The history of Cushing's disease: a controversial tale

V C Medvei MD FRCP *38 Westmoreland Terrace, London SW1V 3HL*

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

Paper read to joint meeting of the Sections of Pathology and History of Medicine, 21 June 1988

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[1]. At that time he still worked in Baltimore.

The subject here concerns, however, his publication in 1932 of a polyglandular syndrome: 'The basophilic adenomas of the pituitary body and their clinical manifestations (pituitary basophilism)'[2]. 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[3] 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,

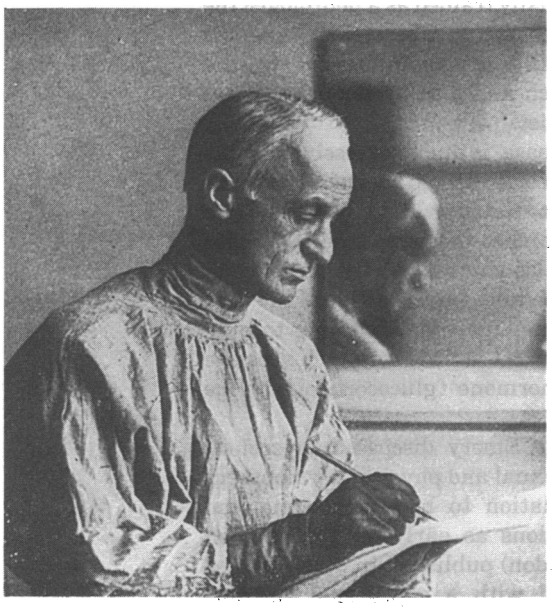

Figure 1. Harvey Cushing, 1869-1939

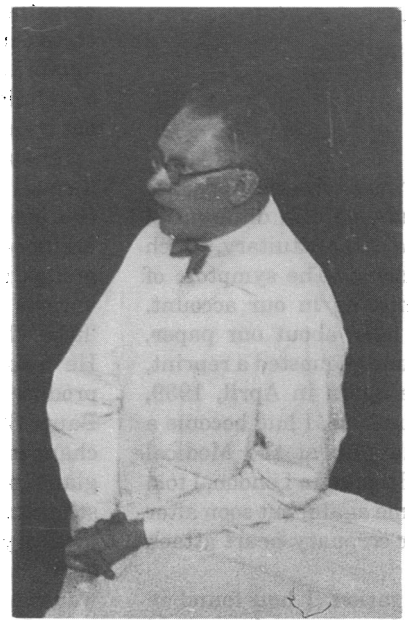

Figure 2. Julius Bauer, 1887-1979

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[4].

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[5]. 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 (Wermer's syndrome), when he worked at the College of Physicians and Surgeons, Columbia University, New York.

0141-0768/91/060363-04/$02.00/0

Table 1

After MEDVEI and WERMER. Med Klin 1934 N 30

SIGN	BASOPHILIC ADENOMA	ADRENOCORTICAL TUMOUR	VIRILISING TUMOURS OF THE OVARY
OBESITY (MASCULINE DISTRIBUTION)	+ + +	++	–
HIRSUTIES	+	+ + +	+ + +
GONADAL DYS (HYPO) FUNCTION	+ + +	+ + +	+ + +
MASCULINISATION OF EXTERNAL GENITALIA IN WOMEN	+	++	+ + +
PURPLE STRIAE	+ + +	+	–
OSTEOPOROSIS	+ + +	+(?)	–
HYPERTENSION	++	++	–
POLYCYTAEMIA	+	++	±
HYPERGLYCAEMIA	+	+	±
DRY AND ROUGH SKIN	+ + +	+	+
ENLARGEMENT OF SELLA	+	–	–
PALPABLE ABDOMINAL TUMOURS	–	+	–
PALPABLE OVARIAN TUMOUR	–	–	+

of the pituitary. Based on those observations, we attempted to present a study on the differential diagnosis of basophil adenoma of the pituitary, which was published in 1934[6] (Table 1). The symptom of depression was, however, missing in our account. Cushing, who happened to hear about our paper, wrote to me in October 1934 and requested a reprint, which I sent him. He wrote again in April, 1939, unaware of the fact that since 1938, I had become a medical student on a scholarship at the Medical College of St Bartholomew's Hospital in London, I told him about it and he wrote to me again, but soon after he died of a sudden posterior coronary heart attack on 7 October 1939.

In an independent investigation, I had found in a consequential series of 100 apparently normal pituitaries histological evidence of basophil micro-adenomas in 6% of the glands examined in 1937, but this remained unpublished as I left Vienna. Unknown to me, R T Costello, of the Mayo Clinic, had reported in 1935 on 72 (7.2%) basophilic adenomas among 1000 pituitaries examined in a routine manner, without any clinical signs, half as many as the chromophobe adenomas and three and a half times more numerous than eosinophil celled adenomas[7]. Susman (Manchester, England) found also in 1935, 8% basophil adenomas in 260 pituitaries, rather more frequent than other adenomas[8]. He, therefore, contested the anatomical basis of Cushing's pituitary basophilism. Autopsy studies have shown, however, that 50-60% of patients with Cushing's disease have pituitary adenomas, about two-thirds of which are of the minute basophilic variety. It seems that in a recent follow-up of these investigations (CT and magnetic resonance imaging scans in the United States) many patients are being found to have symptomless abnormalities in their pituitaries - so-called 'incidentalomas'. Neurosurgeons have concluded that most of these lesions are benign and need not be removed[9].

