Linear growth patterns have been recorded in children for more than 200 years. The first documented longitudinal study was that by Count Philibert Guereau de Montbeillard in 1777 on his son from birth to 18 years. This was an important landmark in the application of the scientific method to the study of the normal physiological processes of growth. Throughout the intervening years, the measurement of height has been extended to populations of healthy children and those at risk from an underlying pathology.

Normal growth in a healthy population is judged by an increase in height measured at regular intervals either cross-sectionally at a given age or longitudinally in a cohort of individuals throughout their period of growth. Increments of height show a steady, but not necessarily continuous, increase from birth to late adolescence when epiphyseal closure of the long bones occurs. If growth is expressed as a rate of change in height (cm/y) and then plotted against chronological age, a growth pattern emerges that is different from a simple height for age profile (Fig. 1). A decrease in growth velocity is shown from birth until puberty, when an acceleration in height gain is demonstrable with a peak velocity that is earlier in girls than in boys. Cross-sectional and longitudinal studies of growth velocity allow the construction of growth charts and centile limits for normal populations that can be used to assess an individual's growth pattern and, with suitable weighting for mid-parental height, the potential height of that individual. Growth during adolescence is not confined to height, but is also shown by an increase in bi-iliac distance, head circumference and hand length, accompanied by a gain of body weight. In addition to these normal physiological changes, there is a major increase in weight of the reproductive organs—testes, prostate, uterus and ovary—during adolescence. Tanner and Marshall have quantified these and other physical changes that occur through the growth period. Additional key phrases: insulin-like growth factors; IGF-I; IGF-II; binding proteins

Correspondence: Dr B T Rudd.
adolescence. These normal data form the basis with which patients with a suspected pathology that affects growth and/or maturation can be compared.

The construction of population norms for growth and maturation has to take into account secular trends. Tanner\(^1\) quotes striking data for this. Between 1880 and 1950 records from five separate countries show an average increase of 1·5 cm in height and 0·5 kg in body weight per decade for children of 5–7 years, and of 2·5 cm in height and 2 kg in weight per decade in adolescence. Other reports have identified the influence of socioeconomic status,\(^5\) parental height and nutrition\(^6\) on linear growth and underline the multifactorial basis of the growth process.

**GROWTH HORMONE**

**Structure and assay**

Growth hormone (GH) has been isolated from pituitary glands obtained from several species including the pig,\(^8\) the cow,\(^9\) and man.\(^10\) Highly purified GH preparations from non-primates fail to give a biological response when injected into monkeys or man.\(^11\) Structural studies of GH preparations have identified similarities and differences in the amino acid sequence between different species, for example, bovine and human GH.\(^12\) Highly purified monomeric human GH (hGH), isoelectric point 4·9, has a molecular weight of 22 kD, and contains 190 amino acids including four cysteine residues at positions 53, 165, 182 and 189. There is a disulphide bridge between cysteine residues 53 and 165 and a second between residues 182 and 189.

Baumann,\(^13\) in an important and comprehensive study, has reviewed the literature on the nature of the forms of hGH secreted by pituitary somatotrophs and the native forms that are demonstrable in plasma. The studies cited by Baumann have clarified how to distinguish hGH variants generated by storage or proteolytic degradation from the natural forms (Table I). The studies quoted further highlight the importance of those factors that affect the proportion and detection of immunoassayable hGH variants in the circulation. These are: binding to high and low affinity hGH binding proteins, differences in receptor affinities between the hGH variants, the degree of *in vivo* proteolysis and non-specific immunoreactivity due to immunoglobulins. It is clear from these reports that the relative proportions of immunoassayable hGH present in plasma will vary according to clearance rates of the hGH variants. Selective plasma enrichment has been noted of the 20 kD hGH variant and of the oligomeric forms.

