Cushing’s Syndrome and the Hypophysis
A Re-evaluation of Pituitary Tumors and Hyperadrenalism

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In 1933, Harvey Cushing delivered a lecture before the Harvey Cushing Society entitled “Dyspituitarism: Twenty years later. With Special Consideration of the Pituitary Adenomas.” At that time, he presented an hypothesis linking the characteristic endocrinopathy which now bears his name to basophilic adenomas of the pituitary gland. Concluding the lecture, Dr. Cushing prophesied “but however much of all that I have said regarding these adenomas and their secretory effects may be fact and how much fancy, we may be sure that in the course of time the greater part of it will be modified out of all recognition.” Another three decades have passed and it may therefore be pertinent to re-examine some of the present concepts regarding Cushing’s syndrome and pituitary tumors.

In the naturally occurring forms of this syndrome, the majority of patients are found to have bilateral adrenal hyperplasia. About 15 to 20 per cent of patients have adrenal adenomas or carcinomas capable of autonomous secretory activity. Macroscopic pituitary tumors are present in less than 10 per cent of patients with Cushing’s syndrome. Occasionally the characteristic endocrinopathy is seen in patients with malignant tumors of other organs—lungs, pancreas or thymus. The present report will be restricted to a consideration of those cases of Cushing’s syndrome associated with histologically verified pituitary tumors.

Cushing’s Syndrome and Basophil Tumors of the Pituitary Gland

Although Dr Cushing believed that the primary disorder in “dyspituitarism” was one of pituitary basophilism, it is clear, even on reexamination of his original reports, that the disease entity could on occasion be associated with non-basophilic pituitary tumors. Four of the 14 cases presented in the original series, including 1 from Dr Cushing’s own clinic (patient Miss L.), had non-basophilic adenomas. While minute basophilic adenomas are occasionally found at post-mortem examination in patients with hyperadrenalism, it is often difficult to evaluate their clinical significance since similar microscopic cell aggregates are occasionally seen in normal patients. Also, there is rather conclusive pathological evidence that many of the alterations in the basophilic cells described as characteristic of Cushing’s syndrome may occur as a consequence of increased steroid secretion rather than representing the primary etiologic agent. Moreover, clinical experience has demonstrated that basophilic adenomas rarely attain sufficient size to compress visual pathways, to produce enlargement of the sella turcica, or otherwise to bring the patient to the attention of a neurologist.

The paucity of occurrence of clinically significant basophilic adenomas and the realization that the characteristic endocrinological changes of Cushing’s syndrome could be produced by adrenal cortical hormones of either exogenous or secretory origin have caused many contemporary clinicians to regard Cushing’s syndrome as a primary adrenal disorder. Consequently the potential etiological role of the pituitary in this disease has been steadily downgraded. This view of Cushing’s syndrome as a primary adrenal disorder fails adequately to account for bilateral adrenal hyperplasia which should
most reasonably be either of primary pituitary origin or mediated via hypersecretion of the pituitary gland. Recently scattered case reports have appeared in the literature, associating Cushing’s syndrome with clinically significant non-basophilic tumors of the pituitary gland (see Table 1). Many of these pituitary tumors which are most commonly composed of chromophobe cells produce their initial manifestations only after adrenalectomy has been performed. In this report, we will present 5 cases from the Jefferson Medical College Hospital and review 50 cases previously reported in the literature associating Cushing’s syndrome with non-basophilic tumors of the pituitary gland.

Clinical Material

We have summarized the clinical records and pathological data of 5 patients with Cushing’s syndrome, proven to have non-basophilic pituitary tumors. Four of these cases were obtained from the files of the Jefferson Medical College Hospital over the past 17 years. No patient with Cushing’s syndrome associated with a proven basophilic adenoma was seen in this clinic during this period of time.

Case 1. (JMCH #U-5391). M.W., a 25-year-old white woman, was admitted in October, 1947, with the clinical stigmata of Cushing’s syndrome. Three years prior to admission, she noticed the onset of amenorrhea and weight gain. A year later, diabetes was discovered which subsequently required daily injections of insulin for control. There were no specific complaints of headaches or visual disturbances.

Examination disclosed a markedly obese, plethoric female with obvious facial hirsutism, a moon-face, truncal obesity, purple abdominal striae, and a “buffalo hump” (Fig. 1). The patient was hypertensive. Skull x-ray revealed an expanded sella with demineralization of the dorsum sellae. Bone radiographs disclosed severe osteoporosis of the spine.

Laboratory studies disclosed an elevation of the fasting blood sugar and a positive glucose tolerance test. Urinary 17-ketosteroids were in the high normal range.

Operation, October 28, 1947. A total left adrenalectomy and a partial right adrenalectomy were performed. Both adrenal glands were diffusely enlarged, and the microscopic examination revealed adrenal hyperplasia. The patient’s immediate postoperative course was uneventful, but 48 hours after operation her blood pressure fell precipitously and she expired within a very short time.

Autopsy. The pituitary gland was 3 to 4 times normal size. The enlarged glandular tissue extended laterally eroding the anterior and posterior clinoid processes on the left. The diaphragma sellae bulged slightly, but there was no suprasellar tumor extension. Microscopical examination of the pituitary tumor revealed a well circumscribed, partially cystic, pituitary adenoma composed of polygonal cells arranged in sinusoids and nests. The cells composing the adenoma in some fields were arranged around engorged thin wall vessels and in other areas were scattered loosely. The nuclei were round to oval with scarce chromatin. The nucleoli were prominent. The cytoplasm was pale pink, but no specific granules were revealed with Rasmussen stain. An occasional pale vesiculated giant nucleus was present and a rare mitotic figure was noted. There were scattered areas of cystic and necrotic degeneration as well as areas of old hemorrhage. The surrounding hypophysis was compressed by the tumor and Crooke’s changes were prominent within the remnant of non-adenomatous pituitary tissue.

![Fig. 1. Case 1, on admission.](image-url)
### TABLE 1
Summary of 55 cases of Cushing's syndrome with non-basophilic pituitary tumors

<table>
<thead>
<tr>
<th>Group</th>
<th>Reference (1 case each unless shown)</th>
<th>Case No. (if any)</th>
<th>Reference No.</th>
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<tr>
<td><strong>Group I</strong></td>
<td>Cushing, 1933</td>
<td>T.L.</td>
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<td>Chromophobe Adenomas: Typical (22 cases)</td>
<td>Fuller &amp; Russell, 1936</td>
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<td></td>
<td>Mellgren, 1945</td>
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<td></td>
<td>Plotz et al., 1932</td>
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<td></td>
<td>Doret, 1935</td>
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<td></td>
<td>Kernohan &amp; Sayre, 1936</td>
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<td></td>
<td>Nelson et al., 1958</td>
<td>Pt. C.R.</td>
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<td>Marks, 1959</td>
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<td>Salassa et al., 1959 (6)</td>
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<td>Cassidy, 1960 (2)</td>
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<td>Mannix et al., 1960</td>
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<td>Myerson &amp; Hingston, 1962</td>
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<td>King, 1962</td>
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<td>Rovit &amp; Berry, 1965 (3)</td>
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<td><strong>Group II</strong></td>
<td>Wieth-Pederson, 1932</td>
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<td>Chromophobe Adenomas: Atypical (7 cases)</td>
<td>MacCallum et al., 1935</td>
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<td></td>
<td>Creile et al., 1936</td>
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<td>Wijnbladh &amp; Nirldon, 1939</td>
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<td>Lisser, 1944</td>
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<td>Russfield et al., 1956</td>
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<td>Dingman &amp; Lin, 1962</td>
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<td><strong>Group III</strong></td>
<td>Chromophobe—basophils</td>
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<td>Mixed Pituitary Adenomas (7 cases)</td>
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<td>Siebenmann, 1955</td>
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<td>Montgomery et al., 1959 (2)</td>
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<td>Petit-Dutaillis et al., 1938</td>
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<td>Chromophobe—eosinophil</td>
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<td>Reichmann, 1919</td>
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<td>Eosinophil—Chromophobe—Basophil</td>
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<td>Elie &amp; Pearson, 1951</td>
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<td><strong>Group IV</strong></td>
<td>Albright &amp; McMahon, 1941</td>
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<td>Non-Granular Pituitary Adenomas (3 cases)</td>
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<td>Rees &amp; Baylis, 1959</td>
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<td><strong>Group V</strong></td>
<td>Malignant chromophobe tumors</td>
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<td>Malignant Pituitary Tumors (13 cases)</td>
<td>Forbes, 1947</td>
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<td></td>
<td>Feiring et al., 1953</td>
<td>#7</td>
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<td></td>
<td>Salassa et al., 1959</td>
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<td>Haugen &amp; Laken, 1960</td>
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<td>Bricaire et al., 1961</td>
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<td>Schols et al., 1961</td>
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<td>Rovit &amp; Berry, 1965</td>
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<td>Malignant basophil tumors</td>
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<td>Cohen &amp; Dible, 1936</td>
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<td>Sheldon et al., 1954</td>
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<td>Simkin et al., 1962</td>
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<td>Malignant mixed pituitary tumors</td>
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<td>Browne et al., 1955</td>
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<td>Doret, 1956</td>
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<td>Shrank &amp; Turner, 1960</td>
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<td><strong>Group VI</strong></td>
<td>Graef et al., 1936</td>
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<td>Carcinoma of Adrenal with Pituitary Tumors (3 cases)</td>
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<td>Rovit &amp; Berry, 1965</td>
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Pathological diagnosis: Chromophobe adenoma of the pituitary gland.

