

Neuro-endocrinology

9 BRIEFINGS

THE CAUSE OF CUSHING'S DISEASE

SUMMARY

Cushing's Disease is one of the most fascinating disorders in the whole of endocrinology, a minute tumour in the pituitary giving rise to a whole panoply of symptoms, signs, and changes in mood and behaviour. Recent research has begun to identify the molecular changes in these tumours underlying the reduced sensitivity of the tumour cells to normal feedback regulation and cell cycle control, and which may eventually lead to specific gene therapy.

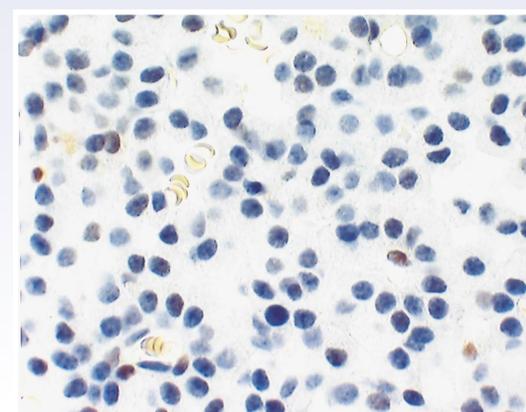
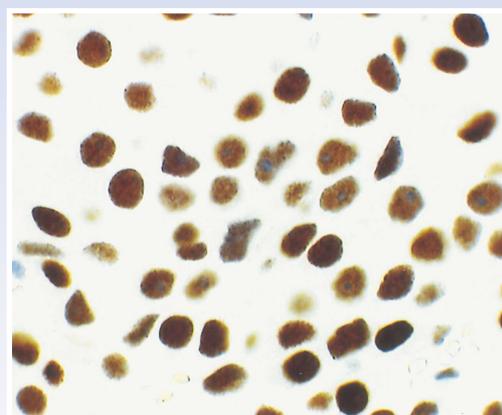
Cushing's Syndrome

There are few situations more dramatic in clinical endocrinology than the remarkable transformation in appearance and behaviour associated with Cushing's syndrome. The body becomes centrally bloated, fat streams into the abdomen, while the muscles of the arms and legs wither. This disorder, first described by the Boston neurosurgeon Harvey Cushing in 1932, is a concatenation of symptoms and signs secondary to excessive exposure to a family of steroid hormones, the glucocorticoids. These hormones, principally cortisol, were originally identified as products of the adrenal gland, but in

the 1950s their remarkable ability to inhibit inflammation was noted, and they rapidly became valuable therapeutic agents in diseases such as rheumatoid arthritis and asthma. Even today, the most common form of Cushing's syndrome is that due to over-zealous treatment with these steroids, either by mouth, by inhalers used for asthma, or even through the skin following the use of topical steroids for a whole variety of skin conditions.

Cushing's Disease

However, the most common cause of Cushing's syndrome in someone not taking any medication is that due to a small tumour of the pituitary gland, Cushing's disease. In this rare disorder, a small tumour of the pituitary (the master gland which sits underneath the brain, behind the eyes) makes too much of the hormone adrenocorticotrophin (ACTH) which in turn stimulates the



Photomicrographs of pituitary tumours secreting growth hormone (left) or ACTH (right) stained for the tumour suppressor gene product, p27, in the cell nucleus.

Note that only the growth hormone-secreting tumour contains significant quantities of p27 protein in the cell nuclei (brown colour). In the ACTH tumour, generally only the blue counterstain is visible in the smaller nuclei of these cells.

Data of M.Korbonits, K.Lidhar, S.Jordan & A.B.Grossman

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adrenal glands to both grow and release excessive amounts of cortisol. The normal daily rhythm of cortisol release, with high blood levels peaking at 8 am and very low levels between midnight and 2 am, is disrupted, and it is this disturbed rhythm that is one of the hallmarks of Cushing's disease. In addition, the ability to switch off ACTH with glucocorticoids is deranged, and this relative insensitivity to feedback control is also made use of in diagnostic tests.

A possible cause ?

Because Cushing's disease causes such widespread changes, it is usually diagnosed when the tumour is only a few millimetres in diameter. Such tumours are almost always 'monoclonal', that is, they represent a disordered proliferation of a single aberrant cell. If one cell undergoes a genetic change or mutation which allows it to make more ACTH than the surrounding cells, it may have a selective advantage. With time, the higher level of cortisol will switch off the other ACTH-secreting cells, or corticotrophs, allowing the monoclonal expansion to have a selective growth advantage. The suppression or atrophy of these surrounding cells

"Such tumours are almost always 'monoclonal'"

had in fact been recognised by pathologists for many years. Unlike other more malignant tumours, which usually represent a whole series of progressive mutations, the small size of the tumours of Cushing's disease suggests that only one or possibly two changes of the cellular control machinery will have

become disrupted. Recent work has begun to explore what these changes may be.

One approach has been to look at the normal feedback control of the corticotroph, and already there are suggestions that the way that the corticotroph senses circulating cortisol may be disturbed. For example, in rare instances levels of the receptor for cortisol, the glucocorticoid receptor, may be abnormally low, or mutated such that it does not work so effectively. More recently, evidence has been produced showing that an enzyme which inactivates cortisol may be over expressed. This may mean that the abnormal corticotroph will 'see' less of the pervading cortisol in its immediate milieu, and secrete inappropriate amounts of ACTH.

"We appear to be very near to precisely defining the molecular basis of this dramatic disease."

Alternatively, genes which generally regulate cell division, tumour suppressor genes (TSG), may be inactivated. One group has already shown that the TSG known as p16 may be switched off by a process referred to as methylation. In another series of studies, a TSG called p27 appears to form a protein which is rapidly broken down and is specifically under-expressed in ACTH-secreting tumours. Some other gene, known as an oncogene, may be selectively removing p27 from the cell nucleus thereby allowing its degradation by a 'dustbin' pathway. We therefore appear to be very near to precisely defining the molecular basis of this dramatic disease.

Is this important ?

While Cushing's disease is rare, with maybe one new case per quarter of a million population per year, glucocorticoids may cause disease in other more subtle ways. The oft-quoted relationship between stress and disease may be mediated in large part by cortisol, which may help explain the inverse association between social status and mortality. It has also been suggested that intrauterine or neonatal stress may imprint one's readiness to release cortisol, which may become clinically relevant in middle age. The obesity, hypertension and hyperlipidaemia so characteristic of the middle-aged in the developed world may thus to a greater or lesser extent be glucocorticoid mediated. Increasing knowledge of the comparatively uncommon pituitary tumour causing Cushing's disease will undoubtedly expand our whole understanding of the impact of stress on survival.

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