The assay performance of polyclonal hGH antisera depends upon the quality of the immunogen that is used to raise them. Imprecision of

| Table 1. The native forms of hGH secreted by human pituitary somatotrophs and the major forms found in plasma |
|-------------------------------------------------|-------------------------------------------------|-----------------|
| **Pituitary**                                   | **Plasma**                                      | 15 min after    |
| Form                                           | Secreted (%)                                   | stimulation (%) |
| Monomers                                       |                                                 |                 |
| 22 kD total                                    | 70–75                                          | 22 kD total     |
| 22 kD                                         | 5–10                                           | 48              |
| ASP (152)                                      |                                                 | 22 kD free      |
| 22 kD                                         | <5                                             | 24              |
| GLU(137)                                      |                                                 | 22 kD bound to high affinity hGH-BP |
| 22 kD                                         | 5                                              | 22              |
| No-acylated                                    |                                                 | kD bound to low affinity hGH-BP |
| 20 kD total                                    | 5–10                                           | 2               |
| Dimer                                          |                                                 | 20 kD total     |
| 22 kD (mixed)                                  | 10                                             | 9               |
|                                              |                                                 | 20 kD free      |
|                                              |                                                 | 6·5             |
|                                              |                                                 | 20 kD bound to high affinity hGH-BP |
|                                              |                                                 | 0·5             |
|                                              |                                                 | 20 kD bound to low affinity hGH-BP |
|                                              |                                                 | 2               |
| Higher oligomers                               | 22 kD (mixed)                                  | 5               |
|                                              | 22 kD total                                    | 14              |
|                                              | 22 kD disulphide                               | 6               |
|                                              | 22 kD total non-covalent                        | 7               |
|                                              | 22 kD disulphide                               | 3               |
|                                              | 20 kD total non-covalent                        | 1               |
|                                              | 20 kD disulphide                               | 0·5             |
assay performance is exacerbated by matrix effects, including the inappropriate use of serum proteins from some animal sources in buffer diluents. Variations in assay precision are also attributable to the instability of radiolabelled hGH tracers and to differences in immunological potency of the hGH standards used as calibrants. Control of these variables and substitution of monoclonal antibodies lead to lower values of immunoassayable hGH than with polyclonal antisera. The difference between polyclonal and monoclonal antisera assay performance can, in part, be explained by the degree of cross-reactivity of the hGH variants in serum with different antisera. These observations emphasize the importance of establishing the characteristics of polyclonal antisera raised to growth hormone preparations. Good quality polyclonal antisera of high affinity and specificity will detect approximately 75% of the 22 kD hGH variant in normal serum.

The genetic control of hGH synthesis has been studied by DNA probing techniques. Two genes, hGH-N and hGH-V, have been located on chromosome 17. The hGH-N gene regulates the synthesis of monomeric (22 kD) hGH that is exclusively synthesized in the pituitary somatotrophs. In contrast, the hGH-V gene controls the synthesis of the 20 kD hGH variant which differs by a 13-aminoacid sequence from the 22 kD monomeric form. There is some evidence that the 20 kD variant is glycosylated16 and immunoassayable concentrations are high during the later stages of pregnancy. In the non-pregnant state, approximately 10% of RIA detectable hGH is of the 20 kD form when polyclonal antisera are used for detection. On the other hand, one monoclonal antibody failed to detect the 20 kD variant.14 The biological significance of the 20 kD species and charge variants of hGH is uncertain, the latter possibly arising during the course of purification.17 Nevertheless, chemically or enzymatically cleaved fragments of hGH have significant biological potency.18,19

**Control of hGH secretion and receptor binding**

Illustrated in Fig. 2 are the principal steps in the control and synthesis of hGH and the relationship between hGH and insulin-like growth factor-I (IGF-I).