Case 2 (CHH #79819).* A.R., a 39-year-old white woman, was admitted to the Chestnut Hill Hospital on October 24, 1961, in stupor. History. According to the patient's mother, she had been very thin and small in stature until the age of 9 years when she suddenly began to gain weight. This weight gain while a change from her previous status was not initially considered excessive. However, 5 years prior to admission the weight gain became especially marked. Two years later she began to complain almost constantly of headaches and was told that she had "high blood pressure." Two weeks prior to admission, she suddenly cried out, began to talk incoherently, and appeared not to recognize her mother or other family members. No definite convulsive manifestations were seen. Following this episode she became progressively lethargic, complained of severe pain in her head and was noted to have paresis of the right side of her face associated with ptosis and proptosis of the right eye. A right carotid arteriogram disclosed a large pituitary tumor, and she was admitted to Chestnut Hill Hospital.

Examination revealed a stuporous female with the obvious clinical stigmata of Cushing's syndrome: obesity, buffalo-hump, moon-face, facial hirsutism, and purple abdominal striae. Blood pressure was 160/100. Neurological examination disclosed ptosis, proptosis, and external strabismus of the right eye and a right peripheral facial paresis. The right pupil was larger than the left and reacted only sluggishly to light. The neck was extremely rigid.

Laboratory studies included a hemoglobin of 12.2 gm., and a white count 19,200 with 89 per cent polymorphonuclear leukocytes. The hematocrit was 39 and the FBS 128 mg. per cent.

Operation, October 26, 1961. A right frontal craniotomy was performed. Inspection of the chiasmal region revealed a "soft encapsulated tumor mass posterior to the right optic nerve encroaching upon and pushing the right internal carotid artery forward." Needle aspiration of this tumor failed to reveal a cyst. Further exposure disclosed that the great bulk of the neoplasm extruded from the sella and had extended behind the chiasm. The posterior limits of the tumor could not be defined. A subtotal intracapsular removal of the neoplasm was performed. The patient never regained consciousness, developed seizures and respiratory difficulty and expired on October 28, 1961.

Autopsy. Both adrenal glands were distinctly larger than normal, each weighing 12.2 gm. The cortex of each adrenal gland measured 0.2 cm. in thickness. Microscopical examination of the adrenal glands revealed diffuse and nodular hyperplasia of the cortex. Other positive pathological findings were left ventricular hypertrophy, uterine and ovarian atrophy, and generalized osteoporosis.

Upon removal of the brain, a large irregular, soft, grey, necrotic tumor was found, arising from the pituitary gland. This tumor compressed the cranial nerves II through VI on the right and extended posteriorly to compress the right side of thepons and medulla, pushing the brain stem towards the left. The tumor also extended superiorly, compressing the right antero-inferior aspect of the third ventricle.

Microscopical examination of the tumor revealed moderate sized cells with normal nuclei containing small amounts of chromatin. These cells contained little or no cytoplasm and no specific granules could be demonstrated with Pearse's Trichrome-PAS stain. The majority of the cells were arranged in trabeculae around the connective tissue stroma. Within the tumor were areas of old and recent hemorrhage. In the compressed residual adrenohypophysis there were several basophilic cells showing Crooke's changes.

Pathological diagnosis: Chromophobe adenoma containing areas of old and recent hemorrhage.

Case 3 (JMCH #18873). D.W., an 18-year-old colored woman, was first seen at Philadelphia General Hospital in June, 1960. She complained at that time of recent obesity with a gain in weight of 14 lbs., menstrual irregularity, and lethargy, all of one year's duration. Examination revealed hypertension (145/105) and the classical picture of Cushing's syndrome with obesity, buffalo-hump, hirsutism, acne, and purple striae (Fig. 2). Visual acuity was normal.

Laboratory investigations disclosed mild diabetes, slight eosinopenia, and elevation of 17-ketosteroids (47.0 mg./24 hr.), and plasma 17-hydroxy steroids (30.9 gamma/100 ml.). Skull radiographs were normal. There was no enlargement of the sella turcica. An i.v. pyelogram was normal. Presacral CO2 insufflation was negative on the right; the left adrenal region could not be demonstrated. Visual field and funduscopic examinations were normal.

Operation, August 24, 1960. A bilateral total adrenalecctomy was performed. Both adrenals were about 3 times normal size, the left adrenal weighing 15 gm. and the right, 10 gm. The pathological report stated "both adrenal glands are characterised by marked thickening of the cortex. The zona glomerulosa is extremely narrow while the fasciculata is hyperplastic with extensive vacuolization of its cells."
The patient's immediate postoperative course was complicated by atelectasis, pneumonitis and a temporary Addisonian crisis, but she was eventually discharged from hospital on September 8, 1960, receiving cortisone 12.5 mg. tid and fluorohydrocortisone 0.1 mg. qd.

Soon after discharge she noticed a gradual, but progressive darkening of her skin, most marked in her surgical scars and in the natural creases of her skin. She lost weight following adrenalectomy and the stigmata of Cushing's disease gradually disappeared (Fig. 8). She resumed her normal menstrual cycle 3 months after operation and her periods continued regularly until April, 1961, when she became pregnant. Coincident with the onset of pregnancy she began to experience left frontal headaches and intermittent attacks of blurred vision mainly in the left eye.

2nd Admission. The patient was readmitted to the obstetrical service of the Philadelphia General Hospital in February, 1962. Ophthalmological examination at that time revealed a diminution in visual acuity with a small central scotoma in the left eye (V.O.D. 6/9, V.O.S. 6/30). Funduscopic examination was normal. Skull radiographs including special views of the sella turcica demonstrated a symmetrical ballooning of the sella turcica with thinning of the floor of the sella and demineralization of the posterior clinoids. Cerebrospinal-fluid pressure was 150 mg. of water and the cerebrospinal-fluid protein 38 mg. per cent. Electroencephalography demonstrated random theta activity most marked in both temporal regions. During this hospital admission, she was delivered of a normal boy under epidural anesthesia. Postpartum convalescence was uneventful and she was discharged from hospital on March 14, 1962, receiving cortisone 12.5 mg. tid.

3rd Admission. Her headaches subsided slightly with the conclusion of her pregnancy—although they still continued to be present. However, her skin progressively darkened and her vision rapidly deteriorated, necessitating admission to the Jefferson Medical College Hospital on June 13, 1962, 22 months after adrenalectomy. Examination revealed none of the stigmata of Cushing's syndrome. Blood pressure was 100/80. Her skin was extremely dark, especially in the natural skin creases. Milky fluid could be manually expressed from the right breast. Eye examination disclosed decreased visual acuity (V.O.D. 6/12, V.O.S. 6/30). There was a right hemianopsia in the right eye and a left superior temporal quadrantopsia in the left eye. Funduscopic examination showed mild temporal pallor of the right disc. Skull radiographs revealed marked ballooning of the sella turcica with erosion of both anterior and posterior clinoid processes and demineralization of the dorsum sella. A fractional pneumoencephalogram demonstrated a large intrasellar tumor with suprasellar extension (Fig. 4). Cerebrospinal-fluid pressure was normal and the cerebrospinal-fluid protein was 24 mg. per cent.

On the morning following pneumoencephalog-
Cushing’s Syndrome and the Hypophysis

The postoperative course was uneventful. Cranial nerve palsies disappeared soon after operation. Two days postoperatively, visual acuity was 6/6 bilaterally and fields were full to confrontation. Temporary diabetes insipidus developed and was controlled with small injections of posterior pituitary extract. Within 1 week after operation, the skin began to lose its dark pigmentation and progressive lightening was maintained for the following year. Postoperatively she received x-ray radiation to the sellar region (4800 r).

She has been followed in clinic since operation and is working full time as a saleslady, taking cortisone 12.5 mg. daily and DOCA 2 mg. b.i.d. There are presently no signs of either Cushing’s syndrome or chiasmal compression.

Case 4 (JMC #2557). A.K., a 34-year-old white woman, was first admitted in October, 1934, with physical changes characteristic of Cushing’s syndrome plus “glassy vision.” Prior to 1949, she had been perfectly well, was married and the mother of three healthy children aged 13, 11, and 8 years. In 1949, she developed menstrual irregularity and amenorrhea. This led to an hysterectomy at another hospital. No primary uterine or ovarian pathology was found. Sixteen months before admission, she noted the onset of generalized fatigue, weakness, swelling of face and extremities, and a progressive gain in weight of 40 lbs. In the month just prior to hospital admission, she was aware of increasing hirsutism, especially around the face, and an acneeform eruption of the face and chest. At this time she also experienced bouts of “glassy vision” occurring 1 to 5 times per day.

