The history of Cushing's disease: a controversial tale

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Keywords: Harvey Cushing; Julius Bauer; Cushing's disease; pituitary

The history of Cushing’s disease now goes back quite a long time. Yet no clear cut definition of the issues involved has emerged. The pathogenesis of the condition is still controversial.

Harvey Cushing (1869-1939) was one of the most outstanding surgeons of the present century and, as Garrison put it, ‘facile princeps in neurological surgery, particularly surgery of the head and the pituitary body’ (Figure 1).

Born in Cleveland, Ohio, and educated at Yale and Harvard Medical Schools, he worked, after spending some time in Europe, mainly at Johns Hopkins in Baltimore and, finally, as Moseley Professor of Surgery at the Harvard School of Medicine in Boston and Surgeon-in-Chief of the Peter Brent Brigham Hospital from 1912 to 1932. He gave his celebrated ‘Oration in Surgery’ on ‘The Hypophysis Cerebri: Clinical Aspects of Hyperpituitarism and of Hypopituitarism’ to the Section of Surgery of the American Medical Association at the 16th Annual Session, held at Atlantic City, in June 1909. At that time he still worked in Baltimore.

The subject here concerns, however, his publication in 1932 of a polyglandular syndrome: ‘The basophil adenomas of the pituitary body and their clinical manifestations (pituitary basophilism)’. This was a review of 12 such patients, the first of whom was a certain Minnie of New York. She developed the syndrome at the age of 16. Cushing had mentioned her briefly in 1912 and thought that her clinical picture resembled those seen in some adrenal tumours. Later he changed his opinion and said, if acromegaly was due to acidophil hyperpituitarism,

![Figure 1. Harvey Cushing, 1869-1939](image)

there was another form, due to excess of the basophil cells, involving sexual function (amenorrhoea in women, impotence in men). Minnie was still alive in 1932. The late F M P Bishop and R G Close of Guy’s Hospital, London, recognized and described such a case in the same year: ‘A Case of Basophil Adenoma of the Anterior Lobe of the Pituitary: Cushing’s Syndrome’, thus giving it this name for the first time.

My own involvement with the subject began between 1932 and 1934, in Vienna. My then chief, Professor of Medicine Julius Bauer (1887-1979) (Figure 2) had published the case report of a patient in 1931. He had been diagnosed as adrenal tumour, operated on, but no tumour was found. He died after the operation. Postmortem examination by Professor Carl Sternberg (of Sternberg cells fame) compelled a change of diagnosis to hyperfunction of the total adrenal system without anatomical basis. Months later, Cushing advised Bauer to look at the pituitary, if still available. It was, and serial section revealed a basophil adenoma.

I was at that time a Chief Assistant on Bauer’s Medical Professorial Unit. Together with my colleague, the late Dr Paul Wermer*, we observed in those years 7 patients (including the Bauer-Sternberg case) in whom we made the diagnosis of basophil adenoma.

*Dr Paul Wermer (1898-1979) later described the MEN (multiple endocrine neoplasia) type 1 syndrome (Werner’s syndrome), when he worked at the College of Physicians and Surgeons, Columbia University, New York.

![Figure 2. Julius Bauer, 1887-1979](image)
Table 1

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<th>Autopsy</th>
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<th>Intermediate</th>
<th>Virilising Tumors of the Pituitary</th>
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<td>Density (macrophage distribution)</td>
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appearance, amenorrhoea and virilism. In July 1914, Mr Percy Sargent removed a tumour, entirely outside the peritoneum, closely attached to the upper pole of the right kidney. The operation was successful. In August 1914 she had the first period for 9 years. The hiruites disappeared. She was re-examined in 1920 and in 1923 when she was 35 years old: she then had normal female characteristics. The histology of her tumour was that of the suprarenal zona reticularis. This and other similar patients, Sir Gordon Holmes discussed with Harvey Cushing, when the latter was visiting London in 1929.

In January, 1926 F Parkes Weber (London) published a case history 'Cutaneous striae, purpura, high blood pressure, amenorrhoea and obesity, of the type sometimes connected with cortical tumours of the adrenal glands, occurring in the absence of any such tumours - with some remarks on the morphogenetic and hormonal effects of true hypernephromata of the adrenal cortex.'18. The patient was demonstrated at the Section of Dermatology of the Royal Society of Medicine in London on 18 June 1925. This was undoubtedly a Cushing's syndrome which Parkes Weber discussed with Cushing. Parkes Weber also referred to a similar (female) patient demonstrated and recorded by Dr H G Turney in 191319. She had precocious plethoric obesity, large purple striae, amenorrhoea, relatively thin legs and arms, a systolic blood pressure of 200 mmHg, polycythemia, spontaneous fractures (osteoporotic); X-ray showed partial absorption of the dorsum sellae. Apart from headaches, there were no obvious symptoms suggesting increased intracranial pressure. She died in May 1914, aged 25. Postmortem examination showed the left suprarenal gland to be nearly twice as large as the right one, which was of normal size. Microscopically there were cortical 'islets' in which the cells were packed with 'lipoid droplets'. Nothing abnormal was found in the pituitary and thyroid glands. The bones (including the sella turcica) were so soft that they could be cut easily with scissors. Parkes Weber finally quotes the case, published by Dr John Anderson in Glasgow in 191520, of a woman of 28 years, with amenorrhoea, obesity, hirsuties, redness of the face, headaches, exophthalmos and petechial haemorrhages. She died. Postmortem examination showed chronic interstitial nephritis, slightly hyperplastic suprarenal glands; in the medulla of the left one was a small tumour, microscopically resembling the zona fasciculata. The anterior lobes of the pituitary contained a small adenoma, and in the rest of the anterior lobe the chromophobe cells were increased at the expense of the eosinophil cells. The pars intermedia was markedly cystic; the posterior lobe was normal.