Growth hormone-releasing hormone (GHRH) is a 44 amino acid amidated peptide that was first isolated from a pancreatic tumour removed from a patient with acromegaly.20 The discovery of this peptide with GH-releasing properties lead to the characterization, synthesis and verification of its biological potency by stimulating the synthesis and release of hGH from the anterior pituitary.21 Human GH is released in a pulsatile fashion and has a half-life of approximately 10 min.22 The pulsatility of GH release is attributed to pulses of GHRH that are under the stimulatory control of the neuropeptides dopamine, noradrenaline, serotonin and the inhibitory control of somatostatin (GHRIH). The pulses of GH are sleep entrained and their frequency and amplitude increase as puberty intervenes.23 In a recent review,24 increasing evidence is cited that IGF-I acts via a feedback mechanism that inhibits the action of GHRH at pituitary level and, in vitro at least, stimulates GHRIH in isolated hypothalamic remnants. These observations add a new dimension to the understanding of the pulsatile release of hGH.

Receptors for hGH are to be found in many tissues including muscle, but are most abundant in the liver; a major site for the synthesis of IGF-I and IGF-II.25 Interestingly, a specific GH-binding protein has been identified in the serum of man26 and other species including the rabbit27 and the pig.28 Investigation of its ontogeny in man has suggested that this binding protein arises from hepatic GH receptor turnover and thus its measurement in serum provides a potential indicator of hepatic hGH receptor development and
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integrity.2y Studies in normal volunteers and patients with the rare syndrome of Laron dwarfism30 in whom receptors for hGH are non-functional,31 support the case for measuring serum levels of hGH binding protein in patients with unexplained poor growth.

SOMATOMEDINS: INSULIN-LIKE GROWTH FACTORS

Salmon and Daughaday32 were the first to question the hypothesis of a direct effect of growth hormone on epiphyseal growth centres. Their experiments showed that epiphyseal growth plates of hypophysectomized rats did not incorporate radiolabelled sulphate into chondroitin when bovine growth hormone was added to isolated viable cartilage cells in vitro. In contrast, serum from hypophysectomized rats that were pretreated with growth hormone enhanced the incorporation of radiolabelled sulphate into cartilage of the hypophysectomized animals. The conclusion drawn from these critical experiments was that growth hormone stimulates the synthesis of a factor (sulphation factor) in serum and it is this that modulates cellular and linear growth.

The term somatomedin(s) (SM) was subsequently proposed.33 Two important growth promoting peptides have been isolated from mammalian serum, SM-C and multiple stimulating activity (MSA). The latter was first characterized from rat hepatocytes. In view of their marked homology with the α and β regions of proinsulin, the preferred names for SM-C and MSA are insulin-like growth factor one and two (IGF-I, IGF-II), respectively.34 The isolation,35 amino acid sequencing36 and synthesis37 of IGF-I and a number of closely-related peptides with growth-promoting properties rapidly followed. Structurally, SM-C and IGF-I are identical but early preparations of SMC, designated SMA, were subsequently shown to have glutamic acid at position 40 as a deamination product of glutamine.38 To qualify as an insulin-like growth factor certain criteria must be met (Table 2). Table 3 lists some of the important physico-chemical characteristics of IGF-I and II. Unlike GH, these two peptides are not species specific except in some non-mammalian species, notably fish.

There is conflicting evidence regarding the relative importance of endocrine versus local tissue (paracrine) mechanisms for IGF production.38 This question has been reviewed and the autocrine role of the IGFs by synergism with trophic hormones in specific endocrine glands discussed.39 The data reviewed provide convincing evidence that all three mechanisms are operating. Further, one or more of the IGF binding proteins may exert an endocrine effect by modulating the concentration of IGFs at tissue level. The injection of IGF-I into animals leads to an enhanced growth velocity and an increased incorporation of radiolabelled thymidine into DNA but, weight for weight, IGF-I is less potent than hGH.40 A physiological role for IGF-II is less well defined. The hypoglycaemic effect of IGF-II has, however, been documented in patients who presented with suppressed insulin levels and inappropriately raised IGF-II concentrations.41 The insulin-like activity of the raised IGF-II was the primary cause of the previously unexplained hypoglycaemia.