Examination revealed an obese plethoric woman with a round hirsute face, and an acneeform eruption of the face and neck (Fig. 5). There was a prominent “buffalo hump” in her upper thoracic region. Abdominal examination demonstrated a large anterior pancreas and several purple striae. The hands and feet were dry and swollen with marked erythema of the palms and soles. The blood pressure was 180/120. Neurological examination was within normal limits. Visual acuity and fields were normal. Funduscopy examination disclosed grade 2 arteriosclerotic changes. The optic discs showed no atrophy or papilledema.

The hemoglobin was 13 gm., there were 4,570,000 red blood cells and 8,500 white blood cells with 89 per cent lymphocytes. The fasting blood sugar was 85 mg. per cent with a positive glucose tolerance curve. The BMR was 14 and the $I^{31}$ uptake 16 per cent. The PBI was 4.4 micrograms/cc. Serum electrolytes were normal. Quantitative urine estrogens were 132 and 440 m. units/24 hr. (normal less than 32 m. units/24

Fig. 4. Brow-up lateral PEG. There is a large intrasellar tumor. The chiasmatic cistern is poorly filled. The anterior portion of the 3rd ventricle is elevated.

raphy, the patient suddenly developed severe headache, blurred vision, lethargy and nuchal rigidity. The right pupil was widely dilated and failed to react to light. The left pupil was slightly dilated reacting only sluggishly to light. There was paralysis of the 3rd and 6th nerves on the right, and hypaesthesia over the ophthalmic and maxillary zones of the right trigeminal nerve. The right corneal reflex was absent. She could not distinguish finger movement with either eye at 6 inches. A diagnosis of acute pituitary apoplexy was made, the patient was given I.V. hydrocortisone, and transported to the operating room.

Operation. A right frontotemporal craniotomy was performed and the chiasmal region exposed. There was a large pituitary adenoma which had grown out of the sella. The optic nerve and chiasm were splayed over the dome of the adenoma which was tense and fluctuant. The capsule was incised and about 1 cc. of chocolate-brown fluid extruded. The remaining contents of the adenoma were soft and necrotic and could easily be removed by suction. About 90 per cent of the adenoma was removed, thoroughly decompressing the optic nerve and chiasm. Histological examination of the pituitary tumor revealed clusters of small polygonal cells separated by a connective tissue stroma. The cell nuclei for the most part were small, round, and pyknotic. At times, however, larger vesiculated nuclei were present. The cytoplasm of the cells varied; some specimens contained sparse fragments of finely eosinophilic material while others exhibited a ground-glass appearance. Within the tumor, there were areas of old and recent hemorrhage.

Pathological diagnosis: Chromophobe adenoma.
of blood vessels. The cells contained abundant eosinophilic cytoplasm. The nuclei were vesicular, with 1 or 2 prominent nucleoli. In cell nests at a distance from the thin walled vessels, the architecture was irregular and the nuclei showed varying degrees of degeneration. The tumor contained foci of mucinous degeneration and occasional calcific deposits. Occasional mitoses were seen.

Pathological diagnosis: Anaplastic agranular carcinoma of the pituitary.

The patient's postoperative course was initially gratifying. Her blood pressure gradually receded to normal levels (162/110 to 126/80), diabetes disappeared and her general strength improved. She was discharged from hospital without hormone medication on December 20, 1954.

She was readmitted to hospital 2 months later for general evaluation. The physical manifestations of Cushing's syndrome were no longer pronounced. Hirsutism had disappeared, the purple striae had faded, the acneiform rash was barely visible, and the timbre of her voice was less husky. General fatigability, hypertension, and the attacks of blurred vision were no longer present. Neurological and ophthalmological examinations were normal. Laboratory studies at this time revealed a mild anemia (10 gm.), mild diabetes (FBS 92 mg. per cent) and hypo-

Fig. 5. Case 4, on admission.

Fig. 6. Lateral skull radiograph. The sella turcica is enlarged. Calcification is seen in or about the pituitary fossa.

hr.). Urinary 17-ketosteroids were 13.7 mg./24 hr. (normal 10–15 mg./24 hr.). The urinary gonadotropine determination was less than 6 m. units/24 hr. (normal 6–40 m. units/24 hr.). The cerebrospinal-fluid pressure was 240 mm. of water and the cerebrospinal-fluid protein was 124 mg. per cent.

X-ray of chest demonstrated multiple calcified pleural plaques throughout both lung fields. Radiographs of the spine revealed generalized demineralization of the skeleton and a compression fracture of the body of L4. Skull radiograph disclosed the sella to be greatly expanded and the external clinoids rarefied. There was an amorphous irregular calcification which appeared to be located in or about the sella, particularly on the left side (Fig. 6). An i.v. urogram was normal. Retroperitoneal air studies disclosed a normal right kidney and adrenal; the left renal area was not well visualized.

Operation, Nov. 17, 1954. Because of persistence of the visual symptoms and the suspicion that a pituitary tumor was contributing to her hyperadrenalism, a craniotomy was performed. Arising from the sella, between the optic nerves and anterior to the chiasm there was a 5 mm. tongue of tumor tissue. This lay free and did not press on either optic nerve or the chiasm. The diaphragma sellae bulged slightly; incision disclosed a large amount of greyish-white, stringy, avascular tumor tissue within the pituitary fossa. This tissue was removed. Microscopic examination of the operative specimen revealed a cellular neoplasm with sheets and nests of polygonal cells often arranged radially around blood vessels. The cells contained abundant eosinophilic cytoplasm. The nuclei were vesicular, with 1 or 2 prominent nucleoli. In cell nests at a distance from the thin walled vessels, the architecture was irregular and the nuclei showed varying degrees of degeneration. The tumor contained foci of mucinous degeneration and occasional calcific deposits. Occasional mitoses were seen.

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She was readmitted to hospital 2 months later for general evaluation. The physical manifestations of Cushing's syndrome were no longer pronounced. Hirsutism had disappeared, the purple striae had faded, the acneiform rash was barely visible, and the timbre of her voice was less husky. General fatigability, hypertension, and the attacks of blurred vision were no longer present. Neurological and ophthalmological examinations were normal. Laboratory studies at this time revealed a mild anemia (10 gm.), mild diabetes (FBS 92 mg. per cent) and hypo-
thyroidism (I\textsubscript{131} uptake 6 per cent, BMR-17, PBI 3.06 micrograms/cc.). Quantitative urine estrogens were 44 m. units/24 hr. (normal 32-200 m. units/24 hr.). Urine gonadotropins were less than 6 m. units/24 hr. and urinary 17-ketosteroids were 11 mg./24 hr. (normal 10-15 mg./24 hr.). She was discharged from hospital 3 weeks later.

2\textsuperscript{nd} Admission. Her improvement was short-lived and within weeks after discharge, her previous symptoms recurred. Over the next few months she again experienced unusual fatigue, hirsutism, acniform rash, buffalo-hump, swelling of hands and feet, pruritus, polydipsia, polyuria and attacks of blurred vision. These symptoms necessitated readmission to hospital on June 17, 1955.

Physical examination at this time again revealed the obvious stigmata of Cushing's syndrome—in all ways comparable to her preoperative appearance—save that she had lost about 20 lbs. in weight. Blood pressure was 150/100. Examination at this time also revealed for the first time a severe impairment of memory, lassitude, and marked restlessness. There was marked visual impairment in the left eye (V.O.D. 20/30, V.O.S. 20/100). Visual field examinations were unreliable because of the patient's confusion. There was a partial third nerve paresis on the right. There was pALLor of the left optic disc.

Laboratory studies revealed severe anemia (6.9 gm.), uncontrolled diabetes and a hypochloremic, hypokalemic alkalosis. The anemia was felt to be hemorrhagic in origin and persisted despite multiple transfusions. The diabetes and electrolyte disorders were brought under control by appropriate fluids and insulin. Urinary 17-ketosteroids were normal (9.6 mg./24 hr.). Urinary estrogens were normal (44 m. units/24 hr.). Total urinary corticoids were elevated (17.75 mg./24 hr.). X-rays of the spine revealed metastatic changes involving the mid-dorsal vertebra. A chest radiograph disclosed old calcified pleural plaques, tortuosity of the thoracic aorta, and fluffy areas compatible with moniliasis in both lung fields. Skull radiographs revealed no increase in size of the sella when compared with early postoperative films. A retroperitoneal air study demonstrated a circumscribed rounded mass in the region of the left adrenal gland.

Operation, Aug. 20, 1955. Because of the recrudescence of the Cushing’s syndrome and the radiographic demonstration of a left adrenal mass, bilateral adrenal exploration was undertaken. Both adrenal glands were grossly hyperplastic (total weight 80 gm.). In addition, there was a small well-circumscribed metastatic nodule in the left adrenal gland. A bilateral total adrenalectomy was performed. Microscopic examination of the adrenals showed diffuse and nodular hyperplasia of both adrenal cortices. This was especially pronounced in the zona fasciculata. In addition to the hyperplasia, the left adrenal gland contained a 1 cm. circumscribed metastatic mucinous adenocarcinoma.

The patient was maintained on supplemental cortisone therapy and her immediate postoperative course was quite good. However, on the 5th day after operation, she experienced a precipitous drop in blood pressure and died 1\frac{1}{2} hours later. Permission for post-mortem examination could not be obtained.

