaches. Her family history was negative and her past history essentially so, though she had never been a particularly vigorous woman. Her catamenia began at the age of 15, was always regular, and the menopause occurred abruptly in 1904 when she was 40 years old. She was married at 18 and her husband, a man of her own age, is still living. No children were born of the union; there were no miscarriages. In 1903 she had been operated upon for a glaucoma with excellent results.

*The Acromegaly.*—The chronology of her symptoms was somewhat difficult to determine because of the patient's want of observation and inaccuracies of memory. She had had dull, persistent headaches for many years, but the first recorded symptom possibly relating to the disease was of numbness in her hands and later in her feet, as if they were asleep. This began when she was about 30 years of age. Some 10 years later a period of drowsiness, lethargy and lack of ambition set in. She became restless, unable to concentrate, and suffered from dull, diffuse pains in the abdo-

men and back. Shortly after this, about 1905, she began to have more severe headaches located as a rule in the temporo-frontal regions, associated with photophobia and lachrymation. They became sufficiently intolerable as time went on to compel recumbency during the more severe attacks.

It was not until 1907 when she was 43 that the increasing stubbiness and pudginess of her fingers were first called to her attention by her friends, after which she herself observed that her nose was markedly enlarged and Dr. Smith, her dentist, noted a



FIG. 67.

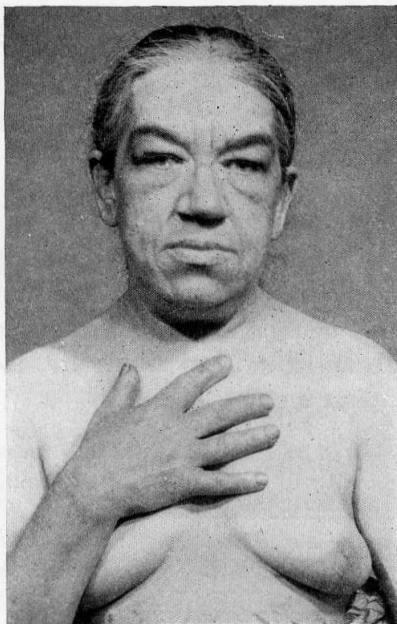


FIG. 68.

FIGS. 67 and 68. Case IV. Showing patient with acromegalic changes.

change in the conformation of the palate and alveolar arches, and recognized the condition as acromegaly.

The *physical examination* showed a woman of small stature who was only 5 ft. 2 in. in height and weighed only 151 lbs. But her head, hands and feet showed the typical configuration of an advanced case of acromegaly (Figs. 67 and 68), with prognathism and the characteristic tufting of the terminal phalanges shown by the X-ray. Her features were coarse, nose broad, the lips thick and eyelids puffy. The skin was coarse and bathed in perspiration. There were many pigmented moles particularly in a zone about the lower thorax (Fig. 68), and several fibromata mollusca. Her tongue was large, thick and unwieldy; the tonsils greatly hypertrophied. The hair of the head was coarse and oily and the hirsutes of pubes and axillæ abundant.

The sella was greatly enlarged (Fig. 69), measuring 25 mm. in an anteroposterior dimension and 20 mm. in depth. There was some pallor of the optic discs and the visual fields showed an upper bitemporal field defect with complete hemianopsia to colors in the right eye.

No evidence of change in the other endocrine organs was made out; the thyroid was not palpably enlarged. Routine blood and urine examinations were negative. Blood-pressure 150/90. No metabolism observations were made owing to Dr. Boothby's absence during the early months of 1915.

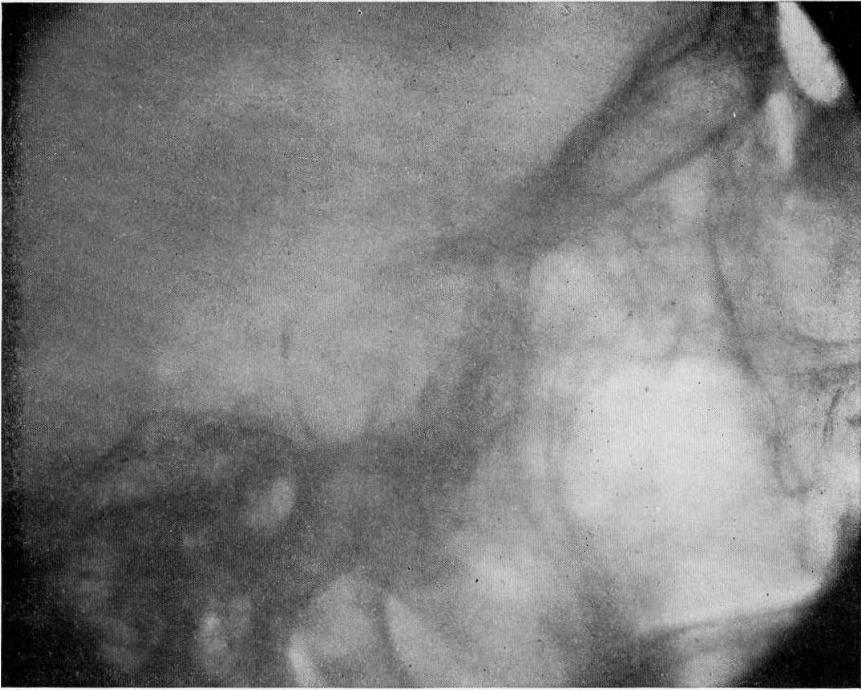


FIG. 69. Case IV. To show the ballooned sella.

A transphenoidal operation was performed, on *July 16, 1915*. A tense glandular capsule was exposed, on incising which soft adenoma immediately began to extrude itself. An unusually large amount of tissue for the time (1915) was successfully removed. This was then reported as showing on H. and E. stains, "the usual type of closely packed pituitary struma without granules." However, a more recent examination of the tissue, with special stains, shows the cells, many of which are multinuclear, to be uniformly filled with coarse chromophilic granules.

She made an excellent recovery from the operation with complete cessation of head-



aches; prompt restoration of the visual fields to their normal peripheries. 10 days after the operation she was discharged.

Two months later, *Sept. 28, 1915*, she was readmitted for study. Though the "numb feeling" in her hands persisted, her general strength was much improved, she had lost her drowsiness, and had been able to engage in her domestic work. She had acquired an unnatural appetite and had gained over 10 kilos in weight. In spite of this, her lips, eyelids and hands were less puffy than before. Her basal metabolic rate was determined at the time and found to be +15 per cent. The urine was negative and contained no sugar on a single examination.

Four months elapsed when, on *Jan. 21, 1916*, she was again readmitted. She had been doing surprisingly well until a month previously when she began having polyuria with pruritus vulvæ. She had finally consulted her physician who examined her urine and found 5 per cent of sugar. The mellituria was not well controlled by the treatment which was instituted. She acquired a troublesome cough, a 'caked' breast from a local infection, and was finally referred to the hospital.

Her condition on this readmission did not seem particularly serious and the urine showed only 1.8 per cent of sugar. However, on the 2nd day she became markedly dyspnoic; acetone and diacetic acid were found in the urine. She was given sodium bicarbonate intravenously and by mouth with only temporary improvement. Two days later she became comatose and died.

The autopsy was performed by the then resident pathologist, Dr. E. W. Goodpasture, 2 hours after death. The essentials of the report are as follows:

#### THE BODY CAVITIES.

**THORAX AND ABDOMEN:** Both cavities showed normal serous surfaces with a somewhat unusual amount of fat.

The *heart* weighed 460 gm. There was much epicardial fat and the coronary arteries showed a few patches of atheromatous degeneration. The base of the aorta was also streaked with subintimal atheromatous areas. The myocardium appeared normal and proves to be so histologically. The valves were normal.

The *lungs* showed no especial change except for a patch of bronchopneumonia with mild muco-purulent bronchitis. The bronchial and mediastinal lymph glands were not modified.

The *liver* was enlarged, weighing 2500 gm. Its cut surface was yellowish and shows microscopically the presence of a considerable amount of fat but is otherwise normal except for the abundance of glycogen in the nuclei, almost pathognomonic of a diabetic liver.

The *spleen* was slightly enlarged weighing 240 gm. Its cut surface had a dark purplish color; small discrete Malpighian bodies were visible. The organ appears histologically to be normal.

Both *kidneys* were large, the left weighing 395 gm. and the right 300 gm. The

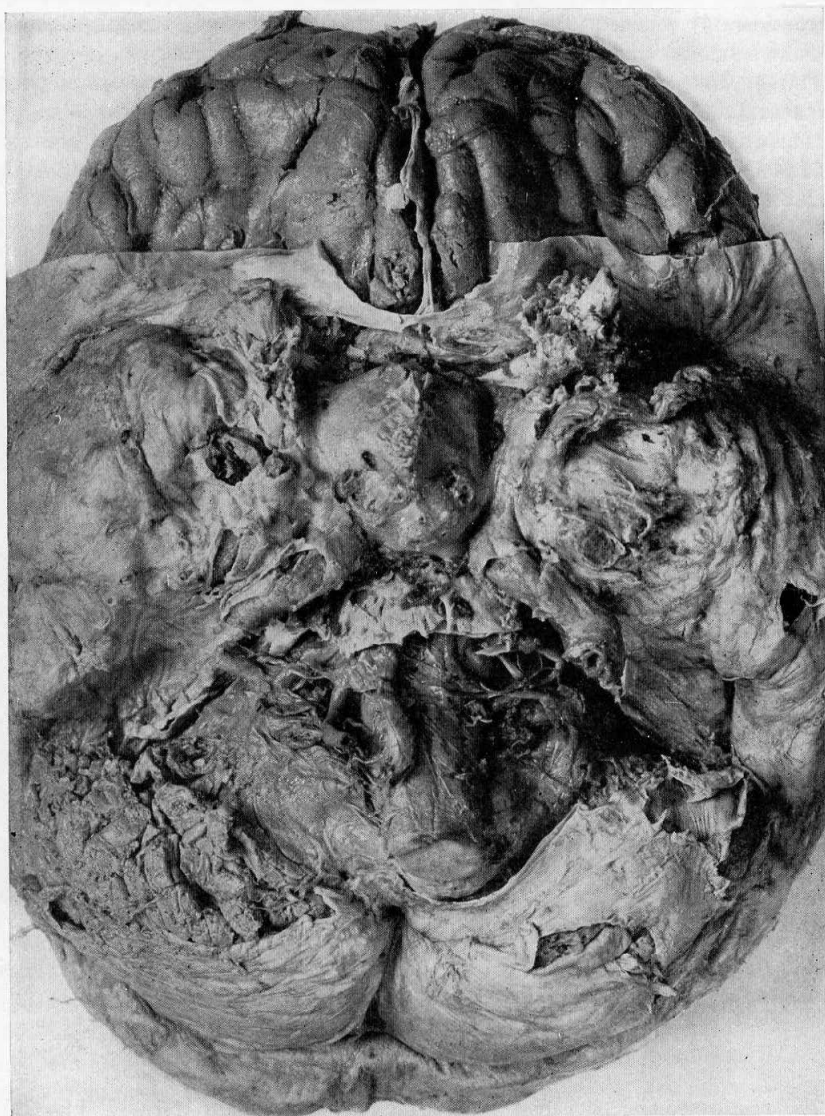


FIG. 70. Case IV. Base of brain (reduced) to show size of adenoma after chipping away base of sella turcica; also scar of previous transphenoidal operation.

surfaces were smooth but more yellow than normal. Sections showed the cortex to be considerably widened (9 to 10 mm.) and irregular. The right renal pelvis contained a small calculus. Histologically they show nothing noteworthy.

The *gastrointestinal tract* appeared normal throughout except for a few small polyps and a small diverticulum in the lower part of the descending coloh.

**HEAD:** Nothing unusual was noted regarding scalp or cranium. The brain was fixed *in situ* by carotid injection as usual. It was removed in its envelopes together with the sellar structures holding the hypophysial tumor. The adenoma proves to be 2 cm. in width. It shows the central healed scar of a preceding operation (Fig. 70). The brain showed no other external abnormalities.

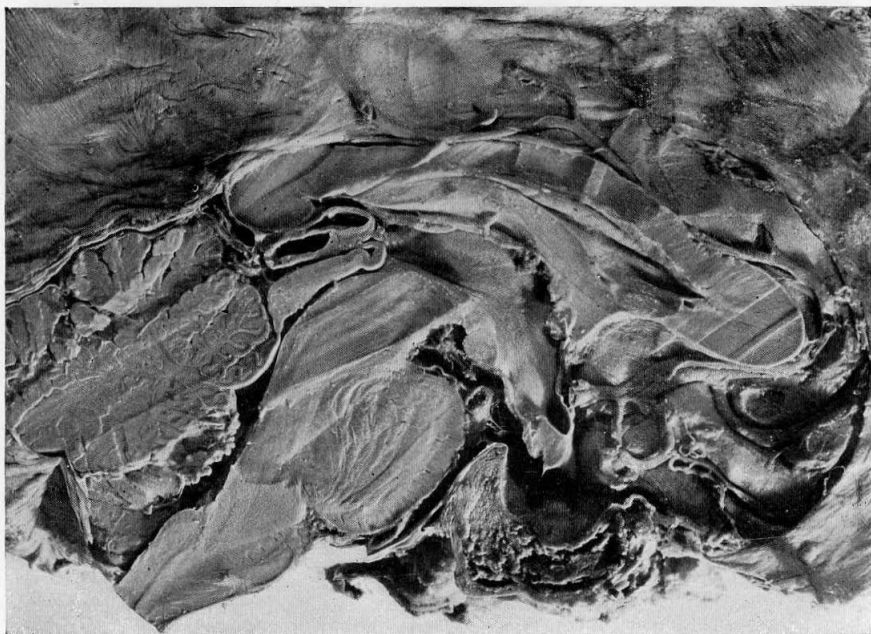


FIG. 71. Case IV. Sagittal section of brain showing cup-shaped hypophysial adenoma lying remote from chiasm and IIIrd ventricle.

#### THE ENDOCRINE SERIES.

*The pituitary body:* A medial sagittal section of the brain revealed (Fig. 71) a distinctly enlarged crescent-shaped hypophysis with a posteriorly placed flattened area 3 mm. in width which was taken to represent the posterior lobe. The tissue was soft and crumbly. Surrounding the gland was a dense, fibrous capsule about 2 mm. in thickness. The superior diaphragm was concave and above it was a large cisterna chiasmatica. There was no possible suggestion that the chiasm could once

have been pressed upon by the tumor mass which must therefore have greatly diminished in size.

Histologically the tissue resembles that removed at operation (Figs. 72-74), and proves to be composed of a loose mass of round cells, with apparently no connective-tissue stroma whatever, and practically no blood-vessels. In the peripheral portion, there is a narrow zone of cells just inside the dural capsule which are arranged in columns like the normal pituitary gland. With ordinary stains the nuclei prove to be

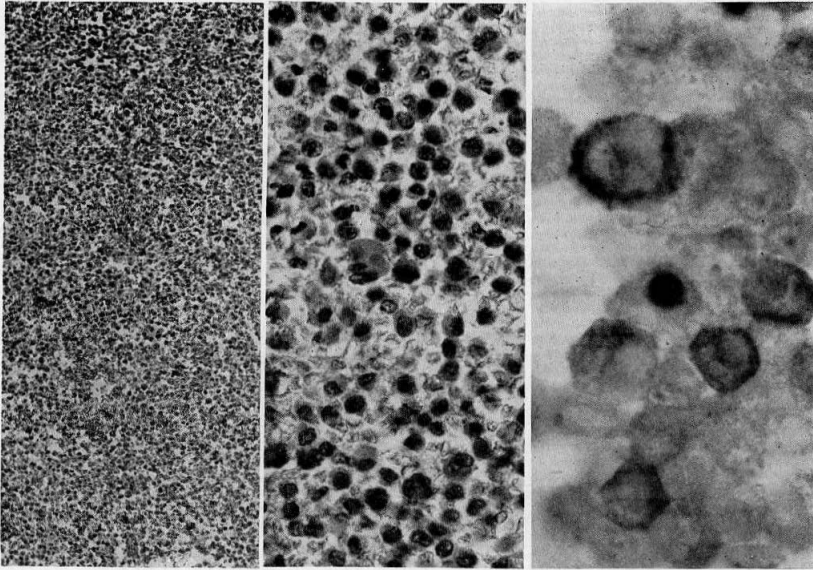


FIG. 72.

FIG. 73.

FIG. 74.

FIGS. 72-74. Case IV. Showing the adenoma ('struma') composed largely of a structureless mass of cells, many of which are strongly acidophilic. Left, H. and E. stain ( $\times 80$ ); centre, H. and E. stain ( $\times 300$ ); right, ethyl violet orange G, showing alpha granules ( $\times 850$ ).

vesicular with a heavily staining nucleolus. Some of the cells are multinuclear. With special stains the majority of the cells show masses of coarse alpha granules. On the periphery of the central structureless mass of essentially chromophilic cells, where compressed cell columns of glandular tissue are present, both acidophilic and basophilic granules occur. The conditions are very similar to those found in Case I and give evidence of a central adenoma.

The *pineal gland* (cf. Fig. 71) shows two small cysts.