DNA probing techniques have revealed that the human IGF-I gene is present on the long arm of chromosome-12 and that of the IGF-II gene on the short arm of chromosome-11, in close proximity to the insulin gene.42

Table 2. Definition of an insulin-like growth factor

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Shows insulin-like activity after neutralization of endogenous insulin</td>
</tr>
<tr>
<td>2</td>
<td>Increases uptake of sulphate into proteoglycans and of thymidine into DNA</td>
</tr>
<tr>
<td>3</td>
<td>Causes demonstrable mitotic activity in selected cell lines</td>
</tr>
</tbody>
</table>

Table 3. Physicochemical characteristics of IGF-I and IGF-II

<table>
<thead>
<tr>
<th>Peptide</th>
<th>M wt (kD)</th>
<th>pI</th>
<th>Amino acids</th>
<th>Disulphide bonds</th>
</tr>
</thead>
<tbody>
<tr>
<td>IGF-I</td>
<td>7·5</td>
<td>8·5</td>
<td>70</td>
<td>3</td>
</tr>
<tr>
<td>IGF-II*</td>
<td>7·5</td>
<td>&lt;8·0</td>
<td>67</td>
<td>3</td>
</tr>
</tbody>
</table>

*70% homology with IGF-I.
proteins could be achieved by shifts in pH, temperature and/or by the addition of heparin. However, none of these manoeuvres yields a quantitative release of IGF-I from binding proteins. Indeed only 70% is actually measured, albeit precisely, in some assays. The selective precipitation of IGF-binding proteins by ethanol-acetic acid and variants of this reagent followed by neutralization of the extract led to assays which can yield quantitative recoveries of IGF-I. Despite temperature and/or by the addition of heparin, quantitative release of IGF-I from binding proteins. However, none of these manoeuvres yields a quantitative release of IGF-I from binding proteins. Indeed only 70% is actually measured, albeit precisely, in some assays. The selective precipitation of IGF-binding proteins by ethanol-acetic acid and variants of this reagent followed by neutralization of the extract led to assays which can yield quantitative recoveries of IGF-I. Despite careful optimization of these procedures, difficulties in removing some IGF-I binding protein from serum from non-primate species, have been documented and reliable estimates of IGF-I in human serum or plasma have not been universally achieved. This is particularly true of attempts to measure IGF-I concentrations in human pathological sera that have IGF-binding protein profiles that differ from normal. Silberfeld and colleagues conducted a comparative study using two commercially available kits. One kit measured IGF-I directly in EDTA-plasma and the second required a pre-extraction step by reverse phase chromatography. The pre-extraction procedure revealed an 85% concordance in the detection of low IGF-I levels in hGH deficient patients and a 100% rise in IGF-I in 5 hGH deficient patients during growth hormone treatment. Without pre-extraction only 55% of the same patients showed low basal IGF-I levels and only two of the hGH treated patients showed a rise in IGF-I. The authors cite some of the other important factors that contribute to unreliable assay performance. Serum protease activity is increased after 24 h pre-incubation at room temperature, and this is believed to alter IGF-binding protein affinities and consequently enhance antibody capture of IGF-I. An upward drift in measured values with time in the non-extraction assay was thought to be attributable to this enhanced proteolytic activity. As with GH assays, the universal acceptance of a single reference standard remains an added difficulty and will not be resolved until a recommended bioengineered standard is employed.