Case 5 (JMCH #35395). J.T., a 68-year-old white woman, was admitted to the Jefferson Medical College Hospital in March, 1956. Three months prior to admission, she first experienced headaches and occasional diplopia which she attributed to “eye strain.” During these 3 months, she also noted the onset and rapid progression of obesity, moon facies, hirsutism, purple abdominal striae, buffalo-hump and hypertension.

Examination. Physical examination on admission confirmed these changes which were consistent with Cushing’s syndrome. Chest x-ray revealed multiple “cannonball” lesions typical of metastases scattered throughout both lung fields. Skull radiographs disclosed numerous small circumscribed osteolytic lesions in the cranial vault. The sella turcica was moderately enlarged, consistent with an expanding intrasellar mass. An I.V. urogram revealed a mass lesion in the region of the superior pole of the left kidney. Laboratory studies indicated mild diabetes, and increased blood phosphorus and alkaline phosphatase. The urinary 17-ketosteroids were 42 mg./24 hr. (normal 5-13 mg./24 hr.).

In view of the sudden onset and rapid progression of the physical signs of Cushing’s syndrome in this patient, together with radiographic evidence of metastatic lesions of the lungs and skull, and an adrenal mass demonstrated by urography, a presumptive diagnosis was made of carcinoma of the left adrenal with generalized metastasis. The patient was discharged from the hospital. No additional information is available about the further course of the disease. She died in November, 1956, 8 months after the initial onset of symptoms.

Autopsy. The left adrenal gland was almost entirely replaced by a large globular, greyish-tan, circumscribed neoplasms weighing 120 gm. Gross sections of this tumor revealed soft variegated material admixed with occasional areas of frank hemorrhage. On microscopic examination, the tumor was found to be a typical adrenal carcinoma. There were obvious metastatic nodules present in the retroperitoneal lymph nodes, liver, lungs, pleura, pericardium, diaphragm, mediasti-
num and posterior chest wall. The right adrenal gland was atrophic (weight 3.5 gm.). Examination of the pituitary region disclosed a large greyish nodule (1 cm. in diameter) arising from and occupying most of the anterior lobe of the hypophysis (Fig. 7). This nodule had expanded the sella turcica. Microscopic examination showed a circumscribed, but not encapsulated adenoma of the adenohypophysis. This was vascular and was composed of rather uniform small round cells with indistinct pale pink cytoplasm containing no specific granules.

Pathological diagnosis: Chromophobe adenoma of the pituitary.

Collation of Symptomatic and Pathological Data

1. Pituitary and Adrenal Pathology (Table 2). Three patients (Cases 1, 2, 3) had chromophobe adenomas of the pituitary and bilateral adrenal hyperplasia. One patient (Case 4) had an anaplastic, agranular carcinoma of the pituitary and bilateral adrenal hyperplasia. This patient also was found at operation to have a small metastatic adenocarcinoma in the hyperplastic left adrenal gland. The final patient (Case 5) had a malignant carcinoma of the left adrenal gland, and, in addition to her adrenal pathology, a chromophobe adenoma of the pituitary.

2. Symptomatology (Table 3). The 5 patients in this series were females, aged from

<table>
<thead>
<tr>
<th>Case No. and Specimen</th>
<th>Adrenal</th>
<th>Pituitary</th>
<th>Remaining Parenchyma</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adenoma</td>
<td>Gross</td>
<td>Cell Type</td>
</tr>
<tr>
<td>1 (Autopsy)</td>
<td>Bilaterally enlarged</td>
<td>Diffuse cortical hyperplasia</td>
<td>Pituitary enlarged</td>
</tr>
<tr>
<td>2 (Biopsy and Autopsy)</td>
<td>Bilaterally enlarged (24.4 gm.)</td>
<td>Diffuse, cortical hyperplasia</td>
<td>Massive adenoma Suprasellar extension</td>
</tr>
<tr>
<td>3 (Biopsy)</td>
<td>Bilaterally enlarged (25 gm.)</td>
<td>Diffuse cortical hyperplasia</td>
<td>Intra- and suprasellar adenoma</td>
</tr>
<tr>
<td>4 (Biopsy)</td>
<td>Bilaterally enlarged (30 gm.) Tumor: left</td>
<td>Diffuse, cortical hyperplasia Lt.: metaplasia mucinous adenocarcinoma</td>
<td>Intra- and suprasellar adenoma</td>
</tr>
<tr>
<td>5 (Autopsy)</td>
<td>Left: Carcinoma (180 gm.) Rt.: Atrophic (8.5 gm.)</td>
<td>Primary adrenal cortical carcinoma metastasis to lymph nodes, liver, lungs, pleura.</td>
<td>Adenoma replacing much of adenohypophysis</td>
</tr>
</tbody>
</table>
Cushing’s Syndrome and the Hypophysis

TABLE 3
Selected clinical characteristics

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Sex and Age</th>
<th>Pathological Diagnosis</th>
<th>Duration of Endocrine Symptoms</th>
<th>Visual Symptoms</th>
<th>Pituitary Apoplexy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F 25</td>
<td>Chromophobe adenoma</td>
<td>2-3 yrs.</td>
<td>None</td>
<td>No</td>
</tr>
<tr>
<td>2</td>
<td>F 39</td>
<td>Chromophobe adenoma</td>
<td>3-5 yrs.</td>
<td>Right III N. paresis</td>
<td>Yes, 2 wks. before operation</td>
</tr>
<tr>
<td>3</td>
<td>F 18</td>
<td>Chromophobe adenoma</td>
<td>1 yr.</td>
<td>Blurring of vision O.S.</td>
<td>Yes, 8 hrs. before operation</td>
</tr>
<tr>
<td>4</td>
<td>Malignant pituitary tumor</td>
<td>16 mos.</td>
<td>“Glassy vision”</td>
<td>III N. paresis</td>
<td>No</td>
</tr>
<tr>
<td>5</td>
<td>F 68</td>
<td>Adrenal carcinoma &amp; chromophobe adenoma</td>
<td>3 mos.</td>
<td>None</td>
<td>No</td>
</tr>
</tbody>
</table>

18 to 68 years. Three patients (Cases 2, 3, 4) experienced visual symptoms, consisting of decreased visual acuity, field defects, and extraocular motor palsies, in addition to the characteristic endocrinopathy. Two cases (Cases 1 and 5) had no visual symptoms. Endocrine changes preceded visual disturbances in 1 patient (Case 2). Failing vision developed pari passu with the endocrinopathy in the patient with a malignant pituitary lesion (Case 4). In Case 3, headaches, blurring of vision, and a bitemporal hemianopsia developed soon after a bilateral total adrenalectomy which had completely reversed the clinical and endocrine stigmata of Cushing’s syndrome. Within a few weeks of adrenalectomy, this patient also developed severe hyperpigmentation, most marked in the abdominal scar and skin creases. The hyperpigmentation and visual symptoms were dramatically alleviated by the subsequent removal of a chromophobe adenoma 22 months after adrenalectomy.

3. Pituitary Apoplexy (see Table 3). Two patients (Cases 2 and 3) spontaneously developed severe headaches and stiff neck associated with signs of bilateral cavernous sinus compression. This syndrome, characteristic of acute pituitary apoplexy, was confirmed in both instances by the finding of a tense hemorrhagic chromophobe adenoma at operation. Histological examination of the pituitary gland revealed areas of acute hemorrhage or hemorrhagic infarction within the adenomas.

4. Operative Procedures and Results (Table 4). Four patients in this series are now dead. One patient (Case 5) died as a result of widespread metastases from an adrenal carcinoma. Two patients (Cases 1 and 4) expired soon after adrenalectomy, presumably as a consequence of adrenal failure. Case 2 died following the subtotal removal of a huge hemorrhagic chromophobe adenoma which had expanded superiorly into the hypothalamic region and extended postero-inferiorly into the posterior fossa, compressing the brain stem and lower cranial nerves.

Case 4 presented with a 16 month history of blurred vision and Cushing’s syndrome. The sella turcica was enlarged with destruction of the left anterior clinoid process and some left parasellar calcification. An anaplastic agranular carcinoma of the pituitary was partially removed. Postoperatively, visual acuity improved and endocrine changes largely abated. This salutary effect was sustained for only a few months when vision again rapidly deteriorated, now in association with a right-sided oculomotor palsy. Progressive memory deficit, increasing drowsiness and lassitude supervened accompanied by return of moon facies, hirsutism, striae, acneiform rash, hypertension and
diabetes. The patient died 5 days after total adrenalectomy despite what appeared to be adequate exogenous hormone therapy.

Case 3 is alive and well 22 months after the removal of a chromophobe adenoma which had undergone acute hemorrhagic infarction 6 hours before surgery. She has no visual symptoms and her previous skin pigmentation has almost totally receded. The sella turcica which had increased in size after adrenalectomy, 22 months before intracranial surgery, is now normal. All clinical and laboratory evidence of hyperadrenalism receded following adrenalectomy.

