Section of Endocrinology

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President's Address

Reflections on Cushing's Syndrome

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Cushing's first case was a certain Minnie of New York who developed the syndrome at the age of 16. Briefly reporting her case in 1912, Cushing likened the clinical picture to that seen with certain adrenal tumours. His ideas changed as it became apparent that the pituitary influenced both growth and sexual function. He argued that, as acromegaly was acidophil hyperpituitarism, there should be another form of hyperpituitarism involving the basophil cells and sexual function; hence the emphasis on amenorrhœa in his case histories.

Perhaps the most informative case he quoted from the literature in his classic paper published in 1932 was one reported by Parkes Weber (1926) who correctly associated obesity, hypertension, purpuric ecchymoses and striæ with adrenal hyperfunction in the absence of an adrenal tumour. The small pituitary tumour that he dismissed as irrelevant was for Cushing the key to the problem, being composed of basophil cells. The influence of the adrenal was forgotten when Cushing announced his discovery of a disease caused by hyperpituitarism arising in basophil tumours. So compelling was his description that Bishop & Close (1932) were able to recognize a case and propose that the disorder be called Cushing's syndrome.

Crooke's description in 1935 of hyaline change found in the pituitary basophil cells in all cases of Cushing's syndrome demoted the basophil adenoma from being the primary cause of the disorder. Then, in 1943, Albright made the syndrome into a metabolic rather than a sexual disorder by incriminating excess adrenal glucocorticoid as the agent responsible for the catabolic aspects of the syndrome such as diabetes, muscle wasting and osteoporosis. Heinbecker (1944) made an inspired guess that the hypothalamus was the site of the lesion in Cushing's syndrome, but he reasoned that the condition was one of severe hypopituitarism. Meanwhile, Kepler was heading the anti-pituitary lobby. When he first described hypokalæmic alkalosis arising in Cushing's syndrome due to an adrenal carcinoma (Kepler *et al.* 1948), he argued that the clinical picture was due solely to excess adrenal function and that, at best, the pituitary only provided the right circumstances for adrenal hyperfunction. Later, the administration of cortisone produced the features of Cushing's syndrome and also Crooke's hyaline change in pituitary basophils: also, the giving of ACTH to patients with Cushing's syndrome produced an exaggerated adrenal response suggesting that Kepler was right and that the adrenal had become unduly sensitive to normal pituitary stimulation. This was the nadir of the pituitary's reputation, from which it has made a complete come-back thanks to the study of the normal hypothalamic-pituitary-adrenal relationships.

While physiology was being rewritten to acknowledge the rightness of Cushing's concept of hyperpituitarism, a new clinical phenomenon was becoming apparent. It had long been considered that Cushing's syndrome predisposed to neoplasia (Crooke 1946), but it was exactly thirty years after Cushing had published his findings that Liddle *et al.* (1962) defined the ectopic ACTH syndrome. In the interval, the death rate for carcinoma of lung in British males had increased nineteen-fold. The intensity of the ACTH stimulus produced by these nonpituitary tumours is so great that the clinical presentation is one of hypokalæmic alkalosis in the absence of

the stigmata of Cushing's syndrome. Thus Cushing would not have identified such cases as examples of his syndrome even if the case material had been available in his time. If we are to create new eponyms there is good reason for the use of 'Liddle's syndrome' to describe all the clinical varieties of cortisol excess caused by ACTH-producing tumours outside the pituitary. Such tumours are by far the commonest cause of cortisol excess in men over 40. My own experience is that 4 of 8 men with adrenal hyperplasia in this age group had lung tumours compared to 1 of 12 women. But this must be an underestimate as the short fatal course of the disease may defy diagnosis or prevent transfer to special units.

Table 1
Effect of adrenalectomy on cortisol secretion rate in one patient

	Cortisol secretion rate (mg/24 h)	*Oxogenic steroids (mg/24 h)*
Pre-operative	97	
Adrenal removed (30 g):		
15 days later	24	
38 days later	57	33
After 5 days ACTH		132
Adrenal removed (33 g)		

The clinical picture of Cushing's syndrome is too well known to merit further description, but there are points in management that appear to be neglected. First, the most troublesome feature has been the severity of the psychosis that has affected 16 of my 55 patients (excluding acute cases of ectopic ACTH syndrome and adrenal carcinoma). The psychiatric prognosis is very good when the cortisol excess has been removed. Second, the advanced atherosclerosis that accompanies chronic Cushing's syndrome may dominate the prognosis after successful adrenalectomy, a point made by Welbourn (1969). Of 10 men in this series of 55 patients, 5 died of coronary thrombosis within a year of restoration of normal cortisol levels; 3 of these had had an initial coronary thrombosis before treatment. In contrast only 1 of the 45 women died in this way.

