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

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I
n 1933, Harvey Cushing delivered a lecture before the Harvey Cushing Society entitled "Dyspituitarism: Twenty years later. With Special Consideration of the Pituitary Adenomas."18 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.1,12,19,27,47,62,70,76 About 15 to 20 per cent of patients have adrenal adenomas or carcinomas capable of autonomous secretory activity.19,27,47,55,70 Macroscopic pituitary tumors are present in less than 10 per cent of patients with Cushing's syndrome.22,45,62,76 Occasionally the characteristic endocrinopathy is seen in patients with malignant tumors of other organs—lungs,5,59 pancreas16 or thymus.41,49 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,17,18 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.18 While minute basophilic adenomas are occasionally found at post-mortem examination in patients with hyperadrenalism,6,18,29,47,70,86 it is often difficult to evaluate their clinical significance since similar microscopic cell aggregates are occasionally seen in normal patients.7,13,85 Also, there is rather conclusive pathological evidence that many of the alterations in the basophilic cells described as characteristic of Cushing's syndrome15 may occur as a consequence of increased steroid secretion rather than representing the primary etiologic agent.19,28,29,30,48,74 Moreover, clinical experience has demonstrated that basophilic adenomas rarely attain sufficient size to compress visual pathways, to produce enlargement of the sphencterica, or otherwise to bring the patient to the attention of a neurological surgeon.19,27,45

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

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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, pellagoric 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. 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.