**Cushing's Syndrome Associated with Non-Basophilic Adenomas of the Pituitary**

1. **Classification of Pituitary Tumors** (Table 5). We have reviewed the previous literature and with the addition of our 5 cases (see above) have collected 55 cases of Cushing's syndrome associated with pituitary tumors other than basophilic adenomas. The original case reports were re-assessed with special attention being directed to the clinical protocols and descriptions of pituitary and adrenal pathology. Photomicrographs when available were closely scrutinized. After thorough review of all pertinent data, we have subdivided the cases of nonbasophilic pituitary tumors associated with Cushing's syndrome into 6 separate groups according to the classification outlined in Table 5. In certain instances where pathological description of the pituitary neoplasm was meager or where the retrospective analysis
allowed a different interpretation of the original histologic data, the present authors have attempted to use their best judgment in determining into which pathological subgroup a particular tumor should best be placed. Table 1 contains an inventory of the non-basophilic pituitary tumors associated with Cushing’s syndrome, listing the separate case reports which were utilized for the present compilation.

Chromophobe adenomas (Table 5, Groups I and II) were the most common tumors in this series, accounting for 29 of the 39 cases of benign pituitary adenomas. There were 7 mixed adenomas (Group III), and 3 “non-granular” adenomas (Group IV) which were, in all probability, chromophobe adenomas. In addition to the 39 benign pituitary adenomas, we have included 13 cases of pituitary tumors where histological characteristics or frank invasive tendencies forced us to classify the tumor as “malignant” (Group V). Seven of these invasive tumors were composed almost entirely of chromophobe cells; in 3 the predominant cell type was basophilic, and 3 were composed of mixed chromophobe and basophilic elements. The final group of cases in this series (Group VI) consisted of 3 patients with pathologically verified adrenal carcinomas who also had a “nongranular” pituitary adenoma.

Whether a pituitary adenoma which has broken through its capsule and invaded surrounding structures, should properly be classified as benign with invasive tendencies, or malignant, remains a somewhat controversial point among clinicians and pathologists. Nonetheless, in this series of pituitary tumors associated with Cushing’s syndrome, even the so-called benign adenomas (Groups I–IV) displayed an extraordinary capacity to extend beyond the confines of the sella (Table 6). Of the 35 benign tumors where adequate pathological description was available, 9 (26 per cent) displayed this aggressive growth characteristic. Six cases, including 2 of our own series (Cases 2 and 3) developed pituitary apoplexy. In 4 instances “benign” adenomas invaded one or both cavernous sinuses. The malignant pituitary tumors, as might be expected, also displayed this tendency to assume a relentlessly aggressive growth pattern (Table 6). Not only did they frankly invade local structures, but 5 of the 13 malignant tumors developed extracranial metastases, an extraordinarily rare event with pituitary tumors.

2. Adrenal Pathology (Table 5). Three patients (Table 5, Group VI) had adrenal carcinomas which were presumably capable of autonomous hypersecretion of adrenocortico-steroids. A description of the adrenal glands was available in 45 of the remaining 52 cases. In all instances where adequate examination of the adrenal gland had been performed, the pathological diagnosis was bilateral adrenal hyperplasia involving primarily the zona fasciculata. One patient had multiple miliary abscesses within the right

<table>
<thead>
<tr>
<th>Classification</th>
<th>Cases with Adequate Pathological Description</th>
<th>Large Extracranial Extension or Invasion</th>
<th>Pituitary Apoplexy</th>
<th>Structures Involved by Local Extension or Invasion</th>
<th>Extracranial Metastases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign pituitary adenomas</td>
<td>35</td>
<td>9</td>
<td>6</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Malignant pituitary tumors</td>
<td>13</td>
<td>13</td>
<td>1</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Total</td>
<td>48</td>
<td>22</td>
<td>6</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

**TABLE 6**

Local growth, extension and invasiveness of pituitary tumors
adrenal gland. One patient in our series (Case 4) had bilateral adrenal hyperplasia and a metastatic mucinous adenocarcinoma within the hyperplastic left adrenal gland. Post-mortem examination was not performed on this latter patient and the source of the adenocarcinoma remains obscure.

3. Visual symptomatology (Table 7). Of the 55 patients, 31 (56 per cent) had visual symptoms at some time during the course of their illness. Visual symptoms were found in 20 of the 39 patients with benign pituitary adenomas, in 10 of the 13 patients with malignant pituitary adenomas, and in 1 of the 3 patients with adrenal carcinoma. The specific visual signs and symptoms were related not only to optic nerve or chiasmal compression, but were indicative in many instances of extracranial extension of the neoplasm. Thus 13 of the 31 patients with visual symptoms at some time experienced extraocular motor palsies. Six patients developed a frank unilateral proptosis. Visual abnormalities predominated in the group of patients with "malignant" pituitary neoplasms, 10 of the 13 patients in this group having positive visual signs or symptoms. Eight of the 31 patients who had visual symptoms, including 5 of the 10 patients with "malignant" tumors, developed compression of visual pathways or extraocular motor nerves prior to the appearance of the somatic stigmata of Cushing’s syndrome. In 10 instances, the endocrinopathy preceded signs of visual impairment and in 11 cases chiasmal compression and endocrine changes developed simultaneously.

4. Visual Symptoms and Adrenal Surgery (Table 8). Of the 31 patients with visual abnormalities, 21 were subjected to bilateral total (13 cases) or subtotal adrenalectomy (8 cases) for control of endocrine symptoms. Adrenal surgery either induced or markedly exacerbated visual symptoms in two-thirds of the patients undergoing this procedure. Only 5 of the 10 patients with benign pituitary tumors who had undergone adrenalectomy failed to develop visual difficulties following surgery, and 2 of these patients died immediately after operation. In half of the instances where clinical protocols allowed accurate delineation of such data, visual symptoms became manifest in the 1st year after adrenalectomy, the majority of the patients developing chiasmal and extraocular motor nerve compression within 6 months after surgery.

5. Hyperpigmentation (Table 9). Gen-

---

### Table 7

<table>
<thead>
<tr>
<th>Classification</th>
<th>Patients with Visual Signs</th>
<th>Specific Visual Abnormalities</th>
<th>Visual Signs and Endocrinopathy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Failing or Blurred Vision</td>
<td>Field Cut or Scotoma</td>
</tr>
<tr>
<td>Pituitary adenomas (39 cases)</td>
<td>20</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Malignant pituitary tumors (13 cases)</td>
<td>10</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td>Adrenal carcinoma (3 cases)</td>
<td>1</td>
<td>1</td>
<td>—</td>
</tr>
<tr>
<td>Total</td>
<td>31</td>
<td>19</td>
<td>15</td>
</tr>
</tbody>
</table>
eralized hyperpigmentation of the skin which
was most pronounced in skin creases and
surgical scars, occurred in 40 per cent of pa-
tients with Cushing's syndrome and pitui-
tary tumors. Darkening of the skin under
these conditions is believed to be related to
eccessive secretion of ACTH or MSH by the
pituitary gland. 4, 19, 23, 62, 64, 65, 66, 76
Although the total number of cases is small, there is some
suggestive evidence that the time of oc-
urrence of hyperpigmentation may provide an
indication of the malignant tendency of the
pituitary neoplasm. The simultaneous oc-
currence of hyperpigmentation in Cushing's
syndrome was 2 times more common in the
patients with malignant tumors than in the
benign group; 4 of the 7 patients (57 per
cent) with malignant pituitary tumors, and
4 of the 14 patients (28 per cent) with
benign pituitary neoplasm developed con-
comitant hyperpigmentation and hyper-
adrenalism.

6. Hyperpigmentation and Adrenal Sur-
gery (Table 9). The development of skin hy-
perpigmentation after adrenalectomy in pa-
tients with pituitary adenomas closely paral-
leled the occurrence and exacerbation of
visual symptoms after surgery. Both the hy-
perpigmentation and increased visual sym-
ptomatology probably have a similar common
denominator, i.e., an increase in growth and
secretory activity of the pituitary tumor.

Accordingly, it is not surprising that 10 of
the 39 patients with benign pituitary ade-
nomas developed hyperpigmentation follow-
ing adrenalectomy, and this usually occurred
in the first postoperative year. In the 11
instances where removal of a pituitary tumor
was subsequently performed in patients dis-
playing hyperpigmentation, 7 patients ex-
perienced a dramatic lightening of the skin
within a few months of surgery.

7. Radiological Abnormalities with Pitui-
tary Tumors (Table 10). Only 6 patients, in-
cluding 5 harboring benign pituitary ade-
nomas, displayed a normal sella turcica on
radiographic examinations during the entire
course of their clinical illness. Of the 44 pa-
tients where x-ray data were available, 24
(55 per cent) showed an enlarged sella turcica
often accompanied by erosion or destruction
of one or both clinoid processes. Two pa-
tients (both with malignant pituitary
tumors) had calcification within the tumor
on skull radiographs (Case 7, 76 and Case 4
in our own series).