There is a lack of good quality monoclonal antibodies to IGF-I, the production of which may obviate rigorous extraction procedures. Kits are available for measuring IGF-I as probes, two glycosylated forms with identical core protein (29 kD) of mol. mass 41.5 and 38.5 kD are demonstrable in serum after SDS-PAGE and Western blotting. A second non-glycosylated binding protein (IGF BP-2), 34 kD, identifiable in serum and CSF, is synthesized by rat liver cell lines (BRL-A). A third non-glycosylated IGF-binding protein (IGF BP-1), 28-30 kD, is unique. It is hGH independent and serum concentrations during short-term fasting, are inversely proportional to basal insulin and glucose levels. Further, IGF BP-I shows a marked rise in concentration during an acute phase of restricted calorie intake. A significant decrease in concentration during the pubertal growth spurt has also been demonstrated coincident with a rise in insulin levels. The latter observation suggests that decreased IGF BP-I synthesis during puberty is related to the enhanced production of insulin. A non-hGH dependent protein, IGF BP-4, (25 kD) whose physiological role is as yet uncertain, is also present in serum. This binding protein and others of molecular mass in the range 25-42 kD require further detailed studies before a specific physiological role can be attributed to them. Reagents are available for the measurement of the

**IGF-binding proteins**

A spectrum of low to high molecular weight IGF-I/IGF-II-binding proteins have been identified in tissues and biological fluids including serum, CSF, amniotic fluid and seminal fluid. The variability of the reported molecular weights of these binding proteins reflects the different physicochemical methods employed and the presence in biological fluids of oligomeric forms of IGF-binding proteins. In addition, authors have frequently used their own nomenclature when recording their findings and have not always stated whether the SDS-PAGE analyses were conducted under reducing or non-reducing conditions. Despite these difficulties, there is general agreement that in normal serum three major species of IGF-binding protein can be demonstrated. Current nomenclature favours the use of the abbreviation IGF-BP followed by numerals 1-3. A growth hormone and calorie-dependent IGF-1/II-binding protein of molecular weight 150 kD predominates in serum when measured by gel permeation chromatography at neutral pH. Acid treatment of this protein gives rise to an acid-stable component of molecular mass 50-60 kD (IGF BP-3) and an acid labile species of 80-100 kD.

Under non-reducing conditions and with the use of specific radiolabelled antibodies to IGF BP-3 as probes, two glycosylated forms with identical core protein (29 kD) of mol. mass 41.5 and 38.5 kD are demonstrable in serum after SDS-PAGE and Western blotting. A second non-glycosylated binding protein (IGF BP-2), 34 kD, identifiable in serum and CSF, is synthesized by rat liver cell lines (BRL-A). A third non-glycosylated IGF-binding protein (IGF BP-1), 28-30 kD, is unique. It is hGH independent and serum concentrations during short-term fasting, are inversely proportional to basal insulin and glucose levels. Further, IGF BP-I shows a marked rise in concentration during an acute phase of restricted calorie intake. A significant decrease in concentration during the pubertal growth spurt has also been demonstrated coincident with a rise in insulin levels. The latter observation suggests that decreased IGF BP-I synthesis during puberty is related to the enhanced production of insulin. A non-hGH dependent protein, IGF BP-4, (25 kD) whose physiological role is as yet uncertain, is also present in serum. This binding protein and others of molecular mass in the range 25-42 kD require further detailed studies before a specific physiological role can be attributed to them. Reagents are available for the measurement of the
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GH-dependent IGF BP-3. A novel approach to its measurement was devised by Martin and Baxter using antibodies raised to the acid-stable glycosylated binding proteins dissociated from IGF BP-3 complex.

There are two different models for the structure of IGF BP-3. The studies of Wilkins and D'Ercole favour multimolecular forms (24–28 kD) as the primary subunits of IGF BP-3. In contrast, Hossenlopp and colleagues and Hardouin et al. support the hypothesis of one or other of two acid stable glycosylated forms (38.5 or 41.5 kD) linked to an 80–100 kD acid-labile moiety. An attempt to reconcile the two structural models leaves open the question of the integrated structure of the two glycosylated forms of IGF BP-3 with the labile moiety. Figure 3 shows diagramatically the favoured structure of IGF BP-3 described by Baxter. The high affinity of IGF BP-3 for IGF-I leads to a low concentration (1–2%) of unbound IGF-I and this unbound fraction is thought to be biologically active. IGF-1 and IGF BP-3 are synthesized in many cell types, but quantitatively the liver is the major source of IGF-I and the binding proteins. The half-life of IGF BP-3 is approximately 15 h whereas unbound IGF-I has a half-life of 10 min. In animal models the synthesis of IGF-I-binding proteins is modulated by the presence of growth hormone, thyroxine and cortisol.