As regards the hyalinization with diminution or disappearance of the granules of the basophilic cells in pituitary basophilism, described by Crooke21, Bauer thought that it was more likely 'as a result rather than as origin of the clinical syndrome, since the changes are associated with the clinical syndrome, whether it be due to primary or secondary hyper-adrenocorticism.' In rare cases22 thymus tumours can cause the clinical syndrome of hypercorticism. For practical purposes, osteoporosis and purplish striae are more common and pronounced in Cushing's Disease, 'whereas virilisation of the female genitalia . . . bespeak an adrenal tumour' (Bauer). The 17-ketosteroids in the urine are also more excessive in the latter.

In a recent lecture, given in Hamburg by Dr A P van Seters of the Department of Endocrinology and Metabolic Diseases of the University Hospital Leiden, The Netherlands, entitled 'The History of Cushing's Syndrome: Controversies Regarding Pathogenesis in the 1930-1950's',23 van Seters was unaware of my hitherto unpublished lecture on the same subject, given at the joint meeting of the Sections of Pathology and History of Medicine of the Royal Society of Medicine in London on the 21 June 1988. The general subject title for the afternoon was 'Pathology Then and Now'. van Seters ended his lecture by saying: '... it has become clear that the eponym 'Cushing-Bauer Syndrome' might have served a historical purpose.'

In 1966, Gene G Hunder of the Mayo Clinic grappled with the 'Pathogenesis of Cushing's Disease'20. He came to the conclusion that the hormonal excess which produces it, may result from the secretory activity of (1) hyperplastic adrenal cortices without any clinically evident endocrine lesion; (2) adrenal cortical adenoma or carcinoma; (3) ectopically located adrenal-like tumour, for example, of an ovary; (4) ACTH secreting tumour of the anterior pituitary associated with adrenal cortical hyperplasia, or (5) non-pituitary carcinoma, for example of lungs or the pancreas26, with secretion of an ACTH-like material which induces adrenal cortical hyperplasia.

Besser and Edwards in London, arrived at a similar grouping, when discussing Cushing's Syndrome in 1972, calling pituitary dependent bilateral adreno-cortical hyperplasia (conventionally) Cushing's disease26. In an updated version, the authors came to the conclusion, that 'Cushing's syndrome remains one of the most challenging problems in clinical endocrinology. Cushing's disease is caused in the majority of cases by basophil pituitary microadenomas which may be successfully treated by transephenoidal hypophysectomy27.

Bauer had already stressed the importance of the differential diagnosis, because of the difference in treatment 'Adrenal tumours require surgical removal, Cushing's disease, X-ray treatment applied to the pituitary' (in 1950)20.

In the 1940s there was an antipituitary lobby, headed by Kepler. He thought (like Bauer) that the clinical picture was due solely to excess adrenal function and that the pituitary only provided the right milieu for adrenal hyperfunction; the adrenal became excessively sensitive to normal pituitary stimulation28.

The diagnosis and management of ACTH-dependent Cushing's syndrome are discussed by the same group with three additional authors, in a later paper29. In 10 out of 16 consecutive patients with ectopic ACTH secreting tumour, that were completely occult to routine and radiological investigation. No basal or dynamic investigation was able clearly to differentiate these patients from those with Cushing's Disease. Successful diagnosis and tumour localization was most frequently achieved by a 'combination of CT scanning of the chest and abdomen and venous catheter sampling for ACTH'. . . 'Occult ectopic ACTH secretion . . . may be impossible to distinguish from pituitary Cushing's disease'.

In 1962, Liddle described the ectopic ACTH syndrome30,31. The intensity of the ACTH stimulus produced by these non-pituitary tumours is so great that the clinical presentation can be one of
hypokalaemic alkalosis in the absence of stigmata of Cushing's syndrome. According to Stuart Mason,' 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. 'Cushing's concept of hyperpituitarism has been completely vindicated by modern research.' Stuart Mason continues, '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'. Stuart Mason draws attention to the fact that pituitary Cushing's disease, although usually involving persistent disorder, can end in spontaneous cure: Cushing's Minnie was alive and better 29 years after she developed his disease. Another confusing point, according to Stuart Mason, is the fact that menstrual function in patients with very high ACTH plasma levels is usually normal and that they conceive easily. Finally, Stuart Mason introduces the term 'inappropriate ACTH secretion' for conditions in which the secretion of ACTH (from any source) is inappropriate for the physiological demands of the body. 'Our knowledge', he says, 'of the hypothalamic role in controlling ACTH secretion makes it virtually certain that corticotrophin releasing factor (CRF) levels must be high to put an excessive output of pituitary ACTH unless the pituitary has developed an autonomous ACTH secreting tumour.'

After adrenalectomy the growth of a pituitary adenoma may be prompted by strong stimulation from CRF.

van Seters also points out that since the introduction of ACTH and cortisone in 1950, all signs and symptoms can be induced by their chronic administration. Against this background, it seems to him appropriate to apply the term 'Cushing's disease' only to patients with an evident pituitary tumour, or to those patients with Cushing's syndrome where ectopic or adrenal tumours have been excluded. He concluded: 'We all realize that, even in 1989, this distinction can often not be made'.

This paper highlights the complexity of the problems surrounding the term 'Cushing's disease', which Harvey Cushing and Julius Bauer so brilliantly anticipated in the 1930s.

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(Accepted 2 July 1990)