Twelve patients, including 10 with benign
pituitary adenomas, had a normal sella tur-
cica when originally seen. These patients
were then subjected to bilateral adrenalecto-
my for control of hyperadrenalism. Within
a short period of time after operation, repeat
radiographs of the sella turcica showed
"ballooning" of the sella and clinoid erosion

<table>
<thead>
<tr>
<th>Classification</th>
<th>Patients with Adrenal Surgery</th>
<th>Visual Symptoms First Noticed or Increased after Adrenalectomy</th>
<th>Time after Adrenalectomy when Visual Symptoms Appeared</th>
<th>No Change in Vision after Adrenalectomy</th>
<th>Deaths after Adrenalectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign pituitary adenomas</td>
<td>16</td>
<td>11</td>
<td>0–6 mos. 6 mos. 6 mos. 1 yr. 1–3 yrs. 3 yrs. 3 yrs. 3 yrs.</td>
<td>2 2 2 5 2</td>
<td></td>
</tr>
<tr>
<td>Malignant pituitary tumors</td>
<td>5</td>
<td>3</td>
<td>0–6 mos. 6 mos. 6 mos. 1 yr. 1–3 yrs. 3 yrs. 3 yrs. 3 yrs.</td>
<td>2 2 2</td>
<td></td>
</tr>
<tr>
<td>Adrenal carcinoma</td>
<td>—</td>
<td>—</td>
<td>0–6 mos. 6 mos. 6 mos. 1 yr. 1–3 yrs. 3 yrs. 3 yrs. 3 yrs.</td>
<td>— — —</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>21</td>
<td>14</td>
<td>0–6 mos. 6 mos. 6 mos. 1 yr. 1–3 yrs. 3 yrs. 3 yrs. 3 yrs.</td>
<td>7 4</td>
<td></td>
</tr>
</tbody>
</table>
Richard L. Rovit and Richard Berry

TABLE 9

Hyperpigmentation

<table>
<thead>
<tr>
<th>Classification</th>
<th>Patients with Pigmentation</th>
<th>Pigmentation Developed with Cushing’s Syndrome</th>
<th>Hyperpigmentation and Adrenalectomy</th>
<th>Hyperpigmentation and Pituitary Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Time after Adrenalectomy</td>
<td>Pigment ↓ Pigment ↑ No Change</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0-6 mos.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>6 mos.-1 yr.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1 yr.</td>
<td></td>
</tr>
<tr>
<td>Pituitary adenomas</td>
<td>14</td>
<td>4</td>
<td>10</td>
<td>5 2 3</td>
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<tr>
<td>Malignant pituitary tumors</td>
<td>7</td>
<td>4</td>
<td>2</td>
<td>— 2 —</td>
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<tr>
<td>Adrenal carcinoma</td>
<td>1</td>
<td>1</td>
<td>—</td>
<td>— — —</td>
</tr>
<tr>
<td>Total</td>
<td>22</td>
<td>9</td>
<td>12</td>
<td>5 4 3</td>
</tr>
</tbody>
</table>

↑ = increased; ↓ = decreased.

indicative of an enlarging intrasellar mass. The radiographic signs of an enlarging pituitary tumor paralleled the increased visual symptomatology and hyperpigmentation following adrenal surgery (see Tables 8 and 9).

8. Results of Pituitary Surgery (Table 11). An operation directed at the pituitary gland was performed on 29 patients with Cushing’s syndrome and evidence of pituitary tumor. The procedure usually consisted of an intracranial operation with an attempted total or subtotal removal of the pituitary neoplasm. Occasionally only biopsies were performed on the enlarged pituitary gland. In several instances biopsies and partial pituitary excisions were carried out by the trans-sphenoidal approach. X-irradiation was often given to the pituitary region after operation. Although surgery and x-ray therapy occasionally provided relief of visual and/or endocrine symptoms in patients with malignant pituitary tumors these benefits were usually transient and within a short time additional signs and symptoms of extrasellar invasion recurred and progressed relentlessly thereafter.

Two patients with benign pituitary adenomas and Cushing's syndrome experienced permanent visual and endocrinological relief

TABLE 10

Radiographs of sella turcica

<table>
<thead>
<tr>
<th>Classification</th>
<th>X-rays Reported</th>
<th>Normal</th>
<th>Enlarged</th>
<th>Enlarged after Adrenalectomy</th>
<th>Enlarged Later without Adrenalectomy</th>
<th>Tumor Calcified</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign pituitary tumors</td>
<td>30</td>
<td>5</td>
<td>15</td>
<td>10</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Malignant pituitary tumors</td>
<td>12</td>
<td>0</td>
<td>8</td>
<td>2</td>
<td>2</td>
<td>2</td>
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<tr>
<td>Adrenal carcinoma</td>
<td>2</td>
<td>1</td>
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<tr>
<td>Total</td>
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<td>6</td>
<td>24</td>
<td>12</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>
following removal and x-ray therapy of the pituitary tumors. Six patients, who had undergone successful adrenalectomy but had subsequent aggravation of visual symptoms, were permanently helped by pituitary surgery. In 5 patients with visual symptoms and hyperadrenalism, the initial surgical efforts were directed to the pituitary region. Although these 5 patients experienced improvement of visual symptoms following partial removal of the pituitary tumor, the visual improvement was not accompanied by complete reversal of hyperadrenalism. Only after subsequent adrenalectomy did the somatic manifestations of Cushing's syndrome disappear. There were 7 operative deaths (24 per cent) in the group of 29 patients who had pituitary surgery.

Discussion

The data which we have just presented allow us to speculate on the patho-physiological disturbance in Cushing's syndrome. In this regard, we will arbitrarily confine our comments to those patients with Cushing's syndrome who have bilateral adrenal hyperplasia with or without a demonstrable pituitary tumor. Two fundamental conclusions emerge from this study.

The first conclusion deals with the role of the adrenal gland in Cushing's syndrome. Although the adrenal cortex represents "the final common pathway" necessary for the overt manifestations of hyperadrenalism,

<table>
<thead>
<tr>
<th>Classification</th>
<th>Patients Having Pituitary Surgery</th>
<th>Improvement Following Pituitary Surgery</th>
<th>No or Temporary Benefit</th>
<th>Operative Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Pituitary Surgery Only</td>
<td>Visual Improvement (Previous Adrenalectomy)</td>
<td>Visual Improvement (Later Adrenalectomy)</td>
</tr>
<tr>
<td>Benign pituitary adenomas</td>
<td>20</td>
<td>2</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Malignant pituitary tumors</td>
<td>9</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Adrenal carcinoma</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>29</td>
<td>2</td>
<td>6</td>
<td>7</td>
</tr>
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The second major inference emerging from this study is related to the cellular pathology of pituitary tumors found in Cushing's syndrome. The data which we have assembled demonstrate that the pituitary tumors which produce signs of suprasellar and extrasellar extension in patients with Cushing's syndrome are usually composed primarily, if not entirely, of "agranular cells." These cells most nearly resemble the chromophobe rather than the basophilic cell as originally described. Since these observations are at variance with certain classical concepts regarding Cushing's syndrome,

it seems pertinent to examine them in further detail.

Recent work utilizing special histochemical techniques has allowed new pathological classifications of pituitary tumors with the tentative assignment of certain hormones to specific hypophysal cells. These pathological studies have been carried out by several investigators working independently in separate clinics. 23, 24, 47, 59, 63, 71, 75 Each group has employed different fixing and staining tech-
niques and has devised its own terminology for interpreting and classifying cytological variations. It is not within the scope of the present paper to compile a detailed summary of concepts and terminology currently employed in this exciting area of cytophysiology. An additional report by us on this subject is currently in preparation. In order to simplify the present discussion, we will arbitrarily employ the classification of Ezrin$^{23,24}$ utilizing cellular characteristics based on iron-PAS and aldehyde-thionin stains (Fig. 8).

Recent studies have demonstrated that a cell with an agranular cytoplasm may not necessarily be incapable of hormonal activity.$^2$ On the contrary, such an agranular cell may have been secreting hormones at such a rapid rate that its cytoplasm has been depleted of granules and no time has been
available for replenishment and storage of the granular hormone precursors. Utilizing Ezrin's classification, ACTH secretion has been assigned to two groups of cells: the beta-1 group, formerly called basophils, and the gamma group, sometimes referred to as amphophils, mucoid cells or beta-3 cells, which are the large non-granular chromophobe cells (Fig. 8). Both the beta-1 and gamma cells arise from the same primordial stem cell, the small chromophobe. Under certain conditions of extreme pituitary hyperactivity, the beta-1 cells become "degranulated" and are converted into gamma cells (Fig. 8). This new schema allows us to understand how Cushing's syndrome, in which demands for increased production of ACTH are inordinately high (see below), may be associated with pituitary tumors composed of large chromophobes (gamma cells) as well as basophils (beta cells). We can also visualize how any disorder which forces the pituitary gland into an excessive state of ACTH secretion will produce a rapid growth and enlargement of the anterior hypophysis. Under these circumstances, the enlarged pituitary gland will be composed largely, if not entirely, of chromophobe cells. For when the pituitary gland is being excessively stimulated from above by an overactive "driving mechanism," ever increasing numbers of beta cells (basophils) may be converted into "agranular" cells (chromophobes) in an attempt to keep up with relentless metabolic demands.