My comments now concentrate on those cases of Cushing's syndrome that involve a pituitary disturbance, what Kepler called Cushing's disease. The natural history for most cases is of persistent disorder, but spontaneous cure can occur; Cushing's Minnie was alive and better 29 years after she developed his syndrome. The disorder may also be episodic and recurrent. Physiologically it is an indolent disturbance; the cortisol production rate is well below the maximum of which the hyperplastic adrenal is capable and can be massively stimulated by exogenous ACTH. Moreover, artificial lowering of circulating cortisol levels by metyrapone increases adrenal activity. These features are shown in Table 1 where removal of one adrenal in a patient lowered the cortisol production rate to normal values and there was a sluggish subsequent rise to supranormal levels. This case is a good illustration of the indolence of the disorder.

Suppression of adrenal activity in Cushing's syndrome is not achieved by doses of dexamethasone sufficient to suppress the normal adrenal, but does occur with high doses. I have found that some clinicians are still confused about the use of the dexamethasone suppression test, failing to distinguish between the low dose (2 mg daily) that will not significantly reduce plasma cortisol in any type of Cushing's syndrome, and the high dose (8 mg daily) that diminishes the plasma cortisol only in cases associated with a pituitary lesion. A constant high level of plasma cortisol, that can be suppressed by large amounts of dexamethasone, is not an invariable rule in pituitary Cushing's syndrome. I have seen examples of a diurnal rhythm maintained at high levels of plasma cortisol and also with complete failure of suppression. The levels and variability of plasma cortisol are matched by plasma ACTH levels. These are usually constant throughout the day, compared to the normal diurnal rhythm and, although raised, are not nearly so high as the levels found after adrenalectomy in cases of Cushing's syndrome or in the ectopic ACTH syndrome. The histology of the adrenal tells the same story. The untreated case shows adrenal hyperplasia with many clear lipid-rich cells. It is easy to see that such an adrenal could produce large amounts of steroid when challenged by exogenous ACTH. In contrast, the hypertrophied adrenal remnant after subtotal adrenalectomy consists only of compact granular cells, the same picture being found in the ectopic ACTH syndrome. Of course, the remnant is producing steroids to maximum capacity and will not respond further to exogenous ACTH.

A curious feature of adrenal hyperplasia, pointed out by Neville & Symington (1967), is the extreme variability of adrenal weights that does not correlate with the rate of steroid production or the duration of the disease. I do not consider it necessary to invoke the unproven concept of two types of ACTH, one maintaining adrenal weight, the other stimulating steroid secretion, to explain this phenomenon. I suggest that it is related to the extraordinary constancy of ACTH stimulation characteristic of Cushing's syndrome

that would produce hyperplasia in contrast to the repeated sudden peaks of ACTH secretion that produce steroid secretion under physiological conditions.

In summary, Cushing's concept of hyperpituitarism has been completely vindicated by modern research. The pituitary output of ACTH is inappropriately high for the level of plasma cortisol, and the normal homeostatic mechanisms are disordered but not destroyed. It follows that adrenalectomy benefits the patient by removing the hypercortisolism, but does not cure the underlying disorder: indeed, it makes it worse. Thus, a study of patients after adrenalectomy gives an insight into the natural history of Cushing's syndrome. It is fortunate that the clinician can detect the presence of large amounts of ACTH by the appearance of Addisonian pigmentation despite the presence of adequate cortisol. This pigmentation is caused mainly by the excess of melanocyte stimulating hormone (MSH) that always parallels the amount of ACTH (Abe *et al.* 1969) but, of course, the ACTH itself does affect pigmentation.