In 1950, Julius Bauer, who by then worked in Los Angeles, California, published a paper 'The so-called Cushing's syndrome, its history, terminology, and differential diagnosis'[10]. In it he said: 'Cushing's disease, therefore, is the association of the known clinical syndrome with pituitary basophilism. Hence it is this association of the known clinical syndrome, that should bear the eponym "Cushing's disease". I stuck to my conception of hyperfunction of the adrenals as sole explanation of the clinical picture ... I presumed in 1933 that, besides the gonadotropic and thyrotropic hormones, the pituitary must produce an interrenotropic hormone, selectively stimulating the adrenal cortex.' 'A few months later, in 1933, this hormone was actually discovered and its existence proved by Collip and his co-workers[11]. It is known as adrenocorticotropic (pituitary) hormone (ACTH). There exist, therefore, in my opinion, two types of interrenalism: one (primary), produced by functioning tumours of the adrenal cortex, and another (secondary), produced by excessive stimulation of the adrenal cortex by a diseased pituitary. Only the latter deserves the eponym "Cushing's Disease".' Although 'the essential features of primary and secondary hyper-corticism must be identical', according to Bauer, 'quantitative rather than qualitative differences in the clinical picture are to be expected, as was pointed out by my co-workers, Medvei and Wermer in 1934'[6].

Julius Bauer discussed since 1930 the fact that such a small gland like the pituitary, containing only a few groups of different cells should produce more hormones than can be allocated to the histological groups. He had a premonition that cells could produce various hormones, perhaps what is now termed 'hybrid hormones' like growth hormone and prolactin. He also suspected that many other organs may produce endocrine material. He said - when the Bauer-Sternberg patient did not display anatomical changes in the suprarenals - that another endocrine gland, perhaps the pituitary might have caused the stimulation of the adrenals. His idea was that the pituitary might produce a general ('mother') hormone acting as a stimulus on other endocrine glands, which would respond with an overproduction of their own manufacture. Accordingly, hypercorticalism of the adrenals may be primary or secondary, due to such a general hormone of the pituitary or even other organs. As regards the role of the basophil cells, he admitted that they could act stimulating the adrenal cortex, but - he argued - who knows, how many other endocrine and non-endocrine organs they could stimulate. Bauer anticipated the discovery of ACTH but more in the form of a pituitary 'mother-hormone', acting on different endocrine and non-endocrine organs. He used the pancreas as an example of a mixed exocrine and endocrine organ and felt that many more such combinations might exist. Incidentally, Bauer was originally trained as a neurologist (he had been Chief Assistant to Obersteiner) and his method of argumentation was influenced by the neurologist's approach and also by his other great interest as a geneticist.

That Cushing's disease 'is due to excessive production of the adrenocorticotropic hormone of the pituitary', was substantiated in 1935 by Jores[12] and in 1941 by Albright and co-workers[13] and by Kepler in 1945[14]. Albright also pointed out the presence of a negative nitrogen balance - irrespective of the type of Cushing's syndrome involved. According to him, Cushing's syndrome was the final result of excessive production of 'sugar hormone' (glucocorticoid) by the adrenal cortex[15].

Guthrie and d'Este Emery discussed precocious obesity, premature sexual and physical development and hirsuties in relation to hypernephroma and other morbid conditions as early as 1907[16]. (Sir) Gordon Holmes (London) published in 1924 'A case of virilism asociated with a suprarenal tumour: Recovery after its removal'[17]. It was the story of a 24-year-old woman with hirsuties, masculine

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 hirsuties 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 hormonic 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 1913[19]. She had precocious plethoric obesity, large purple striae, amenorrhoea, relatively thin legs and arms, a systolic blood pressure of 200 mmHg, polycythaemia, 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 1915[20], 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 lobe 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 Crooke[21], 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 hyperadrenocorticism.' In rare cases[22] 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 1930-1950s'[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'[29]. 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 pancreas[25], 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 adrenocortical hyperplasia (conventionally) Cushing's disease[26]. 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 transphenoidal hypophysectomy[27].

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)[10].

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 stimulation[28].

The diagnosis and management of ACTH-dependent Cushing's syndrome are discussed by the same group with three additional authors, in a later paper[29]. 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 syndrome[30,31]. 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[32] '. . . 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 rôle 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 adrenectomy 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.