*Thyroid*: The gland appeared normal in size and consistency, of the usual brownish color and presented on section numerous small cysts, the largest one in the upper

left lobe about 1 cm. in diameter, containing blood-tinged fluid. Histologically (Fig. 75) the gland proves to contain possibly an excess of colloid, but it is well within the limits of normality. In one area a cluster of lymph follicles (Fig. 76) are present with

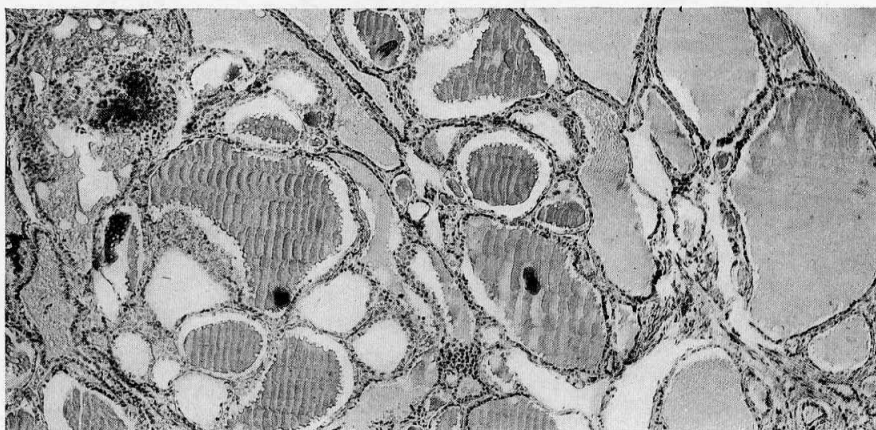


FIG. 75.

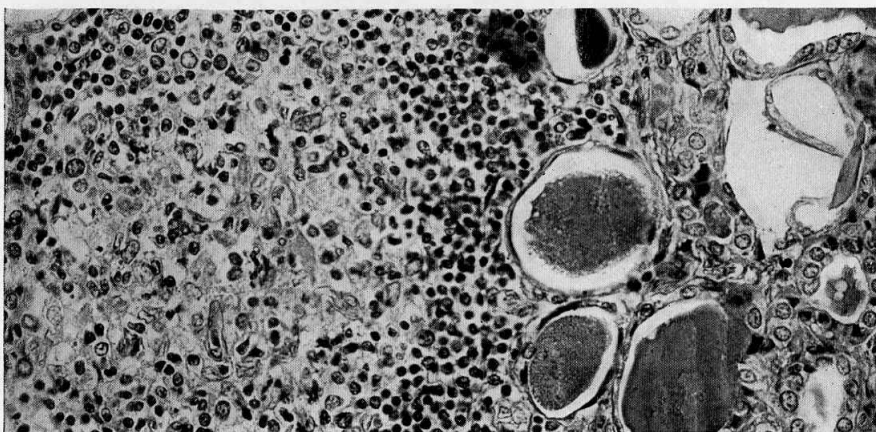


FIG. 76.

FIGS. 75 and 76. Case IV. Slightly colloid thyroid ( $\times 80$ ). Margin of germinal centre ( $\times 300$ ).

endothelial-like cells in their centre. No hyperplasia of the epithelium is anywhere apparent.

*Parathyroid:* No glandules were identified.

*Thymus:* On the removal of the sternum there were found in the fat of the mediastinum some small islets of grey tissue taken for thymic tissue of which there was cer-

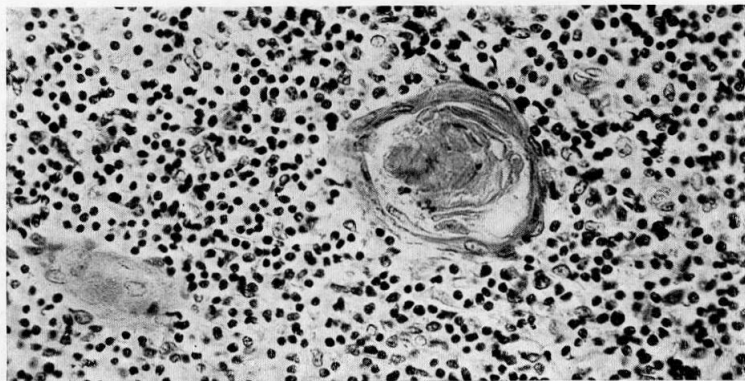


FIG. 77. Case IV. Normal thymic tissue. Stain H. and E. ( $\times 300$ ).

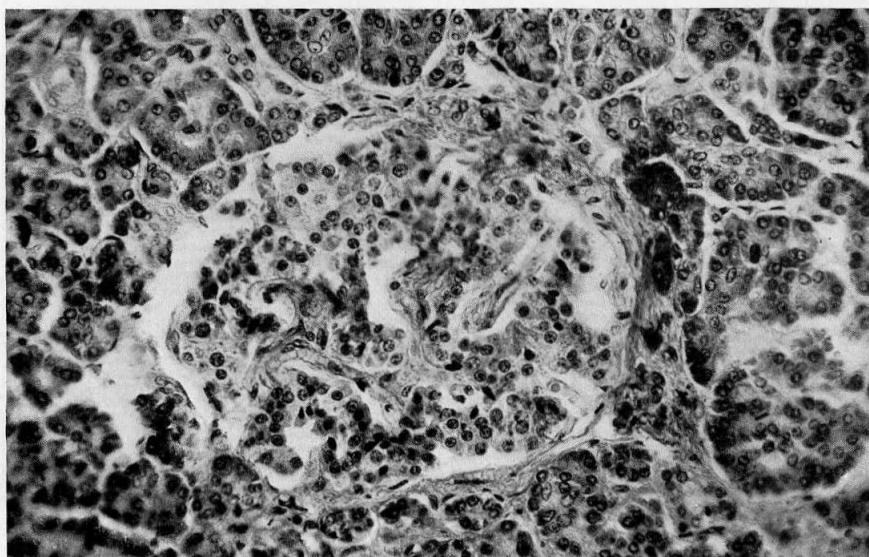


FIG. 78. Case IV. The only slightly sclerosed island of Langerhans found in the slides examined ( $\times 250$ ).

tainly no increased amount. A section of the tissue showed Hassall's corpuscles to be prominent and lymphoid tissue abundant (Fig. 77).



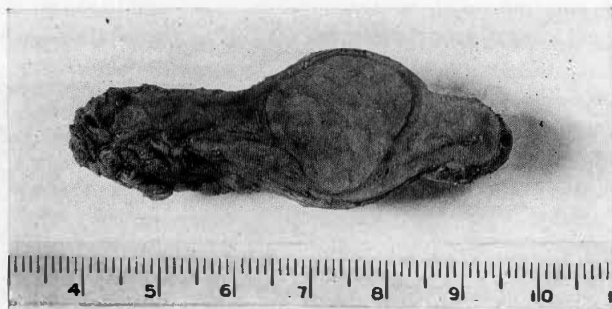


FIG. 79. Case IV. Left adrenal gland with cortical adenoma.

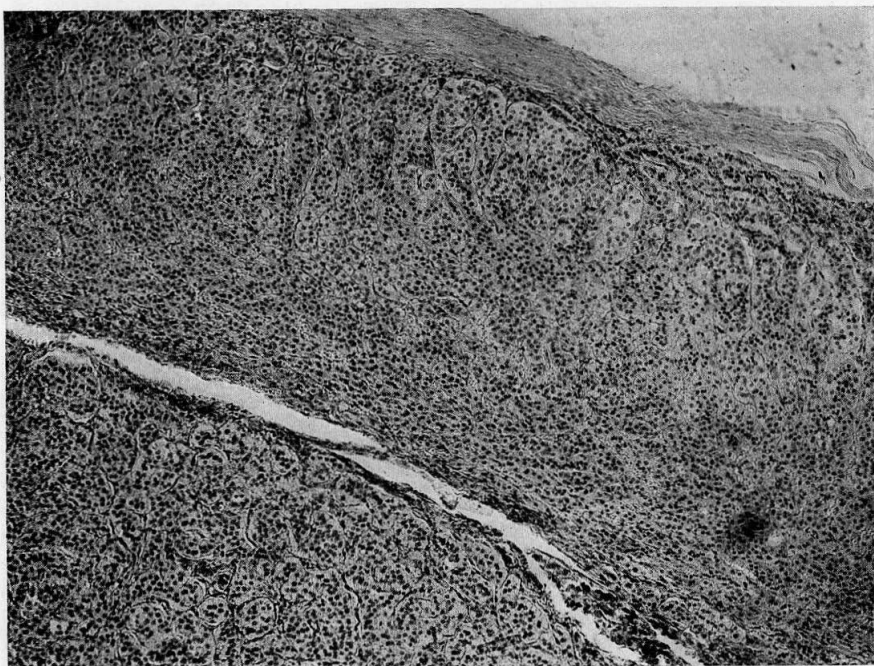


FIG. 80. Case IV. Adrenal cortex with subadjacent cortical adenoma. Stain H. and E. ( $\times 80$ ).

*Pancreas:* It was described as normal in size and consistency, of a light yellowish-grey color with glistening lobules and no apparent increase in connective tissue. Microscopically there are no discernible abnormalities. Zymogen granules are abundant in the acinar cells. The islands appear quite normal: none are hyalinized;

the cells show no hydropic changes; a single island on long search is found to be slightly sclerosed (Fig. 78).

*Adrenals:* Both were moderately enlarged. The right weighed 8 gm. and was normal in its configuration. The left weighed 10 gm. and contained a round, smooth tumor mass 2 cm. in diameter (Fig. 79). The tumor on section was soft, yellow and greasy-appearing, definitely circumscribed and resembling cortical tissue. It was so located in the central portion of the medulla as to be surrounded on all sides, first by a thick layer of translucent medulla-like tissue and then by a thicker zone of yellow cortical substance. Microscopically the single large adenoma proves (Fig. 80) to be of compact cortical tissue. It is somewhat encapsulated and is partly surrounded by compressed glandular tissue which may be medullary tissue. There are numerous microscopic adenomatous islands scattered through the remainder of the gland.

*Pelvic organs:* The uterus appeared normal in size. The bladder showed numerous small mural cysts in the mucosa. The cervix uteri showed a small polyp 3 cm. in length. The fundus of the uterus presented cysts similar to those in the bladder and mucosa. The *ovaries* were described as small and fibrous. Unfortunately no sections appear to have been taken of them and the tissues have been lost or mislaid.

*Anatomical diagnosis:* Pituitary adenoma; moderate splanchnomegaly of liver, kidneys and spleen; colloid thyroid; adenoma of left adrenal; sclerosis of ovaries; normal pancreas (in spite of diabetic coma).

*Comment.*—Here, then, was a comparatively mild though clinically unmistakable example of acromegaly in a woman in whom the evidences of overgrowth had not appeared until relatively late in life, or at least were not recognizable until then. ● One may reasonably doubt whether a pathologist, who had not seen the intact body after death, could possibly have reconstructed the clinical syndrome from a study of the organs alone. The diabetes would probably have been suspected by the glycogen deposits in the hepatic cells; there was an adenoma in one adrenal, a slightly colloid thyroid and an hypertrophied hypophysis, but it is doubtful if the cause of death, unless it might have been ascribed to the mild bronchopneumonia, could have been positively determined.

It is regrettable, since this case concerns the only female patient of the four, that there were no histological studies made of the ovaries. They, however, were described as small and sclerosed and doubtless on gross appearance were taken to represent the normal organs of a woman of her age. Certainly there was nothing about them to have suggested the mulberry ovary of Evans' experimental hyperpituitarism in rats nor, so far as the writers are aware, has such an ovary ever been observed or described in the human. It may be recalled that normal and regular

menstruation continued, or so her history records, until she was 40, that is, some 10 years after the onset of the numbness and tingling which were considered to be indications of the onset of her disorder. This is an unusual occurrence, for though there are exceptions to most rules in acromegaly, when the disease affects women amenorrhœa is apt to be one of its early symptoms.

In marked contrast to the other three cases in the series, the pathological findings aside from a moderate splanchnomegaly and a single adenoma in the adrenal were relatively inconspicuous. And it is our impression from the cases in the literature that on the whole the secondary splanchnomegaly and enlargement of the endocrine series are much less conspicuous in acromegalic women than in men, for some, as yet, unexplained reason.

In this case, the crescent-shaped hypophysis in itself hardly filled the enlarged sella. Indeed the superior diaphragm was depressed instead of bulging, and there was a large suprasellar arachnoid cistern. One is inclined to believe that the adenomatous lesion had either retrogressed or had been stayed as a result of the comparatively recent operation.

#### *The Skeletons of Cases II and III.*

The skeletal changes in acromegaly were so ably and graphically described even before Marie's original account of the disease as to make repetition superfluous. Indeed one could scarcely improve on Brigidi's detailed description<sup>12</sup> of the skeleton of the unfortunate *Ghirtenzoni* published in 1877 long before acromegaly was baptized; and though Brigidi, it may be added, was the first to make mention of the enlarged sella and its contained tumor, he regarded the disease as primarily skeletal in origin.\*

Most of the more characteristic bony changes are now familiar and are in daily use as an aid to diagnosis through the medium of röntgenology. It therefore is hardly necessary for us to more than briefly comment upon the two skeletons which we were privileged to remove, the more so since we wish particularly to dwell in this report upon the splanchnomegaly

\* Descriptions of the acromegalic skeleton have been given by Virchow (1889),<sup>91</sup> Thomson (1890),<sup>90</sup> Osborne (1897),<sup>73</sup> Regnault (1896),<sup>79</sup> Israel (1901),<sup>50</sup> Keith (1911)<sup>52</sup> and many others.

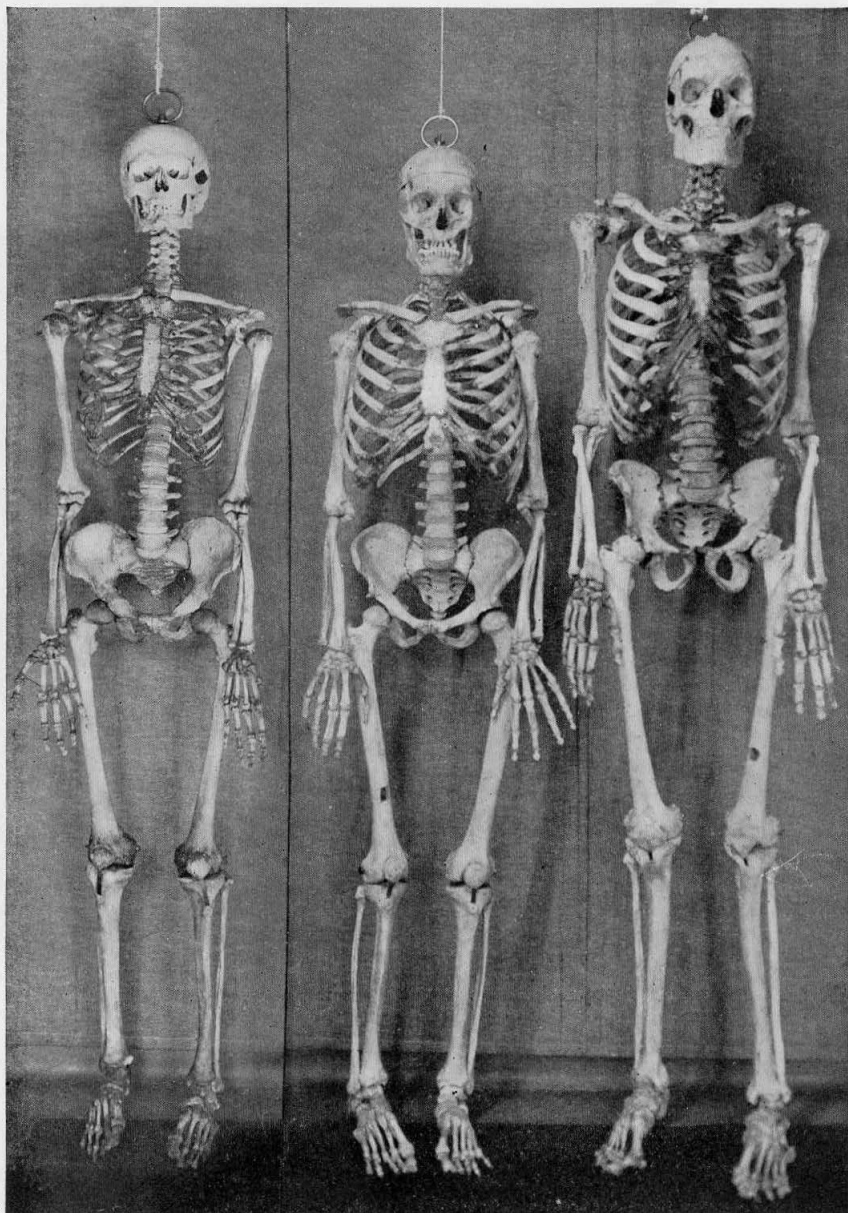


FIG. 81. Skeleton of a normal adult contrasted with those of Case III and Case II in the anterior aspects.

