

# Harvey Cushing and Cushing's syndrome

Ashley B. Grossman

*Professor of Neuroendocrinology, St Bartholomew's and the Royal London School of Medicine,  
London, UK*

*Corresponding address: Ashley B. Grossman, Professor of Neuroendocrinology,  
St Bartholomew's and the Royal London School of Medicine, London EC1A 7BE, UK.  
E-mail: a.b.grossman@qmul.ac.uk*

Date accepted for publication 19 January 2004

## Abstract

Harvey Cushing's first description of the eponymous disease attributed to him is reproduced here together with a modern commentary.

## Keywords

Cushing's syndrome.

## Introduction

The concatenation of symptoms and signs that are now considered to be the hallmarks of Cushing's syndrome remain of continuing fascination to endocrinologists. In the first instance, the symptoms and signs can be so florid, and the different manifestations so protean, that the clinical presentation in its most severe form is always dramatic. The list of possible abnormalities is long, and extends to include almost every system. Furthermore, the transformation in appearance before and after the disorder has started, and hopefully after it has been cured, can appear almost miraculous.

It seems strange now that such a clinically obvious syndrome had not previously been identified prior to the advent of the seminal description by Harvey Cushing, since with an incidence of some 5 per million per year many cases must have previously been seen by clinicians. However, the clinical description first given by Harvey Cushing in his monograph published in 1912, following on from his Harvey lecture in December 1910, incorporates almost all of the features that we now know to be characteristic<sup>[1]</sup>. The young patient, known as Minnie G., was in particular notable for her hirsuties and loss of head hair, her central obesity, florid bruising, and interestingly as well, her short stature. It is now well known that any form of cortisol excess will blunt growth hormone release, and the original history suggests that the disorder may have been present for many years.

## Pathophysiology

We now use the term Cushing's syndrome to describe any patient with symptoms or signs of corticosteroid excess, and in the first instance the most common form seen in the clinic is in patients taking exogenous steroids for diseases such as asthma and rheumatoid arthritis. The causes of endogenous corticosteroid excess are all secondary to excess cortisol secretion, usually in response to autonomous production of ACTH (adrenocorticotrophic hormone), or less commonly adrenal or adrenal abnormalities, in particular adenomas and carcinomas. In general, some 70% or

so are due to a tumour of the pituitary secreting excess ACTH, with around 15% secondary to the ectopic ACTH syndrome, usually a bronchial carcinoid.

It is particularly interesting that in the original description by Harvey Cushing he noted the abnormality of the pituitary gland in this disorder, and this was more greatly elaborated in his survey of 47 cases of what he referred to as the 'polyglandular syndrome'. He brilliantly speculated in his description of Minnie G. that the disorder may be one of hyperadrenalism, noting that the only previously recognised clinical state associated with adrenal disease had been Addison's disease: this was more fully incorporated into his later monograph, published in 1932, where he also associated the disorder with a basophil adenoma of the pituitary gland<sup>[2]</sup>. Indeed, he had earlier explored the possibility of removal of the pituitary experimentally, but this was later abandoned, mainly due to the rather primitive state of neurosurgical procedure and anaesthesia at that time.

## Harvey Cushing

Harvey Cushing originally graduated from Harvard in 1895, and then worked in Europe for some time before he returned to the Johns Hopkins Hospital where he trained in neurosurgery. He eventually returned as Professor of Surgery at Harvard Medical School and at the Peter Bent Brigham Hospital. Not only did he describe the clinical features and correctly identify the pathological lesion in Cushing's syndrome, but he was also involved in various other forms of neurosurgical innovation and description, and indeed was also awarded the Pulitzer Prize in 1926 for his book on the life of Sir William Osler.

## Diagnosis and treatment

We now know that the great majority of patients with ACTH-dependent Cushing's syndrome do indeed have an adenoma of the pituitary gland. ACTH released by these cells stimulates the release of cortisol, which has a variety of metabolic effects but most significantly limits in time and place the effects of the inflammatory response, increasing blood glucose and breaking down protein to provide increased fuel in times of inflammatory or other types of stress. Untreated, the disorder is generally associated with a high mortality. Diagnosis can be difficult; in the 1940s and 1950s the principal diagnostic techniques were the measurement of cortisol metabolites in the urine, but this was only helpful in the most severe cases. Even now, with the sophisticated blood and urine analyses available, the diagnosis may be problematic even to the most experienced endocrinologist, especially in its milder manifestations<sup>[3]</sup>. In spite of the best diagnostic and imaging techniques, transsphenoidal surgical cure is probably not better than 60% even in the most experienced centres, but a range of salvage therapies are available.

It is also of interest that while these tumours are very rarely large, Minnie G. appeared to have raised intracranial pressure, presumably associated with a large ACTH-secreting tumour, and was clinically improved by surgical decompression by Harvey Cushing. We do not know for certain her long-term outcome, but it was certainly the case that she was seen alive and reasonably well many years later. To have described and realised the significance of this fascinating condition makes Harvey Cushing one of the greatest figures in modern endocrinology.

## References

1. Cushing HW. *The Pituitary Body and its Disorders*. Philadelphia: J.B. Lippincott Co., 1912.
2. Cushing HW. The basophil adenomas of the pituitary and their clinical manifestations. *Bull Johns Hopkins Hosp* 1932; 50: 137-95.
3. Newell-Price J, Trainer P, Besser M, Grossman A. The diagnosis and differential diagnosis of Cushing's syndrome and pseudo-Cushing's states. *Endocrine Rev* 1998; 19: 647-72.