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Treatment of Cushing's Syndrome

Cushing's syndrome results from sustained and inappropriately high concentrations of corticosteroid in the plasma, whereas physiological increases that accompany physical stress such as infection, trauma, or psychological disturbance do not produce it. The causes of the syndrome may be conveniently divided into two main groups. Firstly are those that are ACTH-dependent. They include pituitary-dependent bilateral hyperplasia of the adrenals (conventionally called Cushing's disease), ectopic production of ACTH by various benign or malignant tumours, and ACTH therapy. The second group, not dependent on ACTH, includes adrenocortical adenomas and carcinomas and corticosteroid therapy. Of the causes not due to therapy those that are ACTH-dependent are far commoner in adults than those not dependent on ACTH, but this is not so in children. All types are commoner in women than in men.

Treatment of the different forms of Cushing's syndrome will depend on accurate diagnosis of the particular cause. This can usually be made with little difficulty with the aid of tests of the pituitary-adrenal axis, recently reviewed in these columns,[1] together with selective adrenal arteriography and venography. If unilateral or bilateral adrenocortical tumours are present they must be removed.

The best treatment for pituitary-dependent bilateral adrenocortical hyperplasia is not generally agreed. A detailed review of the outcome of treatment of 60 patients with Cushing's syndrome by R. B. Welbourn and his colleagues,[2] of the Royal Postgraduate Medical School and formerly at the Royal Victoria Hospital, Belfast, now make a valuable contribution to the analysis of this problem. Of 36 patients with bilateral adrenal hyperplasia, but without preoperative evidence of an enlarged pituitary fossa, 30 were treated by subtotal adrenalectomy. Of the 28 survivors, 17 (61%) required long-term replacement therapy. Many of the others had low basal excretion of steroid in the urine, while only four (14%) had an adequate adrenocortical reserve, as shown by a response to exogenous ACTH. This suggests that the remainder would not be capable of an adequate adrenocortical response to stress and that, in all, 86% of the patients would require replacement therapy at some time. In three patients the residual adrenal remnant regenerated sufficiently to induce a recurrence of the Cushing's syndrome. Since so many patients treated by subtotal adrenalectomy appear to require replacement therapy, and a few suffer recurrence, most clinicians would agree that total adrenalectomy is preferable.

Removal of the overactive adrenal glands or an adrenocortical tumour results in prompt disappearance of the clinical features of Cushing's syndrome and usually in the improvement or cure of the complications. After successful excision of a localized adrenal tumour the other atrophied gland eventually recovers, and replacement therapy is required only temporarily, but in Cushing's disease lifelong replacement therapy is necessary after total adrenalectomy.

In Cushing's disease the adrenal hyperplasia is the result of excess secretion of ACTH from the pituitary, which in turn may result from a hypothalamic defect.[3] With the passage of time levels of ACTH usually increase progressively. Adrenalectomy does nothing to halt this and may accelerate it.[4-6] Occasionally there is an undoubted pituitary tumour before adrenalectomy, but in 10% to 20% of patients a large fossa develops a few months to several years afterwards. Some of these patients become severely pigmented (Nelson's syndrome[6]), since melanocyte stimulating hormone (MSH) is secreted in great excess as well as ACTH.[7]

Some clinicians have therefore attempted to ablate the pituitary gland as primary treatment for Cushing's disease rather than remove the adrenals. Implants of radioactive yttrium have produced satisfactory results in only about half the cases,[8] but bombardment with heavy particles may be an improvement.[9] Hypophysectomy without irradiation is seldom adequate. Rarely the pituitary tumours are locally invasive, and once they are established treatment is of little help. Professor Welbourn and his colleagues suggest that all pituitary tumours in Cushing's disease should be regarded as potentially invasive, and so they recommend hypophysectomy and packing the fossa with yttrium. There is no evidence, however, that this alters the eventual outcome.

In a recent review of 108 cases of Cushing's syndrome treated at Vanderbilt University Medical Center, U.S.A., D. N. Orth[10] reported that conventional external irradiation of the pituitary may permanently cure or improve a substantial proportion of patients. While agreeing that subtotal adrenalectomy is too often unsatisfactory and that total

bilateral adrenalectomy rapidly cures this condition, he found that operation had been avoided in 23 of 51 patients given 4,000-5,000 rads to the pituitary gland. Ten patients followed up for one to 14 years (mean nine years) have been "cured"—that is, the plasma concentrations of corticosteroid were normal when averaged throughout the day (less than 10 μg/100 ml), and so was the 24-hour urinary excretion of corticosteroid. A further 13 were "improved" (plasma corticosteroids less than 13 μg/100 ml, and slightly raised urinary corticosteroid excretion) and have not required further treatment except in some cases by means of an inhibitor of cortisol synthesis such as amino-glutethimide.