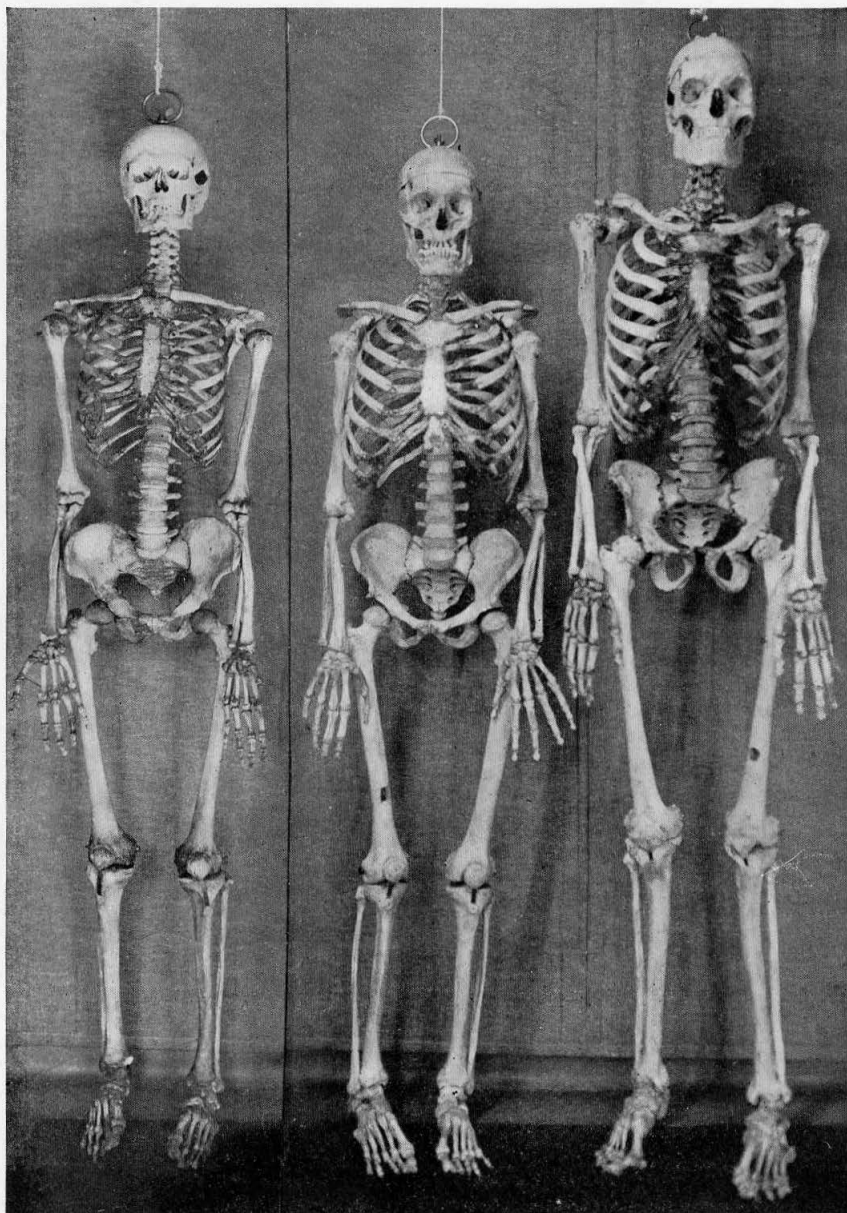


FIG. 81. Skeleton of a normal adult contrasted with those of Case III and Case II in the anterior aspects.

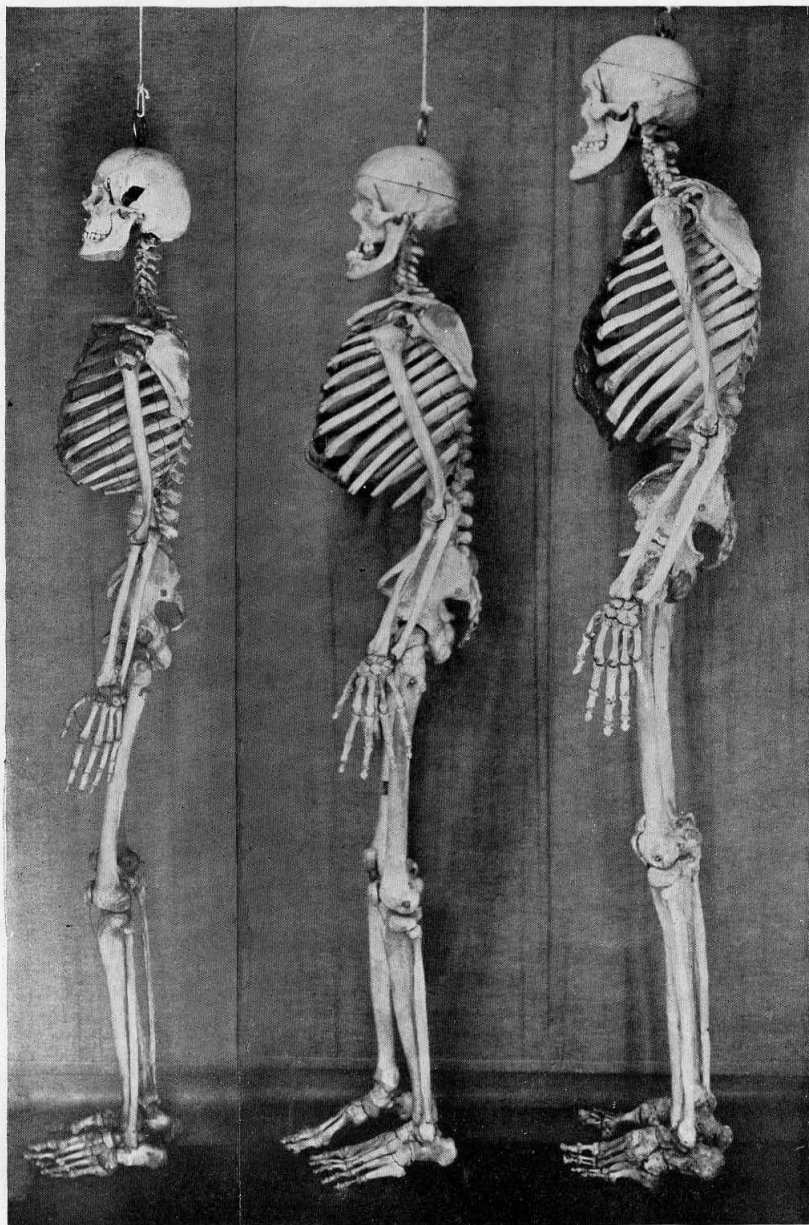


FIG. 82. The skeleton of a normal adult contrasted with those of Case III and Case II in the lateral aspects.



and endocrine changes. However, it is unusual to have two acromegalic skeletons for study, side by side, and the contrast in these two happens to be extreme, one being of an acromegalic giant with widespread periosteal bony changes, whereas the other was a relatively small individual with changes chiefly limited to the acral parts.



FIG. 83.

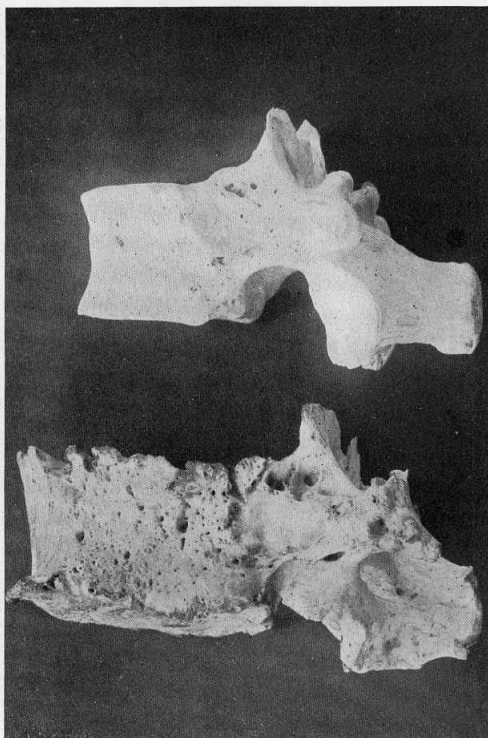


FIG. 84.

FIGS. 83 and 84. The eleventh thoracic vertebra of Case II compared with the normal, to show the extraordinary hyperostotic changes.

Notable and characteristic of most examples of the disease are (1) the sellar enlargement, and (2) the tufting of the terminal phalanges which in one of the patients in our series was so marked that a bony spur actually protruded underneath the nail through the skin of the great toe, crowding the nail backward. It is these two particular osteological tell-tales of the disease that chiefly serve, through the medium of the X-ray, as an aid in diagnosis in early and mild examples of the disease.

The process, however, is a general one and the skeleton in advanced cases is markedly and characteristically changed throughout. Some of the more notable deformities such as the dorsal kyphosis and the bovine chest with its flat ribs and greatly increased anteroposterior diameter are well shown in the accompanying figures (Figs. 81 and 82), in which the two skeletons are contrasted with that of a normal adult.

In the skeleton of pure gigantism such as that at the Wistar Institute pictured in Hinsdale's monograph,<sup>48</sup> the bones are long rather than mas-

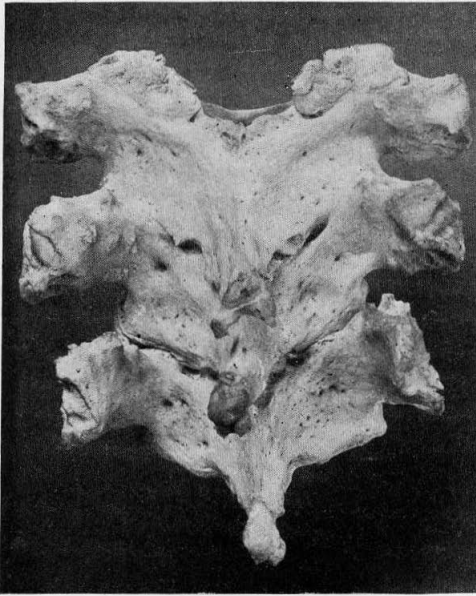


FIG. 85.

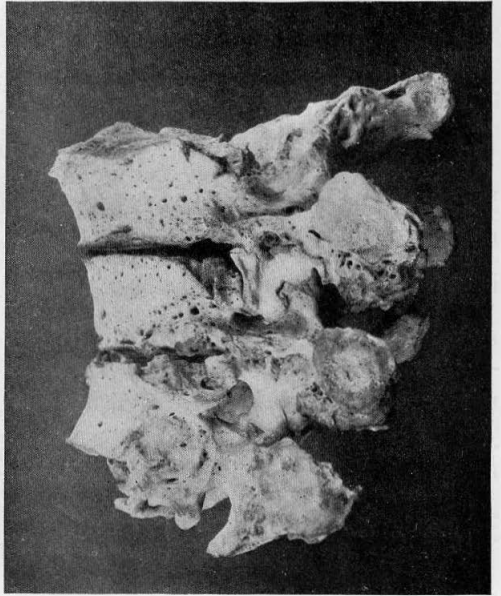


FIG. 86.

FIGS. 85 and 86. To show the fusion of the three upper thoracic vertebræ of Case II with practical occlusion of the intervertebral foramina. (Reduced.)

sive as in extreme degrees of acromegaly, the two conditions differing supposedly in that there is increased epiphysial growth in the one and largely periosteal bone formation in the other. The skeleton of our Case II, shows how all the points of muscular attachment may become greatly roughened and hypertrophied. The vertebral exostoses, for example, (Figs. 83 and 84) may become so excessive as actually to fuse one vertebra to another (Figs. 85 and 86) so that even the intervertebral foramina are solidly closed.

The changes in the skull, particularly in respect to the mandibular deformation, are too well known to deserve special mention. However, a comparison of the three crania seen from below serves to make the disparity between the relatively small superior maxillæ and the misfit mandibles of the two acromegalic skulls particularly striking (Fig. 87). Not only is the arch of the lower jaw broadened and lengthened but the mandibular angle is greatly increased as shown particularly in Case III on the lateral views (Figs. 88 and 89). The mandibular deformity, as

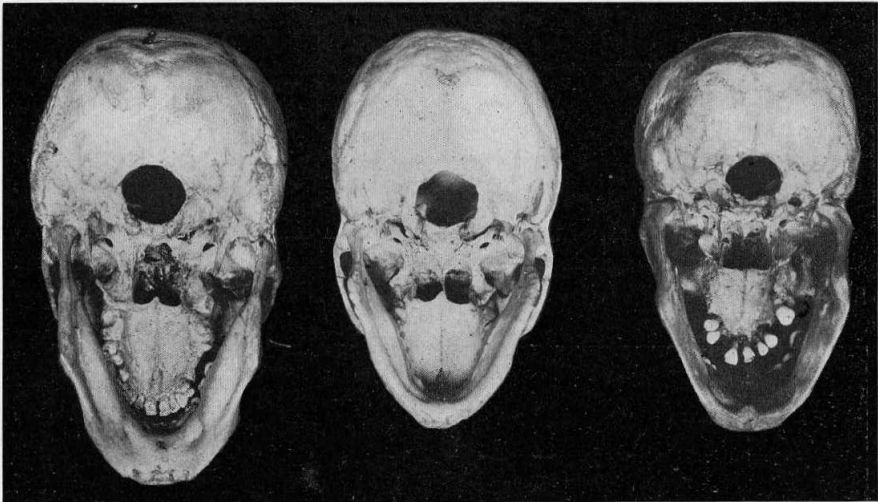


FIG. 87. Inferior aspects of the skulls of Case II (left), a normal skull (centre), and Case III (right), to show the mandibular hypertrophy of the acromegalic skulls.

well known, may be most asymmetrical and in the front view of the three crania (Fig. 90) it may be seen that the molar teeth of the larger skull are in opposition only on the left side, the lower teeth of the opposite side being 2 cm. outside of those of the upper jaw.

The configuration of the sella turcica is naturally an important consideration in the skeletal deformations provoked by the disease, for it serves in the majority of cases as a measure of the size of the hypophyseal adenoma. This, however, is not invariable as the cases in the present series will exemplify. For it is only when the enlarging lesion remains long confined within the sellar envelopes that the fossa becomes hugely

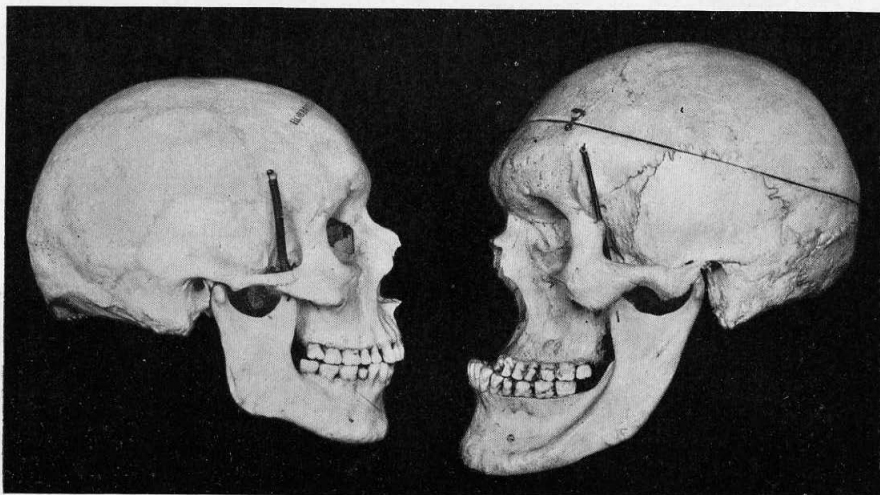


FIG. 88. Lateral aspect of the cranium of Case II compared with a normal adult skull. The maxillary spur in the acromegalic skull had been removed in the transphenoidal operation.

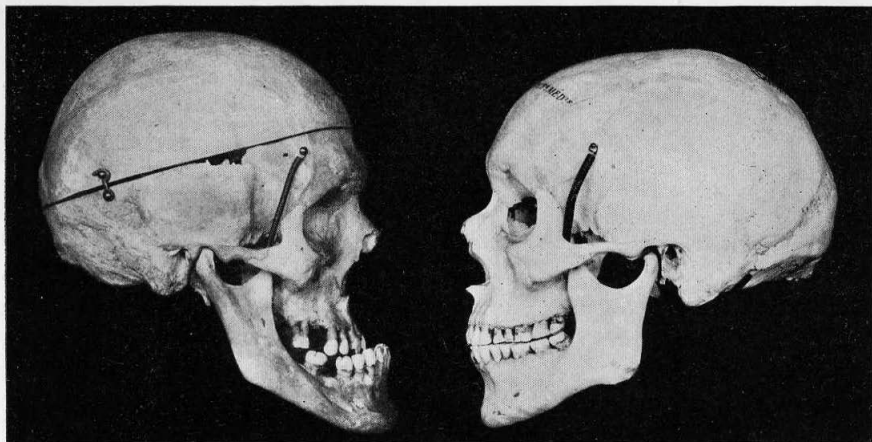


FIG. 89. Lateral aspect of cranium of Case III compared with the normal skull.

distended. When, as in Case III, the growth has broken through the envelopes early in its progress the sella may remain relatively small, or when the adenoma never attains any considerable size the fossa as in Case I may not appear to be enlarged at all. But even under these circumstances it is apt to be heavy in outline, sharing as it does in the general bony overgrowth. And even when there is a large tumor, such as was present in the acromegalic giant (Case II), bone production accompanies the pressure absorption which accounts for the huge dorsum sellæ seen in this particular case (*cf.* Fig. 23).