DNA sequences are known for all three major IGF binding proteins found in normal serum. The amino-acid composition reveals a high content of cysteine residues in each binding protein, suggesting a significant degree of disulphide bridge conservation between the three.

Receptors for IGF-I

Hormones elicit their biological responses at cellular level when specific receptors are present. Figure 4 illustrates two specific receptors for IGF-I and II that are found in a variety of tissues including placental membranes, myoblasts and fibroblasts. The 130 kD receptor (type R1) has a binding site with a high affinity for IGF-I and has a structure that is similar to that of the insulin receptor. On the other hand, the 260 kD receptor (type R2) has a high affinity for IGF-II and the presence of insulin increases the number of these receptors on the cell surface. Two immunologically distinct binding sites on the 130 kD receptor have been identified, one selectively binding IGF-I and a second which binds IGF-II. The full significance of this is not understood. It is not known whether the free (non-protein bound) fraction or a complex of IGF-I/II bound to one of the specific binding proteins is the trigger for the intracellular events that follow receptor binding and are depicted in Fig. 4. There is a progressive decline in the binding affinity of IGF-I for fibroblast receptors as the age of the fibroblast donor increases. This observation suggests that the binding of growth factors to receptors is dependent not only on their adequate synthesis but also on receptor number, avidity, and age. The effect of age on receptor binding of IGF-I in other tissues is well illustrated by Hill and colleagues in a study of IGF binding to receptors in pre- and post-natal rat cartilage. The discovery of a paracrine or autocrine secretion of IGF-I in many tissues has posed the question of the biological importance of peripheral levels of IGF-I compared with local tissue production. For example, modulation of steroid synthesis induced by trophic hormone-binding to specific ACTH or LH receptors in the adrenal or gonad, respectively, has been attributed to local synergistic effects of IGF-I.
FIGURE 4. Tissue receptors for IGF-I and IGF-II, illustrating the biological response induced when the growth factors bind to their respective receptors.

CLINICAL RELEVANCE OF hGH, IGF-I AND II

hGH
The radioimmunoassay of hGH in serum has been available since the early 1960s. Since then it has been widely applied to the differential diagnosis of growth defects. The plethora of reported dynamic tests (at least 25) for the diagnosis of hGH deficiency or syndromes of excess hGH release support the view that none of the protocols adopted is entirely satisfactory. More recently, urinary hGH measurements have been advocated as a non-invasive test.92 A number of well-tried tests have, however, been identified92 and with notable exceptions they are not cost effective. Table 4 outlines those tests in current use which, when conducted according to the precise protocols described by the authors, are helpful in the diagnosis of hGH deficiency in different age groups. Figure 5 illustrates the relative cost of these tests.93

IGF-I
The application of immunoassays for IGF-I has led to the view that a basal IGF-I measurement may be all that is required for the diagnosis of hGH deficiency or excess. Earlier expectations of an IGF-I concentration as a cut-off differential diagnostic tool have not, however, been borne out. An overlap is demonstrable between IGF-I concentrations in the serum from patients that have either an adequate or inadequate hGH release during hGH provocation tests.94,95 This finding is the same whether a bioassay96 or an RIA is used for IGF-I measurements.