Patients not improved by pituitary irradiation alone then underwent total adrenalectomy. The irradiation has resulted in neither hypopituitarism nor local neurological complications, and no patient has required substitution treatment unless subjected to adrenalectomy as well. Furthermore, unlike patients in other reported series treated by adrenalectomy without pituitary irradiation, none in Orth's series has developed progressive hyperpigmentation or enlargement of the sella turcica. This form of treatment for Cushing's disease deserves more widespread trial.

The Cushing's syndrome due to production of ACTH by an ectopic tumour is best treated by excision of the tumour, but this is rarely possible unless it is benign—for example, bronchial carcinoid. Some relief from the metabolic complications can be achieved by giving the patient an inhibitor of cortisol synthesis, amino-glutethimide or metyrapone. Another antiadrenal agent, *o,p'*-DDD, destroys adrenocortical cells and is a valuable drug to treat inoperable adrenocortical carcinoma and its metastases. Metastases become smaller and production of corticosteroid is lowered, though only temporarily.[10 11] Unfortunately nausea and ataxia limit tolerance to the drug. *o,p'*-DDD has been successfully used in lower doses than for carcinoma as primary treatment in Cushing's disease.[12] While Cushing's syndrome due to adrenal adenomas can be treated satisfactorily, we still await as good a treatment when the syndrome is associated with malignant disease or excessive secretion of ACTH by the pituitary.

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Hiccup

Hiccup is a strange phenomenon. It appears to serve no useful purpose as vomiting does, for instance. Most people have experienced it. Few have seriously considered its mechanism, for the symptom is usually transient, the cause is usually obvious (at least to the mind of the hiccupper), and the treatment is merely to wait for it to stop or to try and arrest it by bizarre manoeuvres most of which have in common a temporary cessation of respiration.

Persistent hiccup can be serious, intractible, and exhausting, and its cause often obscure. L. Samuels[1] listed 33 conditions known to be associated with it, dividing them into disorders of the central nervous system, neck, thorax, and abdomen. As the symptom may originate at so many different sites, it is not surprising that views on its mechanism have varied. It is often assumed to be some aberration of respiratory rhythm. A. Kuntz[2] described it as an involuntary reflex, respiratory in nature and purely automonic, mediated perhaps through respiratory centres in the brain stem. Samuels[1] carried out fluoroscopic diaphragmatic studies in great detail and thought that the respiratory, phrenic, and hypothalamic sympathetic centres might combine to perform the work of a special cerebral centre. But M. R. Salem and his colleagues,[3] considering afferent impulses to pass via the vagus, phrenic, and sympathetic pathways from T 6 to T 12, the efferent route being entirely phrenic, suggested there might be a centre controlling hiccup in the cervical cord between C 3 and C 5.

J. Newsom Davis[1] has now carried out an electrophysiological investigation of persistent hiccup. Such a study is not as easy as it may seem, for common hiccup is transient and even persistent hiccup is often stopped by excitement or other emotion—such as having electrophysiological studies carried out. However, he has shown from his studies on three persons that the diaphragm is not the only muscle involved and that, though previously classed as a respiratory reflex, hiccup has in fact only a minimal effect on ventilation. Each spasm consists of synchronous bursts of activity in the diaphragmatic and external (inspiratory) intercostal muscles, with inhibition of expiratory intercostal activity. The glottis is closed from just after its onset to after its completion, this explaining the lack of ventilatory effect. Breath-holding (a well-known remedy) and an increased P_{CO_2} reduces frequency but does not alter amplitude of hiccupping, while decreased P_{CO_2} considerably increases amplitude without altering frequency. He considers that hiccup is influenced by supraspinal mechanisms distinct from the paths for normal respiration, and that whereas its behavioural significance is uncertain it is more gastrointestinal than respiratory in nature.

Careful studies of this type are of great value in explaining mechanisms, but much remains unexplained about the association between this mechanism and known causes of hiccup. Samuels[1] considered that many (presumably persistent) cases had a psychogenic basis, but its occurrence in association with general toxic states such as uraemia, local gastrointestinal disturbances, and focal lesions of the brain stem serves to emphasize how diverse can be its causes. It is partly for this reason that the response to treatment shows the well-known inverse relationship between the number of methods recommended and the lasting effectiveness of any one of them. Benzedrine, quinidine, inhalation of carbon dioxide and oxygen, barbiturates, galvanism, ethyl chloride sprays to the neck, deep anaesthesia, hypnosis, phrenic dissection and interruption, or sympathetic interruption all have their advocates, and all fail in many cases, including phrenic interruption—an interesting fact in view of Newsom Davis's work.[4] A. E. Gibbs[5] found orphenadrine citrate helpful in terminal cases, and A. H. Douthwaite[6] advocated amitriptyline, while some clinicians have found a combination of metoclopramide with chlorpromazine effective.