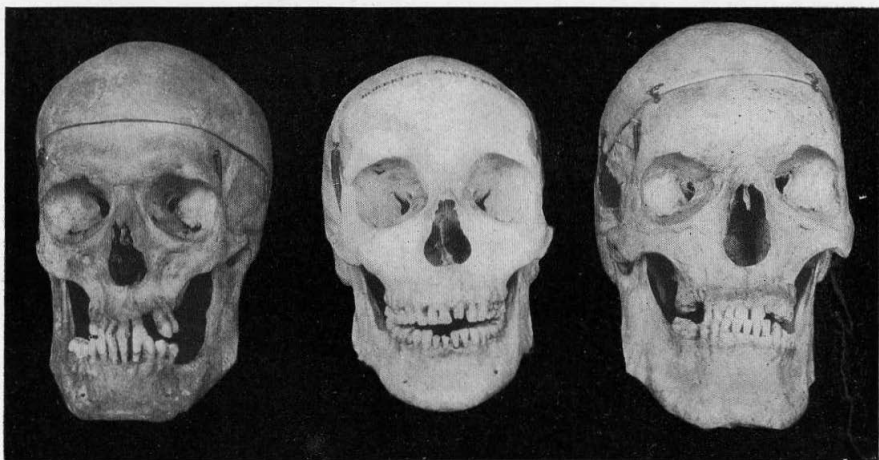


FIG. 90. Anterior aspect of the three skulls, Case III, normal, and Case II, to show malocclusion of teeth. The vomer of the acromegalic skulls was removed in the transphenoidal operation.

There is another change that takes place in the skull, less commonly mentioned, namely the great increase in thickness and density of the cranial vault, more pronounced in the frontal region. This in some cases may be seen radiographically to increase from year to year. In one of our cases after an interval of several years the vault was found to be almost doubled in thickness.

### III.

#### GENERAL DISCUSSION.

Interest in the subject of the postmortem findings in cases of acromegaly has unquestionably waned if one is to judge from the fact that most of the reports in the literature prove to be more or less contemporaneous with the primary wave of curiosity about the malady which followed Marie's papers. This is surprising since proportionately many more deaths of acromegalics must occur in hospitals in recent years than formerly owing to the increasing interest in the surgical aspects of the malady. If this is true, not many of the cases have come to be described in print, and of late years the results of few postmortem examinations have been given in any such detail as, for example, was the well-studied case reported in 1913 by Reinhardt and Creutzfeldt.<sup>20</sup>

The earlier autopsies, notably those which antedated Marie's first account of the disease,<sup>64</sup> were given over, naturally enough, to detailed descriptions of the striking hypertrophy of the skeleton and its coverings. However, Brigidi in 1877,<sup>12</sup> Henrot in 1882, Klebs in 1884<sup>10</sup> and Lancereaux in 1885<sup>55</sup> had all previously described an enlargement of the sella with pituitary tumor in cases we now recognize to be acromegaly; but other changes in the body were so striking that the significance of this particular finding was obscured and remained unemphasized.

In 1887 the woman *Héron veuve Beaufils*, one of the two patients described the year before in Marie's classic paper, died at the Salpêtrière and Marie was given his first opportunity to examine postmortem an example of the disease he had named. The first published report upon the autopsy findings by August Broca<sup>13</sup> in 1888, was devoted solely to the skeletal changes, which suggests that they were still the matter of chief interest at the time, even though Minkowski<sup>69</sup> the year before had clearly suggested the probable or possible pituitary etiology of the disease. Marie, however, was not yet ready to acknowledge the hypophysial parentage of the child he had baptized, if one is to judge from his statement in *Brain* in 1889,<sup>65</sup> wherein the possible relationship is first mentioned in his papers.



"Independently of the bones of the limbs [he says], I may point out the considerable hypertrophy of the vertebræ, the sternum and the clavicles. The frontal sinuses are the seat of a very well-marked dilatation. Finally, amongst the lesions affecting other organs, and which after what has been observed in other autopsies seem to me to be constant in acromegaly, must be mentioned hypertrophy of the pituitary body with enormous dilatation of the sella turcica, persistence of the thymus, and finally hypertrophy of the cord and ganglia of the sympathetic system. Until proof to the contrary is brought forward I shall cling to the belief that these last three anatomopathological characters manifest themselves not only with a remarkable degree of frequency, but may even be looked upon as constant."

And when with Marinesco the final account of the autopsy on the *Héron* woman was ultimately published in 1891,<sup>67</sup> they say: "On ne saurait voir dans cette lésion de la glande pituitaire une altération *sui generis*, spéciale à l'acromégalie, d'autant plus qu'on ne connaît pas la relation qui existe entre cette maladie et la tumeur pituitaire." They were unable even to subscribe to Klebs' opinion that "the hyperplasia of the pituitary body is simply a partial manifestation of the process of hypertrophy of all the contents of the cranium." And their conclusions were that acromegaly was a general, systematized, and progressive affection with its principal location in the connective tissues of the extremities, of certain organs, and of the mucous membranes, the enlargement of the hypophysis being placed in the same category as that of the sympathetic nervous system.

One must remember, of course, that the pituitary body was still looked upon in the nature of a vestigial relic, for it was not until 1894 that its extracts were first shown to have physiological activity. Nevertheless, in retrospect, Marie's evident reluctance to pin acromegaly on the hypophysis is the more curious when one comes to read the protocol of the *Héron* case in which the pituitary tumor stood almost alone among the visceral hyperplasias. When one considers the widespread gross alterations of the organs that may be encountered—such as were found, for example, in Case I of this present report in which the hypophysis was to all outward appearances normal—the association of the pituitary tumor with the *Héron* woman's acromegaly would have seemed obvious. For though the spleen was large there was apparently no general splanchnomegaly, and the adrenals, contrary to the usual rule, were atrophied, as was also the thyroid.

It was this finding of an atrophied thyroid that appears to have led Marinesco to have removed the thyroids of three rabbits with the result that what was taken to be a compensatory hypertrophy of the hypophysis showed in two of them. And this finding had much to do, apparently, with Marie's acceptance of Rogowitsch's (1889)<sup>83</sup> hypothesis that these two glands, hypophysis and thyroid, were concerned with the neutralization of certain substances whose retention exerts a toxic action on the central nervous system. The accumulation of these toxic substances in the extremities through some special predisposition of their tissues was what led, in Marie's opinion, to the hyperplasia. Consequently it was to the histological study of the hypertrophy of the nose, tongue and digits that his pathological report with Marinesco was largely devoted.

To be sure the one unfailing symptom, of full-blown examples of acromegaly at least, are these tissue-hyperplasias on which Marie laid such stress; and he showed clearly that there is an hypertrophy of all the elements—bone, fat, skin, nerves and glands—but with particular emphasis perhaps to be laid on the increase of connective tissue.

These hypertrophic changes in the acral parts, however, are merely an expression of the general overgrowth; and though they represent the outwardly striking manifestations of the disease, the accident of the age of onset is apparently all that makes these peculiarities of acromegaly differ from the overgrowth in gigantism. This, to be sure, has not yet been proved experimentally, but now that we are able to produce giant rats we should be able to produce acromegaly by the same procedure, provided we use a species of animal like the dog whose epiphyses become closed when normal growth is attained.

But Marie, if we mistake not, was inclined to ascribe even the splanchnomegaly—the spleen happened to be the only organ markedly enlarged in the *Héron* case—in large part to the same cause, namely to hyperplasia of its connective-tissue elements, a view which seems to us, from a study of our own cases, quite untenable. However, many divergent views on this subject have been expressed. Reinhardt and Creutzfeldt,<sup>80</sup> for example, while ascribing the overgrowth of mesodermal tissues to an abnormal secretion of the pituitary adenoma, attribute the enlargement of the ectodermal organs to the secondary functional disturbances of metabolism, which seems to us merely to be beating round the bush.

At the present day we are far less interested (possibly too little inter-

ested) in these hypertrophic changes in the extremities than in the modifications of the viscera, and though the protocols of our four cases contain the usual descriptions of sections taken from the skin, tongue, subcutaneous tissues and bone, they have been omitted since they bring out nothing new.

It may be said, however, in passing, that there is something essentially peculiar about the enlargement of the extra-skeletal tissues of the acral parts in these patients which must necessarily elude a purely histopathological examination. This had to do with the surprising diminution not only in the apparent but in the measured size of hands and feet which is often observed after an hypophysectomy, a fact which would indicate that there must be some form of tissue œdema which has a part in the enlargement of the skeletal coverings, particularly since the shrinkage in size may be apparent within a day or so after the operation. It may possibly have something to do with the character of the tissue fat which in two of the four autopsy protocols was emphasized as being of a particularly deep golden color. This, however, is more properly another story.

*Comparative Statistics.*—The cause of death in these four patients was as follows: In Case I from a progressive lethargy and weakness associated with widespread arteriosclerosis; in Case II from the secondary consequences of a huge intracranial extension of the adenoma; in Case III from cardiac incompetence leading to chronic passive congestion and anasarca; in Case IV from diabetic coma. In no two cases, in short, was the fatality ascribed to the same secondary effect of the malady upon other organs, and this variability in the cause of death is equally apparent in the cases in the literature.

In the 44 autopsied cases we have listed for comparative study, diabetic coma appears to have been the most frequently recognized cause of death (11 cases); cardiac failure is next in frequency (7 cases); the remainder are scattering—bronchopneumonia (2 cases), apoplexy (2 cases), malignant disease (2 cases), and so on. In 15 of the cases the cause of death was not specifically stated and may in many instances have been indeterminable and due either to the final cachexia of the disease or to the pressure effects of a large hypophysial tumor. However, in the ordinary postmortem examination of fatal cases of intracranial tumor, of myocardial failure or of diabetic coma one sees no such an array of amazing lesions as have been described in the four protocols which are the basis of this present paper.

Table Contrasting Weights of Normal and Acromegalic Organs.

	Height	Weight	Lungs	Heart	Liver	Kidneys	Spleen	Thyroid	Thymus	Adrenals	Pancreas	Gonads
			gm.	gm.	gm.	gm.	gm.	gm.	gm.	gm.	gm.	gm.
Normal male	172 cm.	70 kg.	920	350	1500	300	200	45	14±	12	80	22
Normal female	155 cm.	55 kg.		250								14
Case I: male aged 52 duration 30 yrs.	185 cm. 6' 2"	97 kg. 213 lbs.	2550	1050	3150	853	535	310	(?)	43	225	73
Case II: male aged 40 duration 13 yrs.	198 cm. 6' 6"	122.4 kg. 269 lbs.	1930	480	3380	565	385	105	8.2	43	83	23
Case III: male aged 35 duration 20 yrs.	173 cm. 5' 8"	100 kg. 220 lbs.	(?)	1000	2480	650	(?)	100	78.0	30	150	(?)
Case IV: female aged 51 duration 21 yrs.	157.5 cm. 5' 2"	68 kg. 151 lbs.	(?)	460	2500	695	240	(?)	(?)	18	(?)	18
Largest recorded weights			Osborne 2922	Osborne 1275	Dalle- magne 5900	Dalle- magne 1170	Lewis 1169	Geddes 312	Case III	Schultze 57	Lau- nois 250	(?)

Acromegaly being a ductless-gland disorder, in view of the known physiological interrelation of these organs, might be expected to show changes in these functionally related structures which could so alter them as to give recognizable histopathological alterations; but what is striking is the fact that in no other endocrine affection, whether primarily thyroid, adrenal, pancreatic, or what not, does there occur anything comparable to what happens in hyperpituitarism.

We have become thoroughly familiar with the acral enlargements, on which indeed the name of the disorder is based and on which its clinical recognition rests. We similarly are more or less familiar with the view that the disease is of hypophysial origin and apt to be accompanied by tumor. But the extraordinary splanchnomegaly which seems to characterize most of the cases and which is often out of all proportion even to the large size of an acromegalic giant is less commonly appreciated; nor does the evident tendency of the other ductless glands to show adenomatous changes appear to have been sufficiently emphasized.

In the accompanying table (p. 90) the weights of the viscera and endocrine series of these four cases have been assembled and contrasted with the figures commonly accepted as normal for the average adult man and woman.

#### IV.

##### THE SPLANCHNOMEGALY OF THE DISEASE.

In the published autopsy protocols of cases of acromegaly one is apt to find detailed measurements of the body as a whole, and sometimes measurements of the enlarged organs; but surprisingly few of the reports give the weights of the various organs with any completeness, the terms "very large," "large," "normal," "small" and "atrophic" being all that is usually given. However, we have been able to find dependable figures for some of the organs, at least, from the 44 most completely recorded autopsies, which will serve for purposes of comparison.

*The Lungs.*—These appear to have been rarely weighed by pathologists and we have figures for only eight cases, all of which are fully twice the normal. The heaviest pair (*circa* 2922 gm.) were found in the remarkable case reported in great detail by Osborne in 1897;<sup>73</sup> the next heaviest were in our Case I (2550 gm. ); the third largest (1915 gm.) in the case reported by Widal, Roy and Froin in 1906.<sup>94</sup> It is interesting to note that these three cases were all ones with relatively small hypophyses and a disease of long duration.

*The Heart.*—The largest recorded heart was also in Osborne's case, with the amazing weight of 1275 gm.; the next largest was in our Case I of 1050 gm.; the next in Case III of 1000 gm.; these weights, needless to say, having been taken with the hearts emptied. Osborne's patient died of cardiac failure just as did our Case III, but this was not true of Case I which of the two had the larger heart. In Kraus' case (1920)<sup>54</sup> the heart weighed 950 gm.; in Widal's 875; and in Paviot and Beutter's<sup>76</sup> 830; the only other examples exceeding 500 gm. Several writers have been particularly struck by the absence of valvular disease or of arteriosclerosis to which the huge hearts sometimes seen in acromegaly might be ascribed. Death from valvular incompetence and resultant cardiac failure is not uncommon.

*The Liver.*—In all four of our cases it was greatly enlarged, and that this had no direct bearing on chronic passive congestion is shown by the fact that of the two smaller individuals in our four cases the liver in Case IV was even larger than was that in Case III in which there was a terminal cardiac failure.



The largest recorded liver was in Dallemagne's patient<sup>25</sup> with the astonishing weight of 5900 gm.; the next largest was reported by Launois and Roy<sup>56</sup> (4650 gm.); Brooks' case<sup>14</sup> of 4136 gm. was the next; then Dana's case<sup>26</sup> of 4074 gm.; Osborne's case<sup>73</sup> of 3545 gm., followed by Josefson's case<sup>51</sup> (3400 gm.); our Case II (3380 gm.); Kraus' case<sup>53</sup> (3220 gm.); and our Case I (3150 gm.)—all truly amazing dimensions for livers in the absence of any essential histopathological changes other than the chronic passive congestion which existed in some of them. The average weight of the 29 acromegalic livers, of which we find record, was 2783 gm., and in only four instances are the figures within normal or possibly subnormal limits.

The smallest liver was in Lewis' case<sup>58</sup> and weighed only 1080 gm. Another of only 1200 gm. was reported by Ballet and Laignel-Lavastine<sup>5</sup> in 1905; and the same authors in 1912 recorded<sup>6</sup> another of only 1350 gm.; but their first case was an acromegalic woman who with the exception of an enlarged thyroid had small organs throughout.

*The Kidneys.*—These like the liver are found to be almost uniformly hypertrophied. The average combined weight in the 25 cases in which figures were given was 576 gm. The largest pair (1170 gm.) was in Dallemagne's case; the next largest was Josefson's case (920 gm.); in our Case I (853 gm.); in Launois and Roy's case they weighed 715 gm. The only approximately normal weights were in the same two cases of Ballet and Laignel-Lavastine which were exceptional in showing small organs throughout.

*The Spleen.*—This is a much less dependable organ, for it can become permanently modified by influences which the anamnesis may fail to record. The average for the 24 cases in which the weight is given is 455 gm. The organ was particularly huge in Dean Lewis' case (1169 gm.); in Osborne's case it was also large (1119 gm.); in Dallemagne's case 920 gm.; and as will be recalled in Marie and Marinesco's case of *Héron* it weighed 695 gm. and was the only organ to which they specially called attention as being enlarged. It was at least twice the average normal size in our Case I (535 gm.), a man who had never had malaria or any other known malady to affect its size. On the other hand in Ballet and Laignel-Lavastine's female acromegalic the spleen like the other organs was extremely small and weighed only 45 gm. [*sic*], but this is the one notable exception recorded.

There is unquestionably some underlying law that affects the degree of splanchnomegaly which we do not yet clearly understand, though it is our impression that in female acromegalics it is much less pronounced than in males. Thus, the average weight of the heart in 15 male cases was 714 gm., and in 11 females 545 gm.; of the liver in 18 males 3013 gm., and in 10 females 2342 gm.; of the kidneys in 15 males 635 gm., and in 10 females 486 gm.; of the spleen in 15 males 528 gm., and in 9 women 311 gm.