We must now attempt to explain the underlying patho-physiological disorder in those patients with Cushing's syndrome who have bilateral adrenal hyperplasia. Not all the evidence is presently at hand, but it appears increasingly clear that the basic disorder in this situation must be found in or mediated by those areas of the brain capable of initiating hypersecretion of ACTH by the pituitary gland. These areas are the hypothalamus and supra-hypothalamic limbic system. This assumption is based on the following evidence. Numerous studies have demonstrated that bilateral adrenal hyperplasia associated with increased secretion of adrenal cortical hormones occurs as a response to increased ACTH secretion by the anterior hypophysis. Although many data are still not available, it appears that the stimulus for increased secretion of ACTH by the pituitary in the face of already elevated levels of circulating corticoids, must arise from "supra-pituitary" areas. Animal experiments have demonstrated that stimulation of the hypothalamus and certain supra-hypothalamic limbic areas, especially in the amygdaloid nucleus and septal regions, produces an increased output of adrenal steroids, presumably as a consequence of increased ACTH secretion. The present evidence therefore suggests that in the normal patient the "supra-pituitary"-pituitary-adrenal axis constitutes a delicately balanced homeostatic feedback system wherein increased levels of plasma corticoids lead to a diminution in ACTH production by the pituitary gland (Fig. 9). The control of ACTH production by plasma corticoids is probably related, at least in part, to an inhibitory effect of plasma corticoids on "ACTH releasing factor" in the hypothalamic region.

In patients with Cushing's syndrome who have adrenal hyperplasia with no clinical evidence of pituitary tumors, excessive demands on the anterior hypophysis may reset this homeostatic feedback mechanism at a higher level than normal (Fig. 10). Although such patients maintain an increased level of adrenocortical steroids, the beta-1 cells (basophils) are still capable of maintaining increased ACTH production with only a small increment in glandular size. This increase in basophil elements although apparent on microscopic examination of the pituitary gland, is usually not of sufficient magnitude to produce enlargement of the hypophyseal fossa or compress adjacent neural structures.

Occasionally, for reasons that have not been completely delineated but are possibly related to even greater stimulation of the pituitary by the "pituitary driving mecha-
nism," this homeostatic system may be reset at such an elevated level that the anterior hypophysis must enlarge in an attempt to keep up with its metabolic demands (Fig. 11). In so doing, the expanding adenoma enlarges the hypophyseal fossa and compresses adjacent structures such as the cavernous sinus, optic nerve, and chiasm. The enlarged gland under these circumstances will be composed primarily of gamma cells (large chromophobes) but some beta-1 cells (basophils) may still be present. If the excessively stimulated pituitary cells attain the capacity of autonomous growth and re-
production, a malignant pituitary carcinoma may result.\textsuperscript{56} The foregoing statements describe the hypothetical state of a patient with adrenal hyperplasia and Cushing’s syndrome whose plasma corticoid levels are increased but whose homeostatic mechanisms have been so adjusted that increased ACTH secretion can be maintained without significant pituitary gland enlargement. If adrenalectomy is performed at this juncture for alleviation of the endocrine disorder, plasma corticoid levels decrease sharply.\textsuperscript{19,27,50} The stimulus for increased ACTH secretion persists, presumably emanating from supra-hypophyseal regions, and continues to promote vigorous metabolic activity in the anterior hypophysis.\textsuperscript{50,52} Now, however, high levels of circulating corticoids are no longer available to act as a brake on ACTH production (Fig. 19). Under these particular circumstances, the pituitary gland rapidly enlarges, often out-stripping its blood supply, with resultant pituitary apoplexy. The hypophyseal fossa becomes expanded and adjacent structures are compressed and even invaded by the aggressive growth of the pituitary gland. Beta-1 cells (basophils) become increasingly depleted of cytoplasmic granules and are transformed into “agranular” gamma cells (large chromophobes). High levels of circulating ACTH produced by the pituitary cause hyperpigmentation of the skin.\textsuperscript{4,20,50,64,65,76} Unless the stimulus for increased ACTH production can be eliminated, or the hyperfunctioning end organ, the anterior pituitary, can be retarded by x-ray therapy or removed by surgery, the rapidly growing pituitary tumor will irreparably compress adjacent neurological structures threatening the patient’s vision and life.

The foregoing hypothetical schema still leaves certain important questions unanswered. Among these are the cause, nature and precise location of the “supra-pituitary” disorder which initiates and maintains increased ACTH secretion. There is some evidence that this polyglandular homeostatic system may be unusually sensitive to potential derangement in women, especially of the child-bearing age.\textsuperscript{27} Occasionally the initial manifestations of the endocrinopathy follow directly on a period of intense psychic or physical trauma. The influence of stress as an etiological factor in Cushing’s syndrome warrants further consideration.\textsuperscript{1} It has become apparent that emotional and physical trauma characteristically ignites the pituitary-adrenal axis into intense hyperactivity.\textsuperscript{29,32,33,49,63,69,71,75} Cushing’s syndrome may be a manifestation of such hyperactivity which is no longer related to a suitable stimulus and which continues to function excessively in a manner which is inappropriate for the affected individual.

Despite these and other questions which still demand explanation, an overall view of changing concepts regarding Cushing’s syndrome over the past 30 years suggests that we have begun to come around almost full circle, if not back to the pituitary gland, at least to those neural structures that directly influence the hypophysis.

**Summary**

This report is concerned with a revaluation of pituitary tumors and hyperadrenalism. Three patients are presented who had Cushing’s syndrome, bilateral adrenal hyperplasia, and chromophobe adenomas of the pituitary gland. One other patient with the signs of Cushing’s syndrome was proven to have an adrenal cortical carcinoma and a chromophobe adenoma of the pituitary. A final patient in the present series with Cushing’s syndrome had a malignant agranular pituitary carcinoma.

Review of the literature reveals 50 additional cases of Cushing’s syndrome associated with pituitary pathology other than basophilic adenomas. Of these pituitary tumors 29 (53 per cent) were composed primarily of chromophobe cells. In 13 (24 per cent) of the total 55 cases, the pituitary neoplasm had invaded surrounding nervous or vascular structures; 5 of these 13 malignant pituitary tumors developed extracranial metastases.
Of the 55 patients, 36 (66 per cent) developed visual symptoms at some time during the course of their illness. The visual symptoms in these cases were indicative in many instances of extrasellar extension of the neoplasm. Thirteen (36 per cent) of the 36 patients with visual symptoms developed extraocular motor nerve palsies. Visual symptoms preceded signs of hyperadrenalinism in 25 per cent of the patients (8 patients). Adrenalectomy either induced or markedly exacerbated visual symptoms in 14 (67 per cent) of the 21 patients undergoing this procedure.

Hyperpigmentation, probably related to excessive secretion of ACTH or MSH, occurred in 40 per cent of patients having Cushing's syndrome and pituitary tumors. This pigmentary change was often induced or markedly exacerbated by adrenal extirpation.

We have reviewed recent pathological data based on special staining methods which suggest that ACTH may be secreted by both basophils (beta-1 cells) and large chromophobe cells (gamma cells). These studies indicate that the agranular chromophobe cell may not be hormonally inert as was once thought, but may, at least in Cushing's syndrome, represent an extremely active secretory cell which has been driven to produce excessive amounts of ACTH.

Finally, we have summarized some present concepts regarding the etiology and pathophysiology of Cushing's syndrome. Data have been presented which suggest that the basic disorder in this endocrinopathy may be one of hyperpituitarism related to excessive stimulation of ACTH secreting cells by an overactive "pituitary driving mechanism" or "cortico-trophin releasing factor." It appears possible that Cushing's syndrome may be related to a primary homeostatic derangement in limbic and hypothalamic areas which serve to regulate the secretion of ACTH.

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Discussion

DR. ROBERT M. SALASSA: I think Dr. Rotiv is certainly to be congratulated on a fine presentation of a stimulating and very difficult group of patients. Actually I am an endocrinologist and a little out of place here, so my interest in this group of patients is a little bit different from his. The experience at the Mayo Clinic concerning patients with clinically significant pituitary tumors and Cushing’s disease is, with a few minor exceptions, essentially what he has given
you, and unfortunately I do not have anything to offer which really settles some of the many perplexing questions that still remain concerning this group of patients.

However, I think you might be interested in some of the data we have obtained concerning our group:

[Slide] In 1950, we published our experience with patients with clinically significant pituitary tumors and Cushing’s disease associated with bilateral adrenocortical hyperplasia up through 1958. At that time we had 12 cases out of about 122 patients with Cushing’s syndrome due to adrenocortical hyperplasia for an incidence of about 10 per cent.

As you can see from the slide, the incidence has slowly crept up and we are now finding that about 14 per cent of our patients with Cushing’s disease due to adrenocortical hyperplasia will, either before or after an attack on the adrenal, develop a clinically significant pituitary tumor. We still have not seen a patient with a clinically significant pituitary tumor who also had a functioning adrenocortical tumor, and I was sorry to hear about the one that Dr. Rovit presented today. I would like to ask him what the autopsy showed, if the contralateral gland was atrophic, and also if there was any clinical or pathological evidence that this patient had tumors of the parathyroids or pancreas. I wondered if the patient might belong to the group of multiple endocrine adenomatosis.