In my series, removal of hyperplastic adrenals was carried out only in those patients without radiological evidence of pituitary enlargement and without obvious pigmentation. Eleven patients had no detectable adrenal function following adrenalectomy (in 5 cases the operation had been a radical subtotal adrenalectomy). Seven of these developed marked pigmentation. In 2 other cases adrenal function returned after about 2 years of steroid dependence. Both had a relapse of hypercortisolism accompanied by some pigmentation and both had a small pituitary basophil adenoma removed with lightening of skin colour. These 2 cases illustrate the remarkable increase of pituitary function that in the long run will cause the most minute adrenal remnant to become overactive. Of 9 patients whose adrenal function returned to normal after the operation of subtotal adrenalectomy, to be followed by a relapse of Cushing's syndrome, 2 were pigmented at the time of relapse and 3 developed marked pigmentation after removal of the adrenal remnant. Thus 14 patients developed hyperpigmentation in a series of 38 patients submitted to adrenalectomy. The degree of skin pigmentation was far more marked in patients having no adrenal function than in those who had a relapse of hypercortisolism, indicating that high levels of plasma cortisol still had a restraining effect on pituitary secretion of ACTH. For one who has considered that deep skin pigmentation in these circumstances was an ominous sign of pituitary tumour growth (Mason & Greenbaum 1962), I am surprised at the very low incidence of enlarging tumours in these pigmented patients, most of whom have been followed for more than seven years. For only one of these patients developed a large pituitary tumour, invading the cavernous sinus. The resultant cranial nerve palsies disappeared after hypophysectomy, but the pigmentation lightened only temporarily to become intense once more and remain so over nine years without apparent enlargement of the surviving tumour. One other patient showed enlargement of the pituitary fossa when the pigmentation first appeared, but despite persistent deep pigmentation no further enlargement has been noted over ten years.

Cushing would have been interested to learn that menstrual function in these patients with very high plasma ACTH levels is usually normal and that they conceive easily. This disposes of his concept of a primary pituitary disturbance of menstrual function; the disturbance is secondary to hypercortisolism.

Just as the natural history of the untreated condition varies, so the stimulus of adrenalectomy does not produce a uniform increase in ACTH secretion. One pigmented patient has shown a lightening of skin colour and now has a diurnal rhythm to her ACTH secretion while on maintenance steroid therapy, just like Addison's disease but at a high level, the midnight value being 200 pg/ml and the morning level 800 pg/ml. Obviously the pituitary disorder can die away as it must have done in 5 patients left with inadequate adrenal function after operation. The adrenal remnant would respond to exogenous ACTH, but the natural supply was not sufficient to cause hypertrophy and restoration of full function. Eleven of 31 patients who had subtotal adrenalectomies continued to have normal adrenal function and no evidence of further hypercortisolism.

Most interesting was the occurrence of true Addison's disease in 2 of these patients, $4\frac{1}{2}$ and $5\frac{1}{2}$ years after successful subtotal adrenalectomy and maintained normal adrenal function. Both developed the classical features of Addison's disease with moderate pigmentation, neither had any adrenal response to exogenous ACTH and both lost their symptoms and their pigmentation when replacement steroid therapy was given. Neither had circulating adrenal antibodies and their adrenals had not shown any lymphocytic infiltration. Certainly their pituitaries behaved exactly as if the condition was primary adrenal failure. I cannot explain this failure or find similar cases on record.

Table 2
Types of cortisol excess and their presentation

Type	*Presentation*
Iatrogenic	Clinical (habitus)
Adrenal tumours	Biochemical (hypokalæmia)
ACTH excess	

Throughout this address I have been uncomfortably aware of problems of nomenclature. Cushing's syndrome describes the clinical picture of hypercortisolism, but his pituitary disorder is more obvious when the adrenals have been removed. Therefore, I suggest that in honouring Cushing's contribution to endocrinology we should abandon the term 'Cushing's syndrome' and use a classification that expresses the disorder of physiology. First, we have the clinical patterns of cortisol excess as shown in Table 2 acknowledging that the iatrogenic forms are usually due to synthetic analogues of cortisol. Second, we have the various conditions in which the secretion of ACTH (from any source) is inappropriate for the physiological demands of the body. Consequently, I propose that these should be called 'syndromes of inappropriate ACTH secretion' (Table 3). Our knowledge of the hypothalamic role in controlling ACTH secretion makes it virtually certain that corticotrophin releasing factor (CRF) levels must be high to prompt an excessive output of pituitary ACTH unless the pituitary has developed an autonomous ACTH-secreting tumour. Presumably this can occur with some of the rare large tumours. After adrenalectomy the growth of a pituitary adenoma may well be prompted by excessive stimulation from CRF in the same manner that TSH can induce experimental tumours of the thyroid.

Table 3
Inappropriate ACTH secretion

	CRF	*Pituitary ACTH*	*Cortisol*
Cushing's disease	++	++	++
Cushing's disease adrenalectomy	+++	+++	0
Big pituitary tumour	0	+++	0
Ectopic ACTH	0	0	++ +++

The relationships of CRF, pituitary ACTH and cortisol shown in Table 3 illustrate the disturbance of physiology in the light of current knowledge as a development of Cushing's original concept of hyperpituitarism.

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