The extremes are represented on the hypertrophic side by such cases as that of Dallemagne's in a 47-year-old man the course of whose malady lasted 15 years; by Osborne's case, a man of 47 with a 23-year course; by our Case I, a man of 52 with a 30-year course. On the normal or hypotrophic side fall the two cases of Ballet and Laignel-Lavastine so often quoted above as having small organs. These were both women, aged 70 and 60 respectively at the time of death; and one may again recall the case of Marie and Marinesco in which the splanchnomegaly was so inconspicuous as perhaps to have modified their whole conception of the nature of the disease which was supposed to have local rather than general effects on the body.

Whether the splanchnomegaly is due to an increase in the number of cells or in their size is uncertain. Some who have made studies to determine this have favored one, others the opposite view. Thus Schultze and Fischer<sup>84</sup> showed that the great enlargement of the kidneys in one of their cases was due to an increase in both the number and size of the cells, and stated that the glomeruli were three to four times the normal size. This as a matter of fact is very difficult to determine, and perhaps may best await the exact histological study and measurement of the organs of experimentally produced gigantism in the rat which represents a well standardized animal.

Others have explained the enlargement on still other grounds. Thus Amsler<sup>1</sup> expressed the view that the hypertrophy is due to an increased blood supply which is therefore secondary to the enlargement of the heart and blood-vessels, an opinion which bears a semblance to Klebs' original theory of the disease. So far as we know, however, no blood-volume determinations of these patients have been made.

As is well known, acromegaly is accompanied by notable cardiovascular changes. In all four of our cases the heart was enlarged, in two of them

enormously so: three times the normal size in Cases I and III; but that this has no bearing upon the size of the individual is evident from the fact that Case II, the largest of all, showed only a moderate cardiac hypertrophy. Reinhardt and Creutzfeldt (1913) in searching for an explanation of the cardiac enlargement (790 gm.) in their patient, an acromegalic with a height approximately equal to our Case I (*viz.* 184 cm.), failed to find any explanation of the hypertrophy on the part either of kidneys, valvular disease or arteriosclerosis. However, peripheral arteriosclerosis is not at all uncommon and was well marked in our Case I with a heart which weighed among the largest recorded. Case III on the other hand, whose heart, in the absence of arteriosclerosis or valvular disease was nearly as large, died from cardiac failure associated with generalized anasarca.

So far as the other viscera are concerned, Marie's attribution of the enlargement to an increase of connective tissue can hardly be sustained to judge from our own cases in which the huge organs on the whole have been well within histologically normal limits. Thus we may infer that the tendency to a disproportionate and widespread enlargement of the viscera is, generally speaking, a definite characteristic of the disease. Good examples in the literature are the cases reported by Linsmayer,<sup>59</sup> Bourneville and Regnault,<sup>11</sup> Chauffard,<sup>19</sup> Ravaut,<sup>78</sup> Launois and Roy,<sup>56</sup> and Fischer.<sup>37</sup> An exception to the general visceral enlargement appears to be the brain, whose weight ordinarily is recorded within normal limits for the patient's size. Also the genital organs are exceptions, for reasons to be touched upon later.

## V.

### THE ENDOCRINE SERIES.

The splanchnomegaly which we have been considering has been more often made the subject of comment than the secondary changes in the endocrine organs. These, indeed, are so much more widespread and manifest in acromegaly than in other known ductless-gland disorders as to make the disease stand apart from all the rest. They are so evident as to make one feel that the hypophysis must represent the most important member of the endocrine series.

But here there is some influence at play different from that which brings about the visceral splanchnomegaly, for some of the organs, like the gonads, tend to become atrophic, others like the pancreatic islets appear to become functionally inactive or at least are counteracted in their normal activity, whereas still others like thyroid, parathyroid, thymus and adrenal cortex are not only enlarged but appear to be functionally activated. What is still more apparent, as the following descriptions will show, is that these glands, like the hypophysis itself, tend to become adenomatous. One might almost speak of acromegaly, indeed, as a disease characterized by a pluriglandular tendency to adenomatous formations.

Theoretically all ductless-gland disorders, could we untangle them, may be assumed to centre about a primary and outstanding dysfunction of one or another individual gland, expressed either as a state of over-activity or a state of under-activity. The syndromes of Graves' and of Addison's diseases, of diabetes mellitus, of tetany, myxœdema, eunuchoidism, pubertas præcox and the hypophysial disorders, have all been interpreted on this assumption. There is much to say in favor of this conception of these various disorders, and as a working hypothesis at least we may still effectively use it, no matter what time may show to be the possible underlying basis, neurogenic or biochemical, of the several distinctive maladies.

The deficiency syndromes we may experimentally imitate by glandular extirpations, but the clinical effects of hypersecretion, if such they are, have largely baffled us owing chiefly to the difficulties of identifying

and extracting the active principle of the various glands in usable form. Curiously enough, this has been easier in the neural portion of the two glands closely associated with the nervous system: namely the adrenal medulla and neurohypophysis. But "adrenalin" and "pituitrin," though active substances, have far less to do with the clinical syndromes in question than have the substances, in the adrenal cortex and hypophyseal pars anterior, not yet chemically identified.

Cannon, to be sure, felt that he had produced exophthalmic goitre in the cat by anastomosing the phrenic and cervical sympathetic nerves, and though his interpretations of the effects of this novel procedure have not been generally accepted they nevertheless represent the first step yet taken to get behind the crude working hypothesis of primary glandular oversecretion.

Of all these efforts to reproduce the over-activity syndrome of these various glands by laboratory procedures, the production of experimental hyperpituitarism (gigantism) in rats by H. M. Evans and his co-workers<sup>33,35</sup> has been the one outstanding success and we may hopefully look forward to the experimental production, likewise, of acromegaly. Only when this time comes shall we be able to throw light on the visceral splanchnomegalies and on the secondary alterations of the other ductless glands which so characterize this extraordinary malady as to place it in a class by itself.

There can be no doubt that in each one of the ductless-gland diseases, owing to the close interrelation of the several endocrine organs, functional modifications occur in all of them, but in acromegaly above all other diseases these secondary polyglandular disturbances are particularly outstanding, gross deviations from the normal being apparent in practically all of the other glands. Of this, the first case in our present report is a particularly good example, for though we can have no doubt that the case was one of acromegaly and due to an acidophilic adenoma, the gross changes in the hypophysis itself were far less striking than those in the endocrine series elsewhere in the body.

Probably owing to the many other and perhaps more striking features of this peculiar malady, scant emphasis has been laid on its polyglandular manifestations. There are however a few reports in the literature which call particular attention to the matter. One of these was by Gauckler and Roussy (1905)<sup>41</sup> who reported from the Salpêtrière the

autopsy findings on an acromegalic woman who died at the age of 83. Her malady may have possibly become dormant owing to the formation of a large adenomatous cyst the size of a mandarine orange which practically replaced the hypophysis, only a few traces of glandular cells remaining. The thyroid, a *goitre plongeant*, was of large dimensions, of colloid type and partly calcified. The adrenals were adenomatous and huge, one of them the size of an orange, the other said to be as large as a kidney; whereas the pancreas was striking for its especially large islets of Langerhans. Naturally the authors were led to cogitate upon the existence of a pathological solidarity of the entire ductless-gland series whose physiological interrelationships were just beginning to be appreciated.

*The Hypophysial Adenoma.*—What is the nature of the hypophysial tumor that gradually and hesitatingly came to be hit upon as the probable seat of origin of acromegaly and which for long was regarded as a sarcoma of sorts? The senior author in writing his monograph 14 years ago was put to it to answer this question and fell back upon the oldtime general designation of 'struma' merely to indicate a general enlargement of the gland. To be sure, some of the tumors showed a definite stroma suggesting an adenomatous architecture, whereas others consisted of nothing more than a structureless mass of cells. Moreover, some of them were recognized as chromophile and some as chromophobe in type, but the special stains to show the granules in the cytoplasm had not, at the time, been sufficiently developed to be dependable and many of the lesions in which we today can detect acidophilic granules were then regarded as chromophobe.

● Of late years in the pathological department of this hospital the chromophobe type of tumor accompanying hypopituitary cases has come to be designated as an adenoma, whereas the term 'struma' has been restricted to the acromegalic (chromophilic) lesion under the assumption that it represents an hyperplastic process in which the entire pars anterior participates (just as the entire thyroid is altered in exophthalmic goitre) rather than that a definite adenomatous nodule enlarges and compresses the remainder of the gland. In the neurosurgical laboratory, on the other hand, we had come to quite the opposite view, namely that the enlarged gland in cases of primary hypopituitarism more often represents what appears to be an hyperplasia of chromophobe elements and deserves



therefore to be called a 'struma,' whereas the tumor of acromegaly (*hyperpituitarism*) is more prone to suggest an adenomatous formation.

This confession of a temporary difference of opinion merely serves to emphasize the difficulties of interpretation that exist in respect to these lesions; it is made the more willingly since the difference of opinion has been set aside by both parties coming round to the view that in all probability the tumefaction in both hyper- and hypopituitarism is usually adenomatous. This however does not necessarily mean that a pathological and generalized (non-adenomatous) hyperplasia of either chromophile or chromophobe elements may not occur.

Whether one is entitled to speak of a localized hyperplasia as distinct from an adenoma is quite another matter. Marie and Marinesco (1891) referred to the hypophysial lesion in the *Héron* case<sup>67</sup> as being an adenoma without definite boundaries. Tamburini (1894)<sup>87</sup> expressly stated that the lesion in his case was an adenomatous process in which the entire epithelial lobe participated. Benda (1901) in the four cases reported with Fraenkel and Stadelmann<sup>39</sup> stated that there was no sharp transition between the mass of acidophilic cells and the remainder of the gland, and he spoke of the lesion as an hyperplastic struma. Both Erdheim and Kraus have subsequently emphasized that one can draw no sharp line of division between an hypophysial hyperplasia and certain of the adenomas which fail to compress the outlying portions of the gland.

Nevertheless, in most of the larger tumors evidence is accumulating to show that of the two processes the adenomatous lesion is the more common. Certainly Case III in this report, in which normal though compressed anterior-lobe tissue was identified as quite distinct from the acidophilic tumor, would support this view as far as acromegaly is concerned, even though in Cases I and IV the mass of chromophilic cells was not sharply demarcated from the remainder of the anterior lobe.

Though it is somewhat beyond the scope of this paper to discuss the far more common chromophobe tumors, we are coming to believe that these, too, are really adenomatous even though the stroma is often so scanty as to be negligible. To be sure, we rarely see fragments of tissue removed at operation for chromophobe adenoma in which acidophilic cells, which might represent traces of compressed anterior-lobe tissue, are present. What is more, we have sectioned a number of these large adenomas in their entirety and have searched in vain for any peripheral crescents of remaining compressed glandular tissue.

It is true that there are great technical difficulties in the way of a successful postmortem search of this kind, for the tumor by the time of death has often projected itself in an irregular way into the cranial chamber and may be broken on removal of the brain. Moreover, when it has reached such a size as shown in Fig. 29, a search without serial sections would be almost hopeless. In addition to this the formalin-fixed tissue must be properly mordanted in potassium bichromate if one is to identify the telltale alpha granules in the acidophilic cells.<sup>4</sup> In a large hypophysial tumor of the cellular type which we would formerly have called a chromophobe 'struma' Miss Grace Hiller has demonstrated by specific stains that the residual of the original gland is represented by nothing more than a single layer of subcapsular acidophilic cells loaded with alpha granules. These cells which would otherwise have escaped notice, surely indicate that the central mass is an adenoma and not an hyperplasia.

This question has been gone into in some detail to offset, so far as we may, the confusion which exists on many sides regarding the true nature of these lesions. For example, Paulesco in 1908<sup>75</sup> stated that 75 per cent of the tumors were sarcomas; André Leri in his monograph (1913)<sup>57</sup> called the lesion an epithelioma of glandular character; even as late as 1922 Dr. James Ewing in his well-known text-book<sup>36</sup> quotes Creutzfeldt to the effect that in 56 cases of acromegaly the hypophysis in 12 showed simple hyperplasia designated as struma, in 12 an adenoma was found, in 15 sarcoma, and in 5 no lesion was demonstrable. Hence he concludes that "many of the glandular lesions in acromegaly are therefore not true tumors but self-limited functional hyperplasias."

The view to which we have come to subscribe, namely that the hypophysial lesions under consideration are adenomata and that in acromegaly they are chromophilic in character, is far from new. Many of these tumors had been looked upon as sarcomas until Benda, in 1900,<sup>8</sup> in his study of four cases of acromegaly made the notable discovery that the cytoplasm of the tumor cells contained the same acidophilic granules which are present in the cells of the normal gland; he accordingly regarded the lesion as adenomatous, thereby giving histopathological support to the theory that acromegaly was a consequence of hypersecretion.

The evident precursors of the lesions large enough to give clinical symptoms were apparently first observed by Erdheim, who in his paper

on hypophyseal-duct tumors (1904)<sup>31</sup> casually remarked that he had seen foci of cells in the hypophyseal stalk resembling small adenomata. Löwenstein<sup>61</sup> three years later had the good fortune to find seven small adenomas in nine pituitaries removed from adult individuals at autopsy, showing that the lesions are common. He pointed out that they do not occur in the hypophyses of children, and also that the favorite seat of the nodules in the adult gland is in the periphery (*Markschicht*) of the anterior lobe. Though he did not employ Benda's staining methods, it would appear from his descriptions and illustrations that the lesions he describes are small chromophobe adenomas.

So far as the functions of the different cell types are concerned there are two schools. Some believe that the three varieties, those without granules (*Hauptzellen*) and the two types (acidophilic and basophilic) which possess them, are from the outset functionally different cells. Others believe that they merely represent different stages of activity of one and the same cell. Benda, for example, champions the view that the non-granular cells may become granular—a view which was also supported by Kraus (1914),<sup>53</sup> who, if we read him correctly, was of the opinion that the chromophobe cells (*Hauptzellen*) may become acidophilic and granular, but that the acidophilic cells when they lose their granules (*Entgranuliertenzellen*) do not revert to the chromophobe type.

All this has a bearing on whether the cells of a chromophilic adenoma ever change their histological character and lose their acidophilic granules. The arguments pro and con need not be given here, though the question is one of obvious importance in its relation to the possible self-limitation of hyperpituitarism. That the two common forms of adenoma (chromophobe or acidophilic) are one and the same, and merely represent different degrees, stages, or ages of the same pathological process is not beyond possibility. This would mean that acromegaly and adult hypopituitarism, which we regard as different and opposed diseases, are merely stages or grades of the same malady. It would mean, in other words, that the far more common chromophobe adenomas, unassociated with acromegalic manifestations, are terminal expressions of a transient active stage of hyperpituitarism which has not sufficed to produce obvious evidences of overgrowth.

Prof. Biedl, if we understand him correctly, upholds the view that all hypophyseal adenomas are akin and that the familiar examples of hypo-

pituitarism with chromophobe tumors are merely end-processes of a transient acromegaly. We might from our material build up an argument in support of this view. For we may see clinically all grades of transition, from the outspoken acromegalic of the type described in our Case I, through definite examples of acromegaly which nevertheless show adiposity, thin skin, and hypotrichosis as did our Case III, to patients with obvious hypopituitarism in which traces of possible pre-existing acromegaly are discernible in the skeleton. What is more, one may easily persuade himself that there are transitions in the acidophilic granules from their typical coarse form seen in active acromegaly to the fine, dust-like bodies and even to their ultimate disappearance in those stages of the disease when a mild degree of acromegalism has become masked by adiposity and other changes suggesting insufficiency.

There is another mooted question which in this connection may deserve passing mention. Is the secretory product of the acromegalic adenoma merely an excess of the normal secretion or does it represent a dysfunction of the acidophilic cells as Reinhardt and Creutzfeldt<sup>80</sup> among others contend? This would seem to be answered, at least so far as the rat-gigantism experiments can answer it, in favor of the hypersecretion view if we are to concede that the only difference between clinical acromegaly and gigantism is largely an accident of the age of onset.

Whatever future studies may have to add to these matters, acromegaly, so far as the skeletal changes are concerned, once established is permanent whether or not the activity of the adenoma has died out. On the other hand, if the majority of the patients with supposedly primary hypopituitarism and chromophobe adenomas actually have the same disease they have completely escaped any of its acromegalic or hyperpituitary manifestations.

Certainly in these four acromegalics under discussion, we have the most extreme variations possible. In one (Case I) was a gland of normal dimensions in the centre of which is an adenomatous-like accumulation of chromophilic cells; in Case IV was a gland which has evidently shrunk greatly in size and which contains a similar centrally disposed adenoma; in Case II a huge adenomatous mass had extended into the intracranial chamber leaving no demonstrable trace of the original glandular structure; in Case III there still remains a normally composed though flattened hypophysis from which a huge intracranial adenomatous mass had expanded laterally into the temporal lobe.