We now have tissue on 11 patients with pituitary tumors and Cushing’s disease and, as Dr. Rovit has already pointed out, in each case the predominant cell is non-granular, a chromophobe cell, and again the incidence of malignancy was surprisingly high.

The sub-group that I think deserves perhaps a few comments is the group of patients in which the pituitary tumor antedated the development of Cushing’s syndrome. We are now studying a 4th patient in addition to the 3 shown in the slide. This 4th patient had a pituitary tumor; it was a chromophobe adenoma and caused a field defect. It was treated with craniotomy and cobalt radiation 5 years ago. The patient recovered from her field defect and now in the past 12 months has developed an intense Cushing’s syndrome. So in our series, 4 patients out of 25 with co-existing pituitary tumors and Cushing’s disease actually developed a pituitary tumor of such size as to demand therapy, either surgery or radiation or both, prior to the development of Cushing’s syndrome.

In these particular 4 patients and the other similar patients that have been reported in the literature, it is a little difficult to attribute the development of the tumor to excess stimulation by so-called corticotrophin-releasing factor from the hypothalamus.

Also, you might be interested in an experimental transplantable malignant ACTH-producing pituitary tumor of mice. This was reported in a series of articles, 1954–57, by Bond, Anderson, Perth and others. This tumor developed as a result of exposure to ionizing radiation at one of the atomic detonations in the Pacific. This tumor was also composed of cells that were non-granular and large chromophobe cells. So in this particular case, again, it would be difficult to attribute growth of the tumor to excess stimulation by corticotrophin-releasing factor. Finally, it has now been demonstrated that certain non-endocrine malignancies, such as carcinoma of the lung, can also release a peptide with ACTH activity.

I suspect that when we know a little bit more about the situation, it will turn out that there are probably several factors capable of precipitating development of a pituitary tumor, and that, in general, neoplasia of the pituitary will be about the same as development of neoplasms in other endocrine glands.

[Slide] During the past 5 years, we have attempted to obtain some information on the function of these pituitary tumors so far as release of ACTH is concerned. Dr. Rovit has already outlined very nicely the so-called servo or feed-back mechanism by which the level of plasma cortisol influences the release of ACTH in health and also the current growing theory as to how it is disturbed in patients with Cushing’s disease due to bilateral adrenocortical hyperplasia.

As a result of the work of many investigators, particularly Grant Liddle, of Vanderbilt, it has been pretty well shown that people with Cushing’s disease due to bilateral adrenocortical hyperplasia do not show a significant fall in urinary excretion of 17-ketosteroids or 17-ketogenic steroids or 17-hydroxycorticosteroids, whatever you wish to measure, following administrations of 2 mg. of dexamethasone daily for 2 or 3 days.

The normal level of urinary 17-ketogenic steroids is about 4 to 14 mg. per day so you can see that even after the administration of dexamethasone this patient was still excreting excessive amounts of 17-ketogenic steroids.

If you use an 8 mg. dose, and cause a greater increase in the level of circulating cortisol, or in this case dexamethasone, you do get a depression in urinary 17-ketogenic steroids greater than 50 per cent, which shows that these pituitary tumors are not entirely autonomous and are capable of being suppressed or shut off by 8 mg. of dexamethasone. Sometimes we have had to go to 12 mg. of dexamethasone daily to obtain suppression.

Metopirone is a chemical inhibitor of 11-beta
hydroxylation in the adrenal cortex which is necessary for the formation of cortisol. When you give a patient Metopirone, you lower the level of circulating cortisol and if the tumor is not autonomous and is sensitive to a decrease in the level of circulating cortisol as it was to an increase during the suppression test, there should be outpouring of ACTH, and the adrenal should be stimulated. This is indicated by the increase in urinary excretion of 17-ketosteroids and 17-ketogenic steroids.

Dr. Vance, who was working with Dr. Thorne, checked this woman’s plasma for ACTH during the control period and during the administration of both 2 and 8 mg. of dexamethasone and could not demonstrate any ACTH. However, during the administration of Metopirone, he could demonstrate ACTH.

So I think that we can say that these tumors, as suggested by Dr. Rovit, are not entirely autonomous; they are influenced by the level of circulating cortisol. This particular patient, by the way, did very well with cobalt therapy alone. She had no visual field defect. As you can see, a year later urinary excretion studies showed that her steroids were down, and when challenged with Metopirone she had only a modest rise.

After 2 years, she still has a clinical remission of her Cushing’s disease, but the response to Metopirone is beginning to increase again, and whether or not she will develop a recurrence cannot be answered at this time.

Dr. Donald D. Matson: Dr. Rovit has described with clarity a very provocative and exciting area of neuroendocrinology.

Mr. Norman Dott, when he was here a year or so ago, gave in his wonderful way of expressing things a delightful description of how he felt the central nervous system could now be considered the most recently discovered endocrine gland. I think it is interesting in considering Cushing’s disease, to remember that the common denominator is increased cortisol activity, which is responsible for the various clinical manifestations familiar to all of you. It certainly has become evident, as indicated by the authors and many others, that over the years a number of different way stations may seem to be responsible for this increased cortisol activity. In other words, there may be excessive hyperplasia of the zona fasciculata of the adrenal glands, with no evidence of disease elsewhere, or there may be tumors of the adrenal cortex. There may be adenomas of the pituitary gland producing excessive ACTH, resulting in adrenal cortical hyperplasia. It is also evident that there is a higher area, presumably in the hypothalamus, which may drive a normalized pituitary gland to produce excessive ACTH with the same result.

I would like to show you very briefly examples of 3 of these problems. Dr. Salassa has indicated a 14 per cent incidence of this pituitary lesion in Cushing’s disease; Dr. Rovit has reported that he has collected 55 cases. I am sure there are many more that have never been reported. We have had experience now with 8 or 9 cases at the Peter Bent Brigham Hospital, and I believe only one of these was included in Dr. Rovit’s 55 that have been reported.

[Slide] This first patient I would like to show you had typical Cushing’s disease; at the time she had a normal-sized sella turcica.

[Slide] Hyperplastic adrenal glands were removed.

[Slide] Two years later: this is her picture following her adrenalectomy. Then in a period of 2 years she began to become pigmented. By 3 years she had a bitemporal visual field defect; amenorrhea returned again; she had headaches.

[Slide] Intense pigmentation at this time.

She had an ACTH level in her circulating blood at this time between 200 and 400, the highest levels that had ever been recorded, with zero being normal, of course, and 20 to 30, an Addisonian level. Following sudden collapse after beginning x-ray treatment, she was operated upon.

[Slide] A chromophobe tumor was removed with hemorrhage in it at that time. She had a remarkably rapid fading out of her pigmentation afterwards. The figure on the left shows her sella at the time of her adrenalectomy, essentially normal in size, on the right 3 years later after she had developed her symptoms and her pituitary tumor.

[Slide] As I say, she improved rapidly after operation. It is now 6½ years since removal of the pituitary tumor and 9 years since her adrenalectomy. She is working regularly as a seamstress, is still having periods, and I operated on her last year for a ruptured intervertebral disk.

The second patient I want to talk about had already a large sella turcica at the time of her adrenalectomy.

[Slide] She became pigmented 2 years later, a sort of a deep tan color, and she had actually the largest pituitary tumor that I personally have ever seen. She also made a good recovery and 4 years later is working as a dental assistant.

[Slide] This shows the enormous destruction in the area of her sella turcica. She presented with headaches, bitemporal hemianopia, virtual blindness in her left eye and a left third nerve palsy. This was not, however, a malignant tumor.

[Slide] The next slide represents a third example of this situation: a lady who developed intense pigmentation, with increased circulating ACTH and M.S.H. Three years after adrenalectomy this patient’s pituitary fossa has remained normal in size; she has never had a headache; she has never
had any visual loss, and her pigmentation has decreased considerably with a course of x-ray therapy. She and 3 or 4 others like her are being followed carefully.

I suppose the only lesson to learn from our point of view as neurosurgeons is that when we are called in consultation to see these patients who have undergone adrenalectomy for Cushing's disease, they should be followed carefully with serial x-rays at intervals, and any occurrence of visual loss, or headache, or pigmentation should be followed with appropriate studies.

DR. RICHARD L. ROVIT: I would like to thank the discussants, Dr. Salassa and Dr. Matson. All those who have reviewed the literature recognize the contributions made by both Dr. Salassa and Dr. Matson in this field. With regard to Dr. Salassa's first question concerning the patient having a chromophobe adenoma and an adrenal cortical carcinoma, the opposite adrenal gland was atrophic. Postmortem examination failed to reveal any neoplasm of other endocrine glands. We are unable to explain the interrelationship of the chromophobe adenoma and the adrenal carcinoma in this particular patient.

Dr. Salassa also alluded to the fact that 1 patient in our present series developed visual symptoms prior to the appearance of the endocrinopathy. Review of the literature on this aspect of the problem (see Table 7) discloses that visual symptoms preceded signs of hyperadrenalism in about one-third of the cases and under these circumstances, the pituitary tumor is more apt to be "malignant" than benign.