References

1 Cushing HW. The hypophysis cerebri: clinical aspects of hyperpituitarism and of hypopituitarism. (Oration on Surgery, given to the Section of Surgery of the American Medical Association held in Atlantic City in June, 1909). *JAMA* 1909;53:249-55

2 Cushing HW. The basophilic adenomas of the pituitary body and their clinical manifestations (pituitary basophilism). *Bull Johns Hopkins Hosp* 1932;50:138-95

3 Cushing HW. *The pituitary body and its disorders.* Philadelphia: Lippincott, 1912:217

4 Bishop PMF, Close HG. A Case of Basophil Adenoma of the Anterior Lobe of the Pituitary: "Cushing's Syndrome". *Guy's Hosp Rep* 1932;82:143-53

5 Bauer J. Ueberfunktion d. gesamten Nebennierensystems ohne anatomischen Befund. *Wien Klin Wochenschr* 1930;43:582-5

6 Medvei VC, Wermer P. Zur Differentialdiagnose des basophilen Adenoms der Hypophyse. *Med Klinik* 1934; No. 30:992-4

7 Costello RT. Subclinical adenomas of the pituitary body. *Mayo Clin Proc* 1935;10:449-53

8 Susman Wm. Adenomata of pituitary: with special reference to pituitary basophilism of Cushing. *Br J Surg* 1935;22:539-44

9 Reincke M, Allolio B, Saeger W, Menzel J, Winkelmann W. The 'incidentaloma' of the pituitary gland. Is neurosurgery required? *JAMA* 1990;263:2772-6

10 Bauer J. The so-called Cushing's syndrome, its history, terminology and differential diagnosis. *Acta Med Scand* 1950;137:412-16

11 Collip JE, Anderson E, Thompson DL. The adrenotropic hormone of the anterior pituitary. *Lancet* 1933;ii:347-50

12 Jores A. Ueber Hormonuntersuchungen bei Morbus Cushing. *Klin Wochenschr* 1945;14:1348-52

13 Albright F. Cushing's syndrome. *Harvey Lecture Series* 1942-1943;38:123-86

14 Kepler EJ, Sprague RG, Claegt OT, Ower MP, Mason H, Rodgers HM. Adrenocortical tumour associated with Cushing's syndrome. *J Clin Endocrinol* 1948;8:499-531

15 Albright F, Parson W, Bloomberg E. Cushing's syndrome interpreted as hyperadrenocorticism leading to hypergluconeogenesis; results of treatment with testosterone propionate. *J Clin Endocrinol* 1941;1:375-81

16 Guthrie L, d'Este Emery W. Precocious obesity, premature sexual and physical development and hirsuties in relation to hypernephroma and other morbid conditions. *Trans Clin Soc Lond* 1907;40:175-202

17 Holmes G. A case of virilism associated with a suprarenal tumour; recovery after its removal. *Q J Med* 1924-25;17:143-52

18 Parkes Weber F. 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 tumour - with some remarks on the morphonogenetic and hormonic effects of true hypernephromata of the adrenal cortex. *Br J Dermatol Syphilis* 1926;38:1-5

19 Turney HG. Discussion on disease of the pituitary body. *Proc R Soc Med* 1912/13;6:69

20 Anderson J. A case of polyglandular syndrome with adrenal hypernephroma and adenoma of the pituitary gland - both of small size. *Glasgow Med J* 1915;new series;133:178-92

21 Crooke AC. A change in the basophilic cells of the pituitary gland common to conditions which exhibit the syndrome attributed to basophilic adenoma. *J Pathol Bacteriol* 1935;41:339-49

22 Hubble D. Cushing's syndrome and thymic carcinoma. *Q J Med* 1949;18:133-5

23 van Seters AP. The history of Cushing's syndrome: controversies regarding pathogenesis in the 1930-1950s. In: Luedecke DK, Chrousos GP, Tolis G, eds. *ACTH, Cushing's syndrome and other hypercortisolemic states.* New York: Raven Press, 1991

24 Hunder GG. Pathogenesis of Cushing's disease. *Mayo Clin Proc* 1966;41:29-39

25 Crooke AC. Basophilism and carcinoma of the pancreas. *J Pathol Bacteriol* 1946;58:667-700

26 Besser GM, Edwards CRW. Cushing's syndrome. *Clin Endocrin Metab* 1972;1:431-90

27 Howlett TA, Rees LH, Besser GM. Cushing's syndrome. *Clin Endocrinol Metab* 1985;14:911-45

28 Kepler ES. Relationship of Crooke's changes in the basophilic cells of the anterior pituitary body to Cushing's syndrome (pituitary basophilism). *J Clin Endocrinol* 1945;5:70-3

29 Howlett TA, Drury PL, Perry L, Doniach I, Rees LH, Besser GM. Diagnosis and management of ACTH-dependent Cushing's syndrome: comparison of the features in ectopic and pituitary ACTH production. *Clin Endocrinol* 1986;24:699-713

30 Liddle GW, Island D, Meader CK. *Recent Prog Horm Res* 1962;18:125-35

31 Liddle GW, Nicholson WE, Island DP, Abe K, Lowder SC. Clinical and laboratory studies of ectopic hormonal syndromes. *Recent Progr Horm Res* 1969;25:283-305

32 Stuart Mason A. Reflections on Cushing's syndrome. *Proc R Soc Med* 1971;64:749-52

(Accepted 2 July 1990)