What is more, there were all grades of neighborhood symptoms. The normal-sized gland in Case I was accompanied by most severe headaches but never gave any visual disturbances; the shrunken gland in Case IV had once produced pressure against the chiasm from which it had apparently receded; the tumor of Case II caused blindness from primary atrophy whereas the much larger tumor in Case III had been entirely unsuspected, the patient never having had any evidence whatsoever of chiasmal pressure.

*The Pineal Gland.*—No changes have been described in this organ as in any way characteristic of acromegaly, and doubtless insufficient attention has been paid to it. This was true of our four cases. In Case IV the gland contained two small cysts, which are not unusual findings under normal conditions. Undoubtedly the pineal body has some definite association with growth whether in itself or secondarily through the hypophysis. The cases of *pubertas præcox* represent a form of early sexual development with overgrowth associated with tumors of the gland, but so far as is known, this peculiar syndrome is a thing apart and bears no relation to acromegaly.

*The Thyroid.*—It will be recalled that in Marie and Marinesco's report of the *Héron* case the thyroid weighed only 27 gm., an atrophic gland therefore if we may consider 45 gm. as the average normal. It was likewise small in the cases recorded by Lewis in 1905<sup>58</sup> (30 gm.), by Ausch in 1918<sup>3</sup> (39 gm.); and it was said to be normal size in our Case IV, in Hunter's case (1898),<sup>49</sup> and in that of Ballet and Laignel-Lavastine (1905).<sup>5</sup> The figures assembled in Hinsdale's monograph<sup>48</sup> which are those usually quoted, would leave one to judge that the thyroid changes in acromegaly are too variable to be in any way significant, the gland having been "enlarged" in one-third, "normal" in one-third, and "atrophied" in one-third of the cases which up to 1898 had been recorded. Biedl in his "*Innere Sekretion*" (1910) refers to the commonly observed secretory inactivity and diminution in volume of the thyroid with which he contrasts the fairly constant hypertrophy of the adrenal cortex.

Our personal experience and studies of the cases in the literature are not in agreement with these observations, for out of 45 cases which we have tabulated, the gland was below normal weight only in the 2 cases of Lewis and Ausch mentioned above; whereas it was said to have been "large" or "very large" in 11 cases; and in the other 29 in which the

weights were given the average was 129 gm. The largest recorded thyroid was in Geddes' case (1909),<sup>42</sup> of 312 gm., the next largest in our Case I (310 gm.), and in Ravaut's case<sup>78</sup> the gland weighed 309 gm.

In a country like ours where goitre is relatively common the "normal" size and weight of the thyroid might be debatable, but there can be no question of the marked goitre in our Case I, whereas Cases II and III had a gland easily twice the normal. What is more, in all the cases the glands proved to be of the colloid type without histological evidence of toxicity, and in all instances they were adenomatous.

This matter has been gone into in an earlier paper in this series<sup>24</sup> dealing primarily with the question of the metabolism in acromegaly. It was told therein that in our personal series of 100 outspoken examples of the disease a clinically palpable or greatly enlarged thyroid was present in 25 cases. Curiously enough, all of these goitrous thyroids were in patients that showed an increased metabolic rate, for which one might therefore be inclined to assume *a priori* that the large thyroid was responsible. However, in three of the cases a thyroidectomy had been performed on the assumption that the patients had hyperthyroidism, and in all three the gland proved to be of the inactive colloid adenomatous type usually found in acromegalics at autopsy.

It is fair to say, therefore, that acromegaly is often accompanied by an adenomatous and enlarged thyroid; but whether actual exophthalmic goitre may co-exist is a question of doubt, even though examples have been described in the literature.

We may gain further information regarding this interrelationship in other ways. In myxœdema and cretinism the hypophysis has commonly been found to be enlarged. Virchow was the first, long ago, to call attention to this in his studies of a cretin. Furthermore, the experiments by Rogowitsch (1889)<sup>83</sup> which showed that thyroidectomy was followed by an enlargement of the pituitary body have been since corroborated by many, most recently by P. E. Smith<sup>85</sup> in the case of an animal so well standardized as the rat. But what is more to our purpose, Smith has shown that the opposite effect follows the removal of the hypophysis not only in the rat but in amphibians as well—namely a diminution in size of the thyroid.

These experimental findings, therefore, so far as they go fit in perfectly with our clinical experiences: for in hypopituitarism rarely is



the thyroid even palpable, and in the few fully recorded autopsies it has been found atrophic. The only thing needed to make the argument complete is to find that experimentally produced gigantism or acromegaly is accompanied by an hypertrophied thyroid.

To be sure, we cannot shirk the finding of an occasional normal-sized or atrophic thyroid; no more can we ignore the fact that mere size is not a measure of physiological activity. However, the glands of normal or subnormal weight in acromegalics have invariably been spoken of as colloid in type; and two of the recorded atrophic glands may well enough be explained on the basis of dormant acromegalism, for at least in both Marie's and Lewis' cases the hypophysis was small and the histological description of the adenoma none too convincing.

Although the thyroid glands we have seen removed at operation were colloid in type, this does not necessarily mean that they may not have passed through a wave, indeed successive waves, of hyperthyroidism, for this in accordance with Marine's view is the way in which a colloid goitre comes to be laid down. We may nevertheless safely say that hyperpituitarism in its acromegalic guise tends to enlarge the thyroid disproportionately to the other tissues and that this enlargement proves histologically in the large majority of cases to be the type of inactive gland familiar in the colloid goitre.

*The Parathyroids.*—In the literature describing autopsies on acromegalics very little attention has been paid to these glands. As is true of other endocrine organs, we have come to know more about their function than structure and are far from having any clear idea of their histopathological changes in disease. At least nothing comparable to what we know, for example, of the histopathology of the thyroid has been worked out in the case of the parathyroids. This is not surprising since the glandules were only described in 1880 and it was not until the '90's that Gley showed them to have an independent activity of their own. It has been claimed that the glands enlarge after thyroidectomy, but their interrelation to other organs is a subject that has scarcely been touched.

Following the discovery by MacCallum and Voegtlin (1909)<sup>63</sup> that the tetany of hypoparathyroidism was a calcium-deficiency phenomenon, attention naturally became directed to those diseases in which disturbances in calcium metabolism occurred, notably in rickets, scurvy, osteomalacia, and so on. These maladies are all apparently characterized by

a calcium want and little if any consideration has been given to the parathyroids in diseases like acromegaly in which there appears to be a calcium retention rather than loss. Our knowledge of these conditions will doubtless advance rapidly now that something approaching the active principle of the parathyroids has been obtained through the studies of Hanson and of Collip; but meanwhile our familiarity with the microscopic alterations in these minute organs which accompany stages of over- or under-activity lags far behind.

Erdheim in his studies of experimental rickets in rats described an hyperplasia of the glands associated with an increase in size of the individual cells. Ritter in 1920,<sup>82</sup> and more recently Pappenheimer and Minor,<sup>74</sup> have shown that the glands are enlarged in human rickets; and though distinctive pathological changes are wanting, one may assume that they are in the direction of a compensatory hypertrophy. We are aware, however, from our knowledge of the hypophysis and thyroid that size is no criterion of functional activity. Indeed, the largest glands, all things considered, are likely to be the least active.

In only two of our own four cases were the organs identified and described. In Case I, four of the bodies were found, one of them definitely, enlarged, and the histological appearance suggests proliferative activity. In Case III, the only two glandules which were identified both showed what is taken to be a central adenoma, and attention should be called to the fact that in this particular case an adenomatosis of the other endocrine organs was particularly marked.

Though the parathyroids have been described in a number of the autopsy protocols in the literature of acromegaly (*e.g.* in the reports by Reinhardt and Creutzfeldt<sup>81</sup> and in that by F. K. Bartlett<sup>7</sup>) as being slightly increased in size, definite histopathological abnormalities appear to have been recorded, so far as we have observed, in only one instance. This case, the essentials of which are as follows, will be found (*Fall 35*) in Josefson's<sup>51</sup> monograph (1915).

An acromegalic youth, aged 26, height 191 cm., weight 94.3 kg., showed at autopsy, in addition to a large chromophilic hypophysial adenoma, organs with the following weights: heart 460 gm., liver 3400 gm., kidneys 920 gm., spleen 480 gm., a colloid thyroid 55 gm., thymus 20 gm., pancreas 100 gm., adrenals 40 gm., with adenomatous formations; testes normal.

The parathyroids are thus described: "At the right of the thyroid there is a parathy-

roid as large as a bean and at the left a rounded tumor-formation larger than a walnut which lies completely separated from the thyroid in a fibrous capsule of its own. It measures  $6 \times 4 \times 2.5$  cm. A section through this shows a compact rather soft mass. Histologically one of the parathyroids is composed of a number of cell islands resembling adenoma, the structure suggesting an hypophysial adenoma, but here and there are cells which are arranged in palisade fashion as if tubulous. The parathyroid tissue itself (apart from the adenoma) shows on the whole normal conditions though they are perhaps richer in cells than usual."

To adenomatous tumors of the parathyroid little attention appears to have been paid. The majority of them have been accidental post-mortem findings and have been regarded as without clinical significance, a number of so-called "parastrumas" having been described as embedded within the thyroid substance itself.

An analysis of the reported cases has been made by Harbitz<sup>46</sup> who adds four personally observed examples, one of which was associated with osteomalacia and another with infantile rickets. They were small circumscribed adenoma-like structures composed largely of oxyphilic cells with colloid spaces. Molineus<sup>70</sup> likewise found parathyroid tumors in three cases of osteitis deformans. Hence adenomas of the parathyroid are apparently not uncommon, particularly in diseases where the metabolism of bones is obviously affected, and it is perhaps therefore not surprising to find that they may occur in acromegaly.

The tumors that have been described have uniformly been encapsulated with rather large cells which tend to be acidophilic. The structure resembles that of the parathyroid with compact columns of opaque epithelium, there being, according to Ewing,<sup>36</sup> much variation in the size and appearance of these columns. He states further that in one of the cases he had studied they varied from thin strands to large alveoli filled with cuboidal cells; that the lesions are prone to be vascular; that the cells may be rich in glycogen; and that groups of strongly acidophilic cells may be present. He gives a drawing of the detail of a parathyroid adenoma which closely resembled the appearance of some of the areas in our Case III.

*The Carotid Body.*—This structure belongs to the chromaffin system which so far as is known is unaffected in acromegaly. It need only be mentioned here since a tumor of the carotid body which is a rare lesion has been reported by A. W. M. Ellis<sup>30</sup> in a case of acromegaly. The

lesion was described as a neuroblastoma and was presumably akin to the tumors that arise from the adrenal medulla.

*The Thymus.*—Reference has already been made to the fact that Fritsche and Klebs in 1884, two years before the appearance of Marie's first paper, published their notable study of the pathology of gigantism (*Riesenwuchs*) in which the postmortem findings, in what we now recognize as a case of acromegaly, are described, one of the most striking features of the case having been the huge thymus. This so far overshadowed the somewhat enlarged pituitary gland that it affected the authors' entire conception of the disease.

A persistent thymus, indeed, proves to be a most common postmortem finding, and Marie himself was sufficiently impressed by the fact to bring the matter to the attention of the Société Médicale des Hôpitaux<sup>66</sup> some years after his original description of the disease. At the time, in commenting upon the singular fact that it was also apt to be enlarged or persistent in Basedow's disease he alluded to the difficulty of determining whether it represented actually the revival or merely a persistence of the infantile organ. This difficulty is no less today.

We know, however, that the third decade represents the average age of onset of acromegaly and by this time the gland should have undergone complete involution, for this sets in at adolescence and in later years thymic tissue may be difficult to find. Hence, it is safe to infer that there has been an actual revival of the structure for purposes of which we have no clear understanding. It is conceivable that it has some secondary relation, even in acromegaly, to the enlarged thyroid, though in our Case III in which the thymus was particularly large the thyroid was relatively small, this being the only patient of the four that had a high metabolic rate.

In all four of our cases thymic tissue was demonstrable, and that the organ may be of surprisingly large size is apparent from the 78-gm. thymus of Case III (*cf.* Fig. 60), the measurements of which are practically the same as those given by Klebs in his 1884 report. Co-existent with this astonishingly large thymus was a generalized hyperplasia of the lymphoid-apparatus tissue through the body, which in the absence of other pathological changes might easily have led in our own case to a diagnosis of status thymico-lymphaticus.

With all this about the thymus in acromegaly it must not be forgotten

that it has not been definitely shown to be a gland of internal secretion in the same sense as the endocrine organs proper. Nor should the fact be overlooked that a greatly enlarged thymus in association with hypertrophic changes in the lymphatic apparatus throughout the body may accompany conditions the reverse of acromegaly—namely states of hypopituitarism. An example of this, with a thymus weighing 30 gm., has already been recorded by one of us.\*

*The Adrenals.*—In all of our four cases these organs were greatly enlarged, and three of them had adenomata of cortical tissue. One cannot, however, ascribe the increase in size solely to these tumefactions. The heaviest pair of glands (Case II), with a combined weight of 43 gm., nearly four times the average normal, showed merely an extensive cortical hyperplasia, whereas the smallest pair (Case IV), with a combined weight which was approximately normal, contained the largest adenoma of all (*cf.* Fig. 79).

The greatest combined weight, in the absence of adenomas, that we have found recorded, was 57 gm. in the case of the 15-year-old acromegalic girl reported by Schultze and Fischer (1912).<sup>84</sup> But when adenomas are present the organs may attain an enormous size. In the case of Gauckler and Roussy<sup>41</sup> they were compared to a mandarine orange, and one of our series of 100 acromegalics has died in another hospital from a large palpable renal tumor diagnosed hypernephroma.

The suprarenals of Marie and Marinesco's celebrated case were described as normal or slightly atrophied, and this statement has come to be more or less generally quoted by subsequent writers. Nevertheless it is apparent from the literature that hypertrophy of these organs has been a common finding. Bernard Fischer, for example, in commenting (1910)<sup>38</sup> on the enlarged adrenals observed in his two cases, in one of which they were said to be five times the normal and due solely to cortical hypertrophy, stated that the increase in size was out of all proportion to the splanchnomegaly in general. He was inclined to ascribe this finding to the effects of hypophysial hypersecretion in accordance with Delille's observations which had just been published.<sup>29</sup> For Delille while investigating the interrelations of hypophysis and adrenals had noted that injections of pituitary extract caused an hypertrophy of the adrenal cortex.

\* "The Pituitary Body and Its Disorders," 1912. Case V, pp. 48-54.

This like many other similar observations on the effects of injections of extracts, so often reported and so often contradicted, might have remained as merely a point of obscure interest had it not received recent confirmation. For H. M. Evans in his Harvey Lecture (1923)<sup>33</sup> speaks of an adrenal enlargement as one of the constant postmortem findings in cases of experimentally produced gigantism in rats; and though Evans makes no mention of the other ductless glands, nor whether the hypertrophy is purely cortical, we may assume that the changes in this particular organ were among the most striking postmortem findings.

Evidently then, hypertrophy of the adrenal cortex, with or without the formation of adenomata, is one of the most constant expressions of hyperpituitarism. What is more, indirect support for this statement and for the close interrelationship of hypophysis and adrenal may be secured from the autopsy findings in states the reverse of acromegaly, that is in cases of outspoken primary hypopituitarism associated with chromophobe adenomas.

Though the hypopituitary states are far the more common we unfortunately have only two autopsies to draw upon for desired information. One of them showed, apart from the hypophysial adenoma, but slight change of any sort in the endocrine series. In the other case however, the adrenals were exceedingly small, their combined weight being only 4 gm. and their greatest length 12 mm.; with a cortex less than a millimetre in thickness, contrasting markedly with the hyperplastic cortex of the acromegalic gland (Figs. 91 and 92). Further support comes from our observations of experimentally hypophysectomized dogs whose adrenals have been notably small, and the same thing has been observed by others (Smith)<sup>85</sup> in the hypophysectomized rat.

Whether in acromegaly the adrenal medulla is also affected must remain conjectural. Many of the patients become darker in complexion, though not necessarily pigmented; many show a marked enfeeblement; many have an abnormally low blood-pressure, hypertension even of low grade being rare, which is the more surprising in view of the hugely hypertrophied hearts and tendency to peripheral arteriosclerosis characterizing certain examples of the disease.

*The Pancreas.*—If 97 gm. (Vierordt) may be taken as the average weight of the pancreas the organ may become disproportionately enlarged and participate in the general splanchnomegaly. In most of the



autopsy reports the gland received scant mention. Exact weights have been given in only 14 of the many protocols we have analyzed, the average having been 143 gm. The heaviest pancreas weighed 250 gm. as recorded by Launois and Roy (1900).<sup>56</sup> The next largest is 225

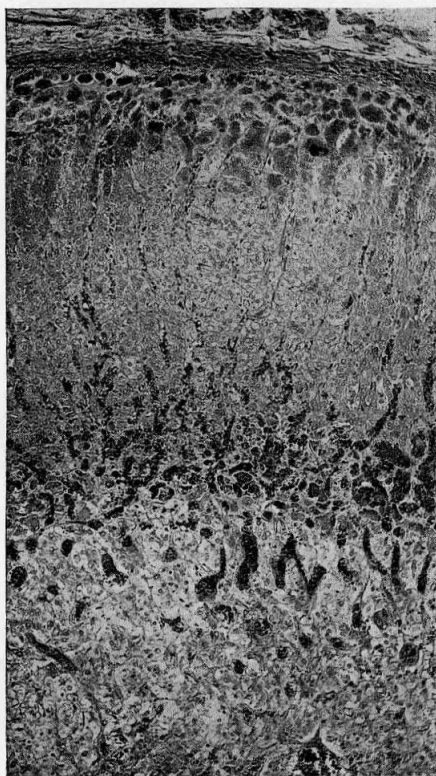


FIG. 91.

