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Growth hormone 1985

1985 has been an eventful year for those concerned with growth hormone therapy. In the spring, treatment with hormone extracted from pituitary glands was stopped in Britain and the United States after three deaths from Creutzfeldt-Jakob disease were reported in the United States in young adults who had been treated with growth hormone in the 1960s and 1970s.[1,2] A fourth case occurred in Britain in 1985,[3] but no more have been reported. Creutzfeldt-Jakob disease is a rare encephalopathy due to slow virus infection with a natural prevalence of one in a million and an average age at death of 57. The young age and common factor of treatment with growth hormone led to the reasonable inference that contagion had occurred through the pituitary extract and treatment was stopped despite the reassuring results of an experiment which had shown that slow virus was not recovered from pituitaries extracted by current techniques.[4]

There has always been a potential shortage of pituitaries for the manufacture of growth hormone, and when the Health Services Human Growth Hormone Committee was created in 1978 its terms of reference included responsibility for selecting patients for treatment according to uniform criteria, determining therapeutic regimens, and monitoring the overall supply and demand for growth hormone in patients in the health service.[5] The development of preparations of growth hormone by recombinant DNA technology was welcomed by the committee, which foresaw a smooth transition from pituitary to biosynthetic growth hormone after the biosynthetic product had been carefully evaluated and granted a product licence. The tempo of transition accelerated sharply when pituitary growth hormone treatment was halted in May. At that time one year was predicted to be the minimum gap before treatment with growth hormone could restart nation wide. Happily this interval has been reduced to six months with the granting in October of a product licence for met-hGH (Somatonorm) produced by KabiVitrum.

Britain is the first country in the world to license a biosynthetic preparation of growth hormone, but this step forward has produced potential problems as well as benefits. The good news is that supplies of met-hGH are virtually unlimited, and there is no risk of viral contamination. But one ampoule of met-hGH will cost initially two to three times as much as the same amount of British pituitary growth hormone, and the price of treating one child with met-hGH throughout 1986 will be over £4000. When the committee supervised treatment with growth hormone the nation's financial commitment was easy to calculate. New patients suffering from total or partial growth hormone deficiency were accepted at a rate only slightly above those stopping treatment. Around 900 children were getting growth hormone at any one time, and a ceiling of 1000 was used in calculations of national need. Pituitary glands were collected under the aegis of the Department of Health and Social Security, which also supervised the manufacture and distribution of therapeutic growth hormone to 21 recognised growth assessment centres throughout Britain through the Health Services Human Growth Hormone Committee, which met quarterly. Finally the whole operation was largely self financing by a system of recharging at the point in the NHS where growth hormone was dispensed.

This system worked efficiently and fairly so long as growth hormone was in short supply and there was only one route of distribution. The granting of a product licence[6] that permits specialist medical practitioners to prescribe met-hGH for "the treatment of short stature caused by decreased or absent secretion of pituitary growth hormone" has far reaching implications. Who is a specialist medical practitioner? What is decreased secretion of pituitary growth hormone? Who will pay?

Clearly the doctors manning the recognised growth centres are experts in analysing growth problems. They have the anthropometric skill which is more important than laboratory investigations in the evaluation of a short child. But no one would claim that excellence is to be found only in these centres, and other paediatricians and endocrinologists will certainly now start to treat patients with growth hormone. The range of children who can be made to grow taller with growth hormone is probably wider than that accepted by the committee and this topic is dealt with in a leading article to be published in a few weeks' time. But I would plead that every physician using growth hormone should be rigorously critical in assessing therapeutic benefit. This requires accurate determinations of height velocity before and during treatment—and for a second period off treatment in patients who do not have clear cut growth hormone deficiency. The risk of

committing to treatment a child who does not need it may be as great as the more commonly perceived risk of missing patients who will benefit.

The doctors in charge of the growth centres have naturally been concerned about the adverse financial effects of restarting treatment with growth hormone: the effect on a hospital's drug bill in the case of the larger centres might be crippling. We know that family practitioners will not be able to prescribe met-hGH for patients in the health service, but the precise mechanism for prescribing, dispensing, and charging has not yet issued from the bureaucratic machine. This is an urgent matter: if patients, their parents, and physicians know that treatment is available but they are unable to get it they will be distressed and angry. Whoever writes the prescription, the patient will need to continue attending a specialist growth centre for evaluation of response to treatment and the assessment and management of related endocrine problems.

