any rise in complement fixing antibody titre and do not excrete CMV in the urine at the time of disseminated infection.

The results of treatment of CMV infection with antiviral agents such as interferon, cytosine arabinoside, and idoxuridine have been singularly disappointing. Adenosine arabinoside, a newer antiviral agent, is apparently also ineffective.[6] An attenuated strain of cytomegalovirus has been developed for use as a vaccine in the hope of preventing congenital CMV infection.[7] Nevertheless, even if such vaccines were shown to protect normal individuals effective immunosuppressive treatment would negate any such benefit.

The depressing results of treatment might suggest that emphasis should be given to prophylactic interruption of viral transmission. How is CMV usually acquired? Routes postulated have included intrauterine infection; transmission to the baby as it passes through the birth canal; infection through the mother's milk; transmission by fresh blood transfusion; transplantation of the virus in infected allografts of bone marrow, kidney, or other organs; venereal transmission; and respiratory droplet infection. Furthermore, since the clinical data suggest that most patients are at risk from endogenous infection, isolation is unlikely to achieve any real benefit—a view supported by Cox *et al*,[8] who failed to reduce CMV infection in 83 children with acute lymphoblastic leukaemia nursed under standard contagious isolation procedures.

While at present neither prophylactic measures nor antiviral agents are of much practical value, awareness of the features of CMV infection may improve its recognition and improve the existing clinical management.

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Pituitary-dependent Cushing's disease

True Cushing's syndrome is rare. A specialised regional centre may see only six new referrals each year, and a district general hospital one new case in five years. Most patients (80%) have bilateral adrenal hyperplasia, the result of excessive secretion of pituitary ACTH—pituitary-dependent Cushing's disease.[1] Often these patients have a small pituitary tumour,[2] as originally described by Harvey Cushing.[3] The minority either have an autonomous cortisol-secreting adrenal adenoma or carcinoma or ectopic production of ACTH from a tumour such as a bronchial carcinoma or a pancreatic carcinoid.

Pituitary-dependent Cushing's disease is associated with a high normal or raised concentration of plasma ACTH[4] and a positive response to the 11-β-hydroxylase inhibitor metyrapone, with an increase in urine 17-oxogenic steroids.[5] Cushing's syndrome due to an adrenal tumour is associated with undetectable plasma ACTH and an absent or impaired response to metyrapone stimulation. In the ectopic ACTH syndrome plasma ACTH concentrations are usually grossly raised and the response to metyrapone is again usually absent or impaired. The high-dose dexamethasone test, which in pituitary-dependent Cushing's disease suppresses both plasma and urine free cortisol, may occasionally give misleading results.[6]

Early recognition of Cushing's syndrome is important: the life expectancy of the untreated patient is less than five years.[7] Bilateral adrenalectomy has been considered the treatment of choice for pituitary-dependent Cushing's disease, since the effect on cortisol production is immediate. The operation is, however, a major procedure[8 9] with a high immediate morbidity and a mortality of 4-5%; patients require lifelong corticosteroid replacement treatment; and they are at risk of developing an infiltrating pituitary tumour. After bilateral adrenalectomy plasma ACTH concentrations rise in all patients, two-thirds will develop skin pigmentation, and one-third an obvious pituitary tumour[10]—a combination termed Nelson's syndrome.[11] The pituitary tumours, which are often locally malignant, may cause cranial nerve lesions and are prone to haemorrhage.

There are, therefore, obvious attractions in directing treatment to the pituitary gland. Conventional external irradiation gives complete remission in only 20% of patients.[12] Interstitial irradiation with implantation of ^{198}Au or ^{90}Y seeds into the pituitary gland is more effective. In one series of 57 patients complete remission was obtained in 65% of patients who had no radiological evidence of an enlarged sella turcica; only 52% of these needed replacement corticosteroids. The failure rate was high in those with an enlarged sella turcica.[13] Treatment with transphenoidal hypophysectomy has also given good results. In Hardy's series[14] eight out of ten patients achieved complete remission, and histological examination showed the presence of either an obvious pituitary tumour or micro-adenoma. Eleven of the 13 patients reported by Carmalt *et al*[15] went into complete remission. There was one partial remission and one late death from myocardial disease. Definite histological abnormalities were found in only ten patients: seven pituitary microadenomas and three with basophilic hyperplasia. Four patients did not require replacement corticosteroid treatment, and in five of the seven premenopausal women normal menstruation returned, pregnancy occurring in three.