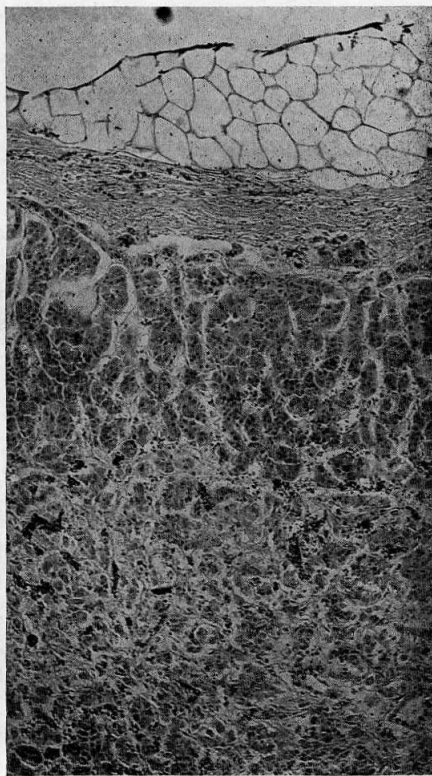


FIG. 92.

FIGS. 91 and 92. Showing relative width of adrenal cortex in acromegaly (Case III—left) and hypopituitarism (right). Stain H. and E. ( $\times 80$ ).

gm., in our Case I, and the autopsy protocol of this case makes special mention of a marked hypertrophy of the salivary glands as well. The weight in Dallemagne's case (1895)<sup>25</sup> was 220 gm. In our Case III the pancreas as stated in the protocol contained an acinar adenoma measuring about 1 cm. in diameter.

*The Islands of Langerhans.*—In some of the protocols, the islets are

mentioned as being distinctly hypertrophic. As this was particularly true of Case III, we felt that possibly the two patients with diabetes might show the largest islets and this proves to be the case. They were

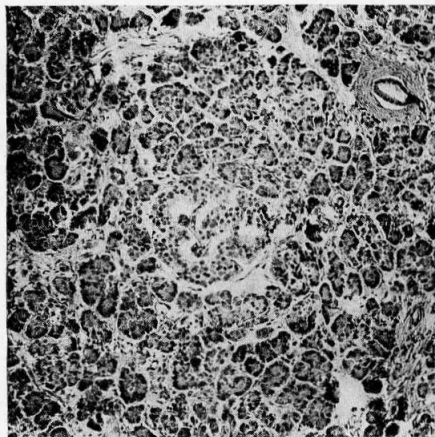


FIG. 93. Case I.

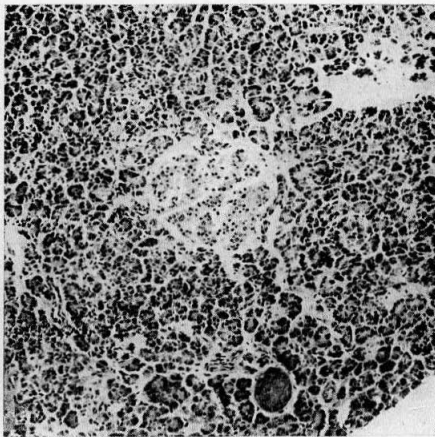


FIG. 94. Case II.

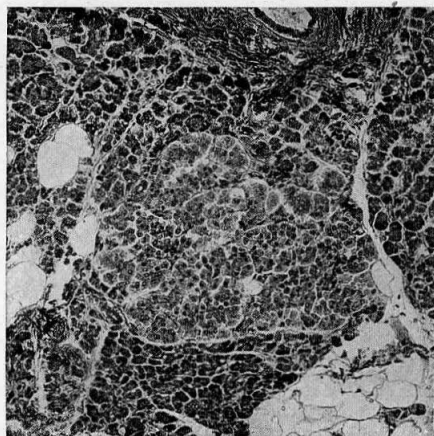


FIG. 95. Case III.

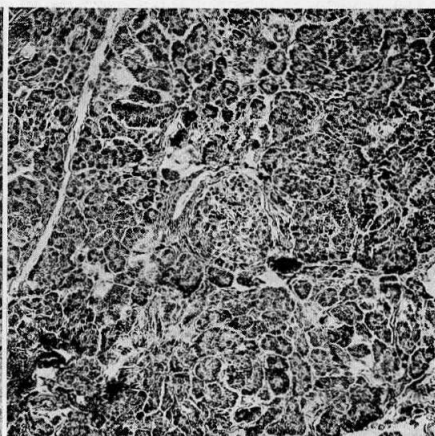


FIG. 96. Case IV.

FIGS. 93-96. Specimen islets from the four cases ( $\times 80$ ). Note the markedly hypertrophic islet in Case III and the sclerosed islet in Case IV.

most obviously enlarged in Case III, some of them measuring  $400\mu$ ; the next largest were in Case I, a non-diabetic, in which they averaged  $220\mu$ ;

those of Case II averaged  $200\mu$ , and of Case IV,  $180\mu$  (Figs. 93-96). According to Cecil<sup>17</sup>  $200\mu$  may be regarded as the average normal measurement,  $400\mu$  as markedly hypertrophic, and anything above  $400\mu$  exceedingly rare. Cecil however in his series of 90 cases of pancreatic diabetes found that the islands in 38 per cent equalled or exceeded  $400\mu$ , and in one case measured  $1600\mu$ —that is eight times the normal.

The protocols of our cases report the islands as being histologically unaffected aside from the apparent hypertrophy in Case III and with this statement we agree except for the trifling strand of sclerosis found in a single island in Case IV (*cf.* Fig. 78).

Adenomas of the islets have been described by Reitmann,<sup>81</sup> Herxheimer,<sup>47</sup> Cecil<sup>18</sup> and others as having been observed in ordinary diabetes. No such changes have been seen in our cases. A more thorough study of the pancreas in acromegaly might be expected to reveal them in view of the obvious tendency in this disease for the endocrine organs to become adenomatous. Shields Warren<sup>92</sup> has recently reported three examples met with in ordinary routine postmortem examinations unassociated with diabetes and he believes them to be not uncommon.

Diabetes mellitus on the whole is a disorder of which we know more from a clinical and biochemical standpoint than from that of morbid anatomy. Since the time of Opie's studies (1900)<sup>71</sup> experimental pathology has convinced us that the pancreatic islets are chiefly concerned and on this basis rests our most satisfactory present-day therapy. But in spite of this, dependable histopathological changes are not always present or demonstrable in fatal cases. This seems to be even more true of acromegalic diabetes, in which the pancreas may be considered to be secondarily involved, than in the ordinary forms in which it is thought to be primarily so. In Case III in our series, the patient apparently recovered spontaneously from his diabetes, an occurrence practically unknown in those more common forms of the malady unassociated with acromegaly. The other patient (Case IV) died in diabetic coma in the days before insulin, yet the islets appear to be within histologically normal limits.

In the course of time, these conflicting and confusing matters will doubtless come to be explained. We have learned that acromegalic diabetes does not respond quite so favorably to the action of insulin as does primary pancreatic diabetes. We have learned, too, that the coin-

cidental injection of posterior-lobe extract counteracts the effect of insulin. Just what would be the effect on sugar metabolism of injecting the pars anterior principle is not known, and may not be until this substance has been isolated in chemically pure form. We have assumed that it would be counteractive to insulin, just as are extracts of the posterior lobe, but have not been able to support this view experimentally.

From what we know of the greatly increased sugar-tolerance acquired by patients with posterior-lobe insufficiency it is physiologically conceivable that the removal of the hypophyseal pars anterior might control pancreatic diabetes even though other equally undesirable disturbances would be left in the train of the procedure.

Though these matters will be taken up in a subsequent paper in this series, it may suffice to say: that cases of acromegaly even in the absence of glycosuria show a tendency to hyperglycæmia; that the hypopituitary cases, on the contrary, show a lowered blood-sugar percentage, which is true of the experimental animals as well. Moreover, the fact that patients with acromegalic diabetes may recover from their malady hints that it is a disorder somewhat different from pancreatic diabetes. Furthermore, the fact, that of the two disorders acromegalic diabetes appears to be less amenable to insulin, may be explained on the grounds that the secretion of the acidophilic pituitary adenoma serves in a measure to counteract its effects.

*The Gonads.*—One would suppose that of all the subsidiary endocrine organs it would be possible to speak more definitely of the alterations of the sex glands in cases of acromegaly than of any of the others. The contrary is true, in spite of the fact that their close functional interrelation with the hypophysis has been appreciated almost from the outset. Yet in most autopsy reports of acromegaly, aside from the bare statement that the organs were enlarged, or small, or atrophic, microscopic details are wanting. This is particularly true of the testis; for out of 35 autopsies on male acromegalics which we have assembled, an histological report accompanies only five of the protocols, and the interstitial cells are mentioned in only one or two instances.

Apart from the mere process of spermatogenesis and of ovulation we indeed know so little about these complicated organs and their numerous secondary functions that histopathological changes other than obvious atrophic ones doubtless have been, and for that matter still are, difficult

to describe. Fortunately, however, progress is being made. The early experimental canine hypophysectomies<sup>22,2</sup> showed that deprivation of the gland led to marked functional and degenerative changes both in ovaries and testis, and in this clinic in 1913 Goetsch and Cushing<sup>43</sup> undertook a series of preliminary feeding experiments to see whether reverse effects upon these particular organs might not be produced by the continued ingestion of hypophysial extracts. These experiments were painstakingly continued by Goetsch who concluded (1916) that definite stimulating effects with a precocious development of the gonads were produced in rats by prolonged feeding.<sup>44,45</sup> His results though striking have not as yet received experimental corroboration.

A new impetus to the subject has been given by the important discovery, first in the guinea-pig by Stockard and Papanicolaou (1917)<sup>86</sup> and then in rats by Long and Evans (1922)<sup>62</sup> of the clock-like œstrous cycle and its betrayal by vaginal smears. This finding has been promptly and effectively followed up by H. M. Evans and his co-workers in ways which are important and illuminating particularly from the standpoint of the disturbances of ovulation which occur in acromegaly. However, we are still much in the dark regarding the function of the interstitial cells of testis and ovary which play such an important rôle in the development and maintenance of the secondary characteristics of sex. Not until the physiology of these cells is better understood and their histopathology better known may we hope to explain the tendency to masculinization so often seen in acromegalic women, and the feminization of men who are victims of hypopituitarism.

*The Ovaries.*—Though the interrelation between hypophysis and ovary both clinically and experimentally is one of the most striking of all the manifold endocrine interrelationships that have been pointed out, our material, unfortunately, limits us to little more than a general discussion of the subject. We however no longer need to grope for an explanation of the amenorrhœa accompanying the disease as did those who have ascribed it to pressure of the tumor against the neurohypophysis. Indeed, the interruption of the œstrous cycle from failure of ovulation has come to be used as a means of testing the activity of our as yet crudely prepared anterior-lobe extracts.

The experiments of Evans and his co-workers have served to shed light on one of the confusing and contradictory clinical findings in acrome-

15564

galy and its opposed state of hypopituitarism, in both of which an early amenorrhœa has long been recognized as a characteristic and early symptom. This apparent inconsistency has been accounted for by the discovery that the parenteral administration of anterior-lobe extract is a specific stimulant to the growth of lutein cells. Hence in experimental hyperpituitarism (gigantism in the rat) the ovum as shown by Evans fails to be discharged from the ripened follicle. Instead of the usual follicular healing with the formation of corpora atretica, solid corpora lutea are formed within which the ova remain embedded, with the result that a 'mulberry ovary' of twice the normal size comes to be formed in a considerable percentage of the cases. In pituitary insufficiency both experimental and clinical, so far as we know, the ovum invariably remains small and atrophic;<sup>32</sup> follicles fail to mature, and naturally no lutein tissue is formed.

It is safe to say that many women, whether acromegalic or with an hypopituitary syndrome, have been subjected early in the course of their malady to exploratory abdominal operations because of their unexplained menstrual interruption. It is quite probable, too, that a single or double ovariectomy has often been performed under these circumstances. Strümpell, for example (1897), records such a case in which the ovaries were merely stated to have been large, whereas at this present writing (1926) we have an acromegalic patient under observation who 6 months ago had a similar operation performed, the ovaries having been reported as "normal." Between 1897 and 1926 the procedure in all likelihood has been often repeated, yet the literature bearing upon the subject is surprisingly silent, or at least fails to describe lesions which would in any way indicate that changes such as Evans<sup>33</sup> and Teel<sup>33,39</sup> have shown to occur in rats have ever been observed in the human.

Many favorable opportunities to observe these or comparable changes postmortem have been lost, in years past, doubtless because of the overshadowing interest in the hypophysial lesion. This was at least true of an autopsy which was performed on a case in the senior author's Johns Hopkins series. The patient was an acromegalic woman, aged 26, who had been married 3 years and had subsequently become amenorrhœic. When the case was reported\* the condition of the ovaries was dismissed

\* "The Pituitary Body and Its Disorders," 1912. Case II, p. 36 *et seq.*



with the brief statement that "they were large, cystic and degenerated." Our present interest in the subject has led to a re-examination of the original protocol, which reads:

*"Pelvic organs.* The right ovary measures about 4 cm. in length and about 2 cm. in width. On section there are numerous small cystic areas. The left ovary measures about 6 cm. in diameter. On section the greater part of this is found to be made up of smooth-walled cysts containing perfectly clear colorless fluid. The ovarian tissue has been compressed and spread out and measures only 4 mm. in thickness. The uterus is 6 cm. in length and about 3 cm. in width. It is rather dark red in color. The mucous membrane is pale and of a glossy smoothness. The cervix is corrugated."

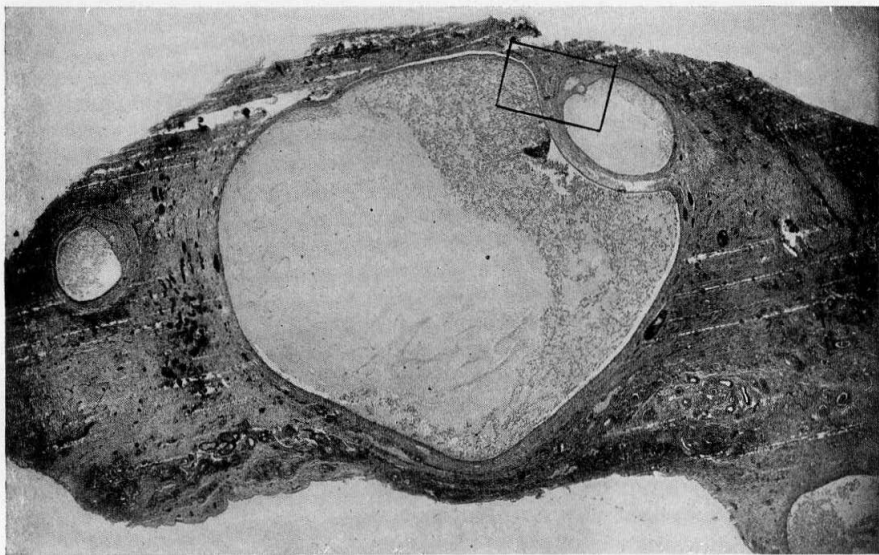


FIG. 97. Section of the ovary of an acromegalic 26 years of age, amenorrhœic for 3 years. H. and E. stain ( $\times 10$ ). For squared area, cf. Fig. 98.

Fortunately a microscopic preparation through one entire ovary has been preserved. This shows an organ which might be regarded as normal were it not for the history of 3 years of amenorrhœa. There are four large, fully developed Graafian follicles, one of which might be regarded as cystic. The section (Fig. 97) happens to pass through the ovum in three of these follicles, all of which appear to be fully ripened, normal in all respects and ready for ovulation (Fig. 98). The peculiar thing about the speci-

men is that there are no corpora atretica and only one or two faint relics of old corpora albicantia. Evidently some process is at work which is preventing ovulation and the scarring which ensues, either from resorption or discharge of the ova. Curiously enough, also, the specimen shows only a single primordial ovum. Whether this human ovary of hyperpituitarism is in any way comparable to the ovaries of the giant rats would seem doubtful. It certainly shows no trace of lutein formation.



FIG. 98. Squared area from Fig. 97, to show the ripened follicle.