What will become of the Health Services Human Growth Hormone Committee? It is clearly no longer appropriate for it to receive applications for treatment with growth hormone, and as practitioners prescribe the hormone on their own responsibility the committee will no longer be able to supervise who is treated or how treatment is dispensed. The committee has one important remaining remit: to monitor the effects of former treatment with the pituitary growth hormone. This will be possible for all patients treated in Britain through the committee since information on the batch and date of dispensing for each patient has been recorded. The question of how actively such patients should be monitored has not been resolved. One view is that an epidemic of iatrogenic Creutzfeldt-Jakob disease lies ahead,[7] and we should document it assiduously. Another view is that there will be few further cases of Creutzfeldt-Jakob disease in British patients treated with pituitary growth hormone, and that to maintain a link with former patients during life might engender anxiety about a fatal disease for which there is no cure. All doctors who meet patients previously treated with pituitary growth hormone should, however, bear Creutzfeldt-Jakob disease in mind when assessing any problem, medical or surgical.

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Water intoxication in patients with psychiatric illness

> Poor Tom; that eats the swimming frog, the toad, the tadpole, the wall newt, and the water; that in the fury of his heart, when the foul fiend rages, eats cow dung for sallets; swallows the old rat and the ditch dog; drinks the green mantle of the standing pool; who is whipped from tithing to tithing, and stock punished, and imprisoned.
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> *King Lear* III, iv.

Shakespeare's description of "Poor Mad Tom" is said to be a classic description of chronic schizophrenia.[1] Such a claim is contentious and untestable, but the poet's description reminds us that "mad" people may be indiscriminate in the amount and character of what they ingest. In 1938 Barahal documented the first case of water intoxication in a patient with schizophrenia,[2] and since then many similar reports have appeared. In 1974 Raskind reported a fatality from self induced water intoxication,[3] and a recent paper in the *British Journal of Psychiatry* describes four cases in which self induced water intoxication threatened life.[4] With the trend towards community care of patients with psychiatric illnesses (including those with chronic psychoses) this syndrome may be seen by non-specialists.

Excessive water drinking may occur in almost any psychiatric disorder. It is seen, for example, in patients with personality disorders and hysterical traits, and may cause difficulties in their diagnosis and management. The role of "modelling" of this pattern of behaviour in families has recently been emphasised.[5] Most cases (about 80%) of self induced water intoxication, however, occur in patients with psychotic illness—usually of the schizophrenic type. The prevalence of compulsive water drinking in state mental hospitals in the United States has been estimated as between 7%[6] and 18%,[7] and about half of these patients suffer from the complications of water intoxication. Self induced water intoxication is associated with a mortality of 10% over two years.[8] Vieweg *et al* found that nearly a fifth of deaths in schizophrenics aged under 50 in a state hospital were attributable to self induced water intoxication or its complications, including cerebral and visceral oedema.[9]

Early features of water intoxication include headache, blurred vision, polyuria, vomiting, tremor, and worsening of psychosis. More severe features include muscle cramps, ataxia, delirium, stupor, coma, and convulsions. Major motor seizures are the commonest presenting feature of self induced water intoxication in patients with psychiatric illness and have been reported in about 80% of the reported cases.[10] Self induced water intoxication should therefore be included in the differential diagnosis of seizures of recent onset, especially in psychiatric patients in hospitals.

The pathophysiological mechanisms underlying self induced water intoxication are not clear. In some cases the excessive intake of water is linked to psychotic delusions. For example, Singh *et al* described a patient who drank large volumes of water (and developed severe hyponatraemia and convulsions) as "an act of offering to the gods."[4] Alexander *et al* described a similar course of events in a schizophrenic who drank large volumes of water to "flush" an imagined parasitic worm from his body.[11] Such colourful histories are not always forthcoming, however, and failure of the homoeostatic mechanisms concerned in thirst or fluid regulation or both may also play a part.

In healthy adults secretion of antidiuretic hormone is predominantly regulated by an osmoreceptor that is ex-