Some patients with pituitary-dependent Cushing's disease undergo surgery in a state of general weakness and potassium depletion. Postoperative respiratory complications are common, and the frail tissues of these patients heal poorly. Such patients would benefit from preoperative control of cortisol production. A combination of metyrapone and aminoglutethimide will inhibit cortisol synthesis completely. This regimen, however, induces rashes and drowsiness, and replacement glucocorticoid and mineralocorticoid treatment is needed.[15] Metyrapone alone will control cortisol production, but the dose has to be monitored by estimating the plasma fluorogenic corticosteroid concentrations.[16]

In pituitary-dependent Cushing's disease there are, then, definite advantages in directing treatment to the pituitary. Nevertheless, if future fertility is important, bilateral total adrenalectomy may be advised, with careful follow-up to detect the early development of Nelson's syndrome.

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Diabetes insipidus—turning off the tap

Advances in pharmacology have produced a dramatic change in the treatment of patients with cranial diabetes insipidus. For many years the standard treatment has been either injections of vasopressin tannate-in-oil (Pitressin) or nasal insufflation of posterior pituitary powder. Pitressin, however, is an impure preparation which contains several peptides other than lysine vasopressin and arginine vasopressin (the human antidiuretic hormone); these include oxytocin, neurophysin,[1] prolactin, and a corticotrophin-like peptide.[2] Patients treated with Pitressin often produce high titres of antibodies against neurophysin[1] and usually find the injections difficult to prepare and painful to receive. The alternative, pituitary snuff, may cause rhinitis[3] and allergic pulmonary lesions.[4]

Since Pitressin tannate-in-oil has been withdrawn for commercial reasons attention has been focused on alternative methods of treatment.[5] Lysine vasopressin was the first synthetic vasopressin preparation to be widely used in treating diabetes insipidus. Given as a nasal spray, its effects last only three to four hours and it is of no value in the treatment of the severe disease. More recently, the synthetic analogue DDAVP (1-desamino-8D-arginine vasopressin) has revolutionised treatment.[7-9] DDAVP has two structural changes[10] from naturally occurring human antidiuretic hormone: it lacks the amino group on the hemicystine in position 1, and has D-arginine instead of L-arginine in position 8. This molecular manipulation has dramatically enhanced antidiuretic activity while lowering the pressor action. The reason for the enhanced antidiuretic effect is not clear but may relate to protection of the molecule against enzymic breakdown. Certainly DDAVP has a much longer half-life in the circulation than arginine vasopressin.[9]

Comparison of the antidiuretic action of DDAVP and lysine vasopressin has shown that in patients with moderate or severe cranial diabetes insipidus the intranasal administration of DDAVP produces good clinical control—whereas lysine vasopressin is often either minimally effective or without effect.[6 8 9 11 12] For long-term treatment patients usually require 10 to 20 μg DDAVP intranasally twice or occasionally three times daily.[7-9 11 12] The drug may also be given intravenously. It produces none of the side effects of lysine vasopressin, such as pallor or abdominal pain. DDAVP also has reduced oxytocic activity compared with lysine vasopressin and so may be used in pregnancy.[13] In children with cranial diabetes insipidus DDAVP seems to be the drug of choice,[14 15] the usual dose being 5 μg twice daily.

Several drugs chemically unrelated to vasopressin may be used in treatment. The paradoxical antidiuretic action of diuretics has been known for many years.[16 17] Unlike the other drugs discussed, diuretics are effective in both cranial and nephrogenic diabetes insipidus, but they usually reduce the urine volume only by about half. A major advance came with the chance discovery that the oral hypoglycaemic agent chlorpropamide was an effective treatment for some patients with diabetes insipidus.[18] Chlorpropamide appears to act by increasing the renal responsiveness to endogenous vasopressin[19 20]; so it is useful in patients with partial diabetes insipidus who have some vasopressin secretion, but ineffective in those with severe diabetes insipidus. Not surprisingly, hypoglycaemia may be a problem, particularly in patients with associated anterior pituitary insufficiency,[21] and many patients are troubled by the disulfiram-like action of the drug. In children hypoglycaemia appears to be more common, so that treatment with DDAVP is indicated.

Two further drugs unrelated to vasopressin also have antidiuretic effects—namely, clofibrate and carbamazepine.[22 23] Clofibrate probably acts by releasing endogenous vasopressin,[24] while the action of carbamazepine is similar to that of chlorpropamide.[25]

Recently, therefore, the life of the patient with cranial diabetes insipidus has been made much more tolerable. Both science and serendipity have had major roles in turning off the tap.

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