Physiologically speaking, the conditions in the ovary are far more complex than in the testes, since the liquor folliculi, the granulosa cells of the follicle, the cells of the corpora lutea, and the interstitial cells of the stroma, all apparently play a differing rôle in the endocrine functions of the organ. There are, however, two accepted facts to which we may cling. The ripening of the Graafian follicles is what brings on menstruation; and it has been shown that even in the spayed animal the parenteral injection of liquor folliculi will bring on œstrus. The corpora lutea on the other hand inhibit menstruation. But how we may account for the amenorrhœa in the case under discussion is difficult to say unless it may be that the anterior-lobe hormone serves in the human to inhibit

the final stage of follicular ripening and that the lutein formation seen in the injected rats does not occur.

In the patient, Case IV, in this present series, catamenia had continued for many years after the malady was established, and though the menopause had occurred at 40, one might hardly have expected to find anything more than lutein scars, for she lived to be 52. Unfortunately the ovaries at the autopsy were merely passed over with the statement that they were small and fibrous and they do not appear even to have been sectioned. We may at least assume that there was nothing to call the pathologist's particular attention to them.

This appears to have been the case with most autopsies on acromegalic women, the ovaries receiving scant attention in the autopsy protocols. Those few in which the ovaries have been described do not help us greatly though definite abnormalities have been observed. Thus Löwenstein's Case I (1906)<sup>60</sup> was a young woman who died at the age of 16 after 5 years of evident acromegaly—one of the few well-recorded and undoubted examples of the disease which has begun thus early in life. The ovaries were described as showing an absence of follicles, the entire organ consisting of a connective-tissue stroma in which were vessels lined by a single layer of cuboidal epithelial cells. There were in addition a number of pea-sized cysts lined by several layers of cuboidal epithelium and otherwise filled by a homogeneous material.

Similarly Kraus (1914)<sup>53</sup> mentioned, though somewhat cursorily, the condition of the ovaries in the two acromegalic women that he had studied postmortem, the cases unfortunately being unaccompanied by a clinical history. One of them (Case XXIV) was a woman of 34 whose uterus was atrophic and whose ovaries were free from follicles but rich in corpora atretica. His other case (No. XXV) was a 54-year-old woman, one of whose ovaries though free from follicles abounded in stroma through which were scattered many cystic spaces lined by cylindrical epithelium, whereas the other was composed of multilocular cysts with a pseudo-mucinoid content.

A comparable observation was made by Messedaglia\* in a multiparous peasant-woman who at the age of 41 following her fifth pregnancy began to show signs of acromegaly and who died 7 years later from a

\* "Studi sull'acromegalia."<sup>68</sup> (Osservazione VI, p. 69.)

cardiac failure with anasarca. The ovaries were said to have been large with visible follicles. Histopathologically:

"The germinative epithelium was absent in some parts of the tunica albuginea; the remaining superficial portion of the existing ovary shows attenuated rather than cylindrical cells. The albuginea is very thick, consisting of layers of compact connective tissue. The glandular part is reduced to small proportions and infiltrated with abundant connective tissue. The numerous vessels of the hilus show hypertrophied walls, especially marked in the adventitia. Follicles are entirely absent. In certain points are observed cicatrized remains of corpora lutea."

It is hardly conceivable that any of these descriptions which agree in their emphasis on the absence of follicles represent the end-stage of the multiple corpora lutea which Evans and Teel have described. Certainly now that they have called attention to this extraordinary effect of experimental hyperpituitarism in rats more attention will be given in the future by gynæcologists and pathologists to the condition of the ovaries in early cases of acromegaly.

*The Testes.*—If we have been at a loss to ascribe to the ovaries any histopathological change definitely characteristic of the disease it is no less difficult to do so on the part of the testes. What is more, experimental hyperpituitarism in the rat, for reasons which are apparent, has been chiefly restricted to the female. One of the earliest evidences of the reciprocal effect of hypophysis and testes to be recognized, and experimentally the easiest to check, is the hypophysial enlargement which follows castration. On the other hand it was the sexual dystrophy and adiposity in their experimentally hypophysectomized animals that first led Crowe, Cushing and Homans (1909-10)<sup>21,22</sup> to appreciate the fact that they had produced experimentally a state of hypopituitarism.

These deprivation effects are naturally far more easily brought about than the reverse state, namely that of glandular oversecretion which in the case of the testes remains purely an hypothetical possibility. The matter is complicated for we are dealing, as in the ovary, with a double function—that which concerns spermatogenesis alone and that which concerns the so-called secondary sex characters. The latter, as is well established by many observations, is essentially influenced by the interstitial cells; but nevertheless we cannot apparently by any such simple formula separate the two testicular functions. For example, in

animals recovering from hibernation there is an enormous increase in the interstitial cells as there is in other animals during the rutting season.

Clinically we know that in infantile hypopituitarism there may be complete sexual dystrophy with undeveloped genitalia and more or less complete failure of the adolescent secondary sex characteristics to appear. We know, too, that when in adult males the pituitary function is impaired

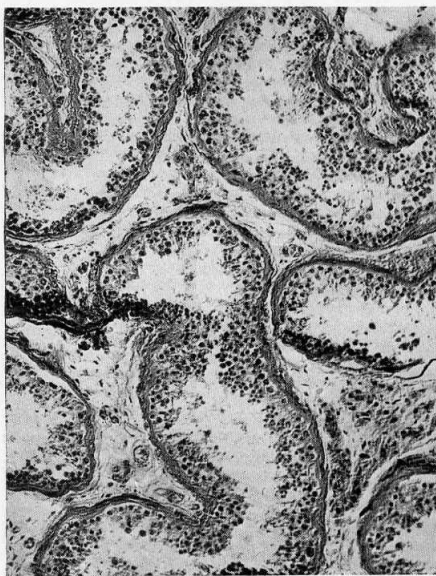


FIG. 99.

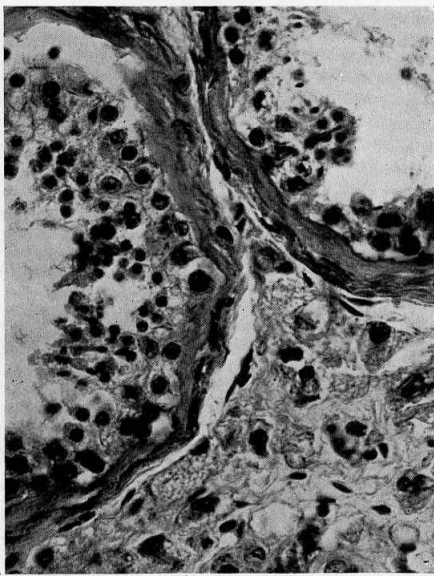


FIG. 100.

FIGS. 99 and 100. Case I. Sections of testis showing spermatogenesis and increase in interstitial cells. Stain H. and E. Left,  $\times 80$ ; right,  $\times 300$ .

by the common adenomata of chromophobe type genital atrophy occurs, with impotence and loss of libido. At the same time a marked recession of the secondary sex characters takes place with loss of pubic and axillary hair, thinning of the beard, and a tendency to adiposity with a feminine distribution. On the contrary, the hyperpituitarism of acromegaly is characterized, in its early stages at least, by a more or less evident over-development of the secondary sex qualities of which hypertrichosis is an evidence, and, traditionally at least, by an early period of excessive virility and libido.

These opposed syndromes are suggestive of secondary testicular atrophy in *hypopituitarism* and activation in *hyperpituitarism*, but beyond this there exist enormous gaps in our knowledge. If human gigantism is merely hyperpituitarism which has begun in early life and is actually comparable to the experimental rat-hyperpituitarism it is difficult to explain the absence in most giants of sexual potency and the want of fully developed secondary sex characters. Moreover, in acro-

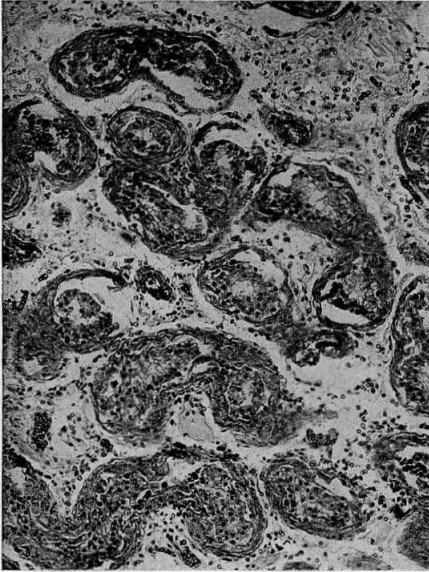


FIG. 101.

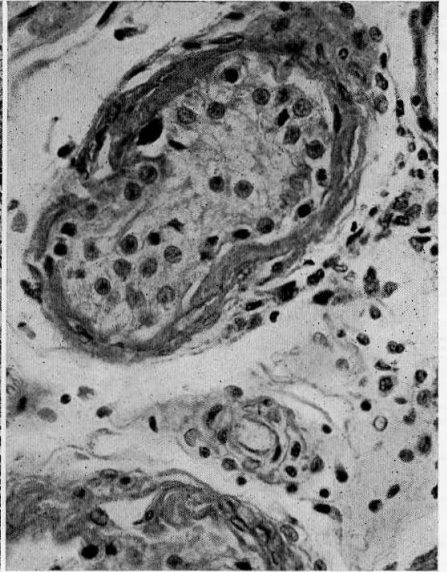


FIG. 102.

FIGS. 101 and 102. Case II. Sections of testis, to show scant differentiation of spermatogenous epithelium and increase of interstitial tissue without cells of Leydig. Stain H. and E. Left,  $\times 80$ ; right,  $\times 300$ .

megaly itself there is a tendency in many cases as the disease progresses for its victims to lose their potency and virility and to become adipose and sexually dystrophic. This might be interpreted as an indication that the 'acromegalism' was becoming dormant and tending to be replaced by a state of ultimate hypopituitarism which would account for the process. However, if this were so one would expect the cells of the adenoma to more definitely lose their acidophilic characteristics than they actually appear to do.



It is unwise to be drawn too far into speculation concerning matters for which there is as yet no experimental basis. There may possibly be two hormones produced by the anterior lobe: one which chiefly influences growth; the other chiefly influencing the activities of the gonads. The authors were inclined to believe this might be so by finding that commercial "Antuitrin" is capable of checking the œstrous cycle in rats

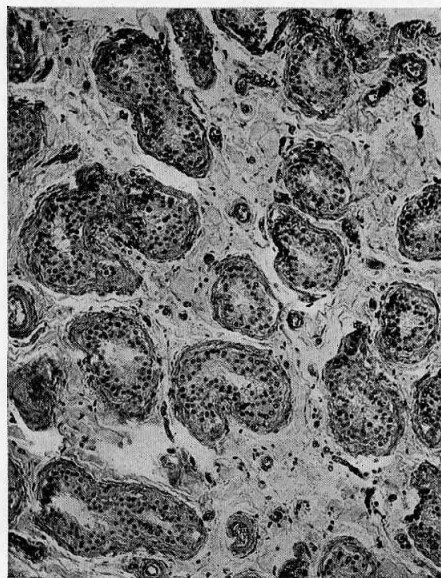


FIG. 103.

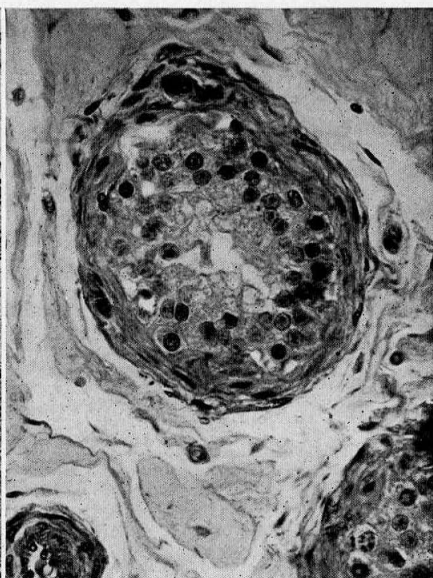


FIG. 104.

FIGS. 103 and 104. Case III. Testis, showing the hyaline character of the interstitial tissue and the absence of spermatozoa. Stain H. and E. Left,  $\times 80$ ; right,  $\times 300$ .

without producing any appreciable effect on growth; and H. M. Evans hints that some of his experiments have suggested the possibility of a double substance. In these questions of multiple hormones for a given gland there are two schools, the believers and the doubters, and as in the case of the multiple properties possessed by the extracts of the hypophyseal posterior lobe we incline to side with those who favor a single hormone rather than multiple ones.

After this discussion of the clinical aspects of the gonadal changes as

they relate to acromegaly we may return to a consideration of the histopathological aspects of the organs in the three autopsied males included in this report.

Case I was a man who retained his outwardly virile appearance to the end. He was hirsute, never became especially adipose, and though possibly impotent showed no genital atrophy. The testes not only give evidence of active spermatogenesis but there appears to be a great excess of the interstitial cells of Leydig (Figs. 99 and 100).

Case II, according to the anamnesis had been notoriously virile during the early years of his marked accession of growth, but subsequently became impotent, adipose, and lost his essentially masculine hirsutes. The testes (Figs. 101 and 102) show atrophy; there is some differentiation in the spermatogenous cells but no formed spermatozoa; the interstitial tissue, though in excess, contains only a few scattered cells of Leydig (Figs. 101 and 102).

Case III had an early post-marital loss of libido with impotence, became adipose, and lost his essentially masculine hirsutes. The testes show a still more advanced atrophy of the seminiferous tubules with no differentiation whatsoever in the cells; the interstitial tissue shows an advanced hyalinization with no cells of Leydig to be recognized (Figs. 103 and 104).

## VI.

### SUMMARY AND CONCLUSIONS.

Four cases of acromegaly of differing clinical types are described, illustrating the kaleidoscopic pathological anatomy of the disease. In one, a man of huge frame, the general splanchnomegaly and widespread changes in the endocrine series quite overshadowed the small hypophysial lesion. In another, an acromegalic giant, the neighborhood symptoms of the tumor dominated the picture. The two other cases were small individuals. In one of them an enormous intracranial adenoma unsuspected during life was masked by cardiovascular and diabetic symptoms, and at autopsy adenomata were found in many of the ductless glands. In the other, on the contrary, a woman who died from diabetic coma, the postmortem findings were relatively insignificant and the hypophysial tumor was small.

Of the two cases which had the smallest hypophysial lesion one was of small stature and the other gigantic. Of the two cases which had the largest hypophysial adenomata one was of small stature and the other an acromegalic giant. Of the two acromegalic giants one had extreme cardiovascular changes, the other but slight; and the same was true of the two small individuals.

The only constant pathological findings in all cases were: (1) the commonly recognized overgrowth of the mesodermal tissue; (2) the less commonly emphasized and disproportionate splanchnomegaly, which chiefly affected the liver and kidneys; (3) the more or less general polyglandular anomalies accompanied by a tendency to adenomatoses; and (4) a central hyperplasia (two cases) or an adenoma of the hypophysis (two cases), the cells composing the lesion in all four instances containing demonstrable acidophilic granules.

Though in the early studies of acromegaly chief stress was laid on the hypertrophic changes in the peripheral, chiefly the acral tissues, upon the enlargement of parts of the central nervous system, and finally on the hypophysial tumor, the general splanchnomegaly, though appreciated, was lost sight of and the condition of the other ductless glands only casually mentioned. Of late years these latter aspects of the malady have come more into the foreground.

There have been many theories advanced in explanation of acromegaly,

which have been presented by one of us<sup>27</sup> in an earlier paper in the series. One of them ascribes the enlargement of the pituitary to a secondary effect of the disease; another considered the disorder to be polyglandular in nature, the hypophysis playing only a part which happens to be a striking one merely because of the accident of its anatomical location; another lays the malady solely at the door of the anterior lobe and of certain of its cells which become functionally modified so as to produce a profound change in the general metabolism of the body.

Even today, any one of these theories on a purely histopathological basis might be sustained by telling arguments, but the unescapable fact remains that all cases of acromegaly show an acidophilic adenoma of the hypophysis. Moreover extracts of the part of the gland from which these adenomata arise alone are capable of producing in an experimental animal overgrowth not only of the mesoblastic tissues but splanchnomegaly as well, together with changes in the ductless glands comparable to that seen in acromegaly and gigantism.

*Acromegaly*, then, is a chronic disease of adult life, outwardly characterized by the acral changes first emphasized by Marie. The pituitary body, though not invariably enlarged, is usually, and sometimes enormously so, by an hyperplastic or adenomatous process composed of acidophilic cells. It is these granular cells which elaborate or at least hold a hormone which injected into certain animals provokes overgrowth (gigantism), and which are almost certainly the cause of acromegaly and gigantism in man.

As an accompaniment of the disease, there usually occurs a general splanchnomegaly of the viscera which is disproportionate to the general enlargement of the body. In addition, notable glandular changes often associated with adenomata, occur in the other endocrine organs, which gives to the malady its unusual polyglandular aspects. There is almost always an increase in the adrenal cortex; usually an enlarged or persistent thymus; in about a third of the cases a colloid goitre; often enlargement of the parathyroids; often a functional derangement of the pancreatic islets; and invariably changes indicative of atrophy or dysfunction of the gonads.

It is safe to say that a derangement of the pituitary anterior lobe affects the body as a whole far more seriously than a primary derangement of any other member of the endocrine series. Figuratively speaking, it may be said to represent the keystone of the endocrine arch.

## VII.

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