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Annotation

Human growth hormone (UK)

Human growth hormone manufactured in the United Kingdom (GH (UK)) has been available since 1959 for the treatment of patients suffering from growth hormone deficiency. At that time a Working Party of the Pituitary Hormone Committee of the MRC was formed to design and carry out a clinical trial of GH (UK) as a growth promoting agent in patients of short stature. Favourable therapeutic results led to extension of the trial from simple assessment of the efficacy of GH (UK) to more detailed studies of the best mode of usage. From being a purely research exercise in the early 1960s the emphasis of the Working Party's remit shifted gradually to a service commitment to provide GH treatment for those who need and can benefit from it. This led to the development of a national system for the evaluation and treatment of patients suffering from lack of GH and in 1977 responsibility for the provision of treatment with GH (UK) transferred from the MRC to the DHSS. The experience accrued by the MRC Working Party has recently been published.[1] A Health Services Human Growth Hormone Committee (HSHGHC) was created by the DHSS to replace the MRC Working Party and in announcing this the department commented[2] '. . .The demand for hGH and the supply from pituitaries are fairly finely balanced and are expected to continue to be so in future. . . .It is likely that treatment with hGH will for some years be regarded as a new and developing service and paediatricians with experience and expertise in this specialised area will tend to be those who have been associated with the MRC trial and the growth assessment centres. Moreover, given the limited availability of hGH it is important that broadly uniform clinical criteria are applied in the selection of patients and the determination of therapeutic regimens.'

Today there are 19 growth assessment centres in the UK at which patients are measured and the effects of treatment monitored. Allocation of GH (UK) is decided by the HSHGHC quarterly on the basis of application by the physician in charge of the patient. An integral part of the application is the anthropometric information provided by the growth assessment centre. The HSHGHC has a co-ordinator who is responsible for collating information from the centres and sending GH (UK) to them for distribution to the patients.

GH (UK) has been extracted at the Department of Biochemistry, University of Cambridge since the beginning of the MRC trial using acetone-preserved pituitary glands as starting material. The GH (UK) prepared in this way has been shown to be therapeutically effective and free from side effects over 17 years with the exception of a few patients (less than 2%) who develop growth inhibiting antibodies. The preparation is known not to be homogenous protein and to contain large molecular weight components inferred to be aggregated GH and small but detectable concentrations of other pituitary hormones when tested by immunoassay.[1] Other methods of pituitary preservation and growth hormone extraction have been studied in an attempt to obtain a purer product. GH (UK) has been prepared from frozen glands at St Bartholomew's Hospital, London and used successfully in the treatment of certain patients who had developed growth inhibiting antibodies to conventional therapy with GH (UK). Commercial therapeutic GH is also prepared from frozen glands. The relative advantage of preserving pituitary glands in acetone or by freezing is not obvious. Freezing is less damaging to the peptide hormones in the pituitary but may also result in the preservation of other contaminants among which viruses are a remote but particular cause of concern. The logistics of preserving and transporting frozen glands nationally is more difficult than for acetone-preserved glands. After considering all the factors carefully, the department has made plans for the future production of GH (UK), initially from acetone-preserved glands using a modified extraction procedure which includes additional steps to remove high molecular weight aggregated and contaminating hormones. Arrangements have been made to transfer production to the Centre for Applied Microbiological Research at Porton Down which should begin to supply GH (UK) at the end of 1979. A research and development programme will operate concurrently at Porton which will include other methods of production.

An important argument against using GH from commercial sources overseas is cost, but even more important is the question of supply. Industry could not provide the quantity of GH needed in the UK from existing stocks and would have to rely on the provision of pituitaries collected in the UK for

hormone extraction. The processing of the glands by the companies could take place in the UK or in Scandinavia, but in either event would raise ethical and legal questions since a Council of Europe resolution,[3] accepted by the UK forbids the offering of substances (human material or extracts of such material) for profit. Finally if the glands were to pass out of our hands there could be difficulty in ensuring the return of *all* extracts from them. All the GH that can be extracted from UK pituitaries is needed for therapeutic purposes in the UK and other extracts from the glands have important research and commercial potential.

Recently it has been alleged that: 'hGH (UK) currently in use or an impurity in it accelerates osseous maturation either via thyroid or gonadal stimulation to a greater degree than it increases linear growth with the result that ultimate short stature (in most cases <3rd centile) is likely to result from the treatment of patients with short stature with hGH (UK)'.[4] This communication was delivered to the annual meeting of the BPA in York on 28 March 1979. The next day an article appeared in the *Glasgow Herald* headed 'HGH "Wonder cure" has turned sour for our poor growth youngsters'.[5]

The communication and the associated publicity were completely contrary to the published experience of the trial,[6] but in view of the distress caused to patients, their parents, and to the parents of potential patients, a new and detailed review of all patients treated with GH (UK) for whom bone age and height records are available was carried out.[7] Of 215 patients, 122 had isolated growth hormone deficiency, 63 had a deficiency of one or more pituitary hormones (panhypopituitarism), and 30 had a craniopharyngioma. Patients with craniopharyngioma or panhypopituitarism were treated with other hormones that could accelerate osseous maturation in addition to growth hormone. The duration of treatment varied from one to 13 years but since there was no relation between the time on treatment and rate of bone maturation it was possible to consider all cases together. The overall mean bone age velocity of patients with isolated growth hormone deficiency and panhypopituitarism was 1·00 and 0·97 bone age years respectively, but that of patients with craniopharyngioma was less: 0·57. These results show that treatment with GH (UK) does not cause pathologically accelerated bone maturation. To compare the growth in height with bone development it was necessary to calculate the height standard deviation score for bone age.[6] If osseous maturation is stimulated by GH (UK) to a greater degree than linear growth as alleged[4] then the height SD for bone age will become lower (that is more negative) as a result of treatment. In fact the opposite was observed in patients with craniopharyngioma and isolated growth hormone deficiency. In both groups the height SDs for bone age became significantly higher as a result of GH (UK) treatment showing that therapy increased growth in bone length more than osseous maturation. In the patients with panhypopituitarism no significant change in height SDs for bone age was observed, indicating that growth in height and osseous maturation was occurring proportionately.

Growth hormone treatment is one of the outstanding therapeutic successes in recent years and all paediatricians will wish to make it available to the greatest extent that supply will allow. The nationally co-ordinated scheme that operates in the UK ensures that this objective is fulfilled for our patients.

References

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