The discriminatory power of serum IGF-I measurements to diagnose children with growth hormone deficiency may be improved when age or sexual maturation is taken into consideration.97 In the normal population, a sex difference in serum IGF-I concentrations is demonstrable, with higher IGF-I levels in girls than boys as adolescence intervenes.98,99 The importance of sex steroid concentration in the interpretation of serum IGF-I levels to diagnose children with growth hormone deficiency may be improved when age or sexual maturation is taken into consideration.97

In the normal population, a sex difference in serum IGF-I concentrations is demonstrable, with higher IGF-I levels in girls than boys as adolescence intervenes.98,99 The importance of sex steroid concentration in the interpretation of serum IGF-I levels to diagnose children with growth hormone deficiency may be improved when age or sexual maturation is taken into consideration.97

A rise in IGF-I concentration after androgen or oestrogen therapy does not mean that sex steroids are the primary agents that cause the rise during the early stage of normal pubertal development. It may be related to enhanced GH-releasing hormone synthesis with a subsequent rise in and an increased pulsatility of hGH.100 A further complication when interpreting serum IGF-I levels during puberty is the increase in insulin levels as puberty intervenes101 that stimulates IGF-I synthesis.104

Low calorie and reduced total energy intake are major causes of a decreased synthesis of IGF-1.105 The quality of calorie intake also changes IGF-I concentrations,106 an improved protein and essential amino acid content of the
Some tests in current use to assess hGH status

**Screening tests**
- Oral aminoacids ('Bovril')
- Prolonged glucose tolerance
- Exercise
- Exercise (energy expenditure related)

**Definitive tests**
- Induced hypoglycaemia in adults
- Induced hypoglycaemia in children
- Glucagon intravenously
- Glucagon intramuscularly
- Clonidine
- Sleep-related (physiological versus pharmacological)

### References to early reports
- Grant DB, Jackson D, Raiti S, Clayton BE. *Arch Dis Childh* 1970; 45: 544-6
- Lacey KA, Hewison A, Parkin JM. *Arch Dis Childh* 1973; 48: 508-12
- Nicoll AG, Small PJ, Forsyth CC. *Arch Dis Childh* 1984; 59: 1177-90
- Roth J, Glick SM, Yalaw, RS, Benson SA. *Science* 1963; 140: 987-9
- Fraser NC, Seth J, Brown NS. *Arch Dis Childh* 1983; 58: 355-8

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**Table 4.** Some tests in current use to assess hGH status

<table>
<thead>
<tr>
<th>Test Type</th>
<th>References to early reports</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening tests</td>
<td></td>
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<tr>
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</tr>
<tr>
<td>Exercise (energy expenditure related)</td>
<td></td>
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<tr>
<td>'Definitive' tests</td>
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</tr>
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</tr>
<tr>
<td>Sleep-related (physiological versus pharmacological)</td>
<td></td>
</tr>
</tbody>
</table>

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**FIGURE 5.** Relative costs of 11 tests for growth hormone deficiency (1988). The components of the costs are: regional 'in-house' reagent service which includes cost of raising antibodies sufficient for 5 years, reagents used and personnel; the cost of drugs as supplied to a NHS pharmacy, senior (sister) nursing staff, and time to complete the test. It has been assumed that medical staff are available for all tests, but their time is not included. **EXAMPLES**

- Short trunk (spondyloepiphyseal dysplasia)
- Short limbs (achondroplasia)
- Silver-Russell syndrome
- Intra uterine growth retardation
- Low birth weight
- Constitutional / familial
- Small /delay
- Generalized disease
- Psychosocial problem
- Endocrine disorder
- Chromosomal abnormality

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In view of all the variables which can influence IGF-1 serum and tissue levels, serum IGF-1 measurements alone are unlikely to be of definitive diagnostic value in the detection of hGH deficiency. Despite these limitations, a single basal IGF-I level when normal for chronological age may, in prepubertal children at least, obviate the need for an hGH provocation test in approximately 80% of patients under investigation for hGH deficiency. Figures 6 and 7 summarize recommended protocols for the assessment of children with poor growth who may have hGH deficiency. The protocols are based on detailed clinical and biochemical observations.
Looks normal

Consider:
(A) Psychosocial problem
(B) Underlying infections
(C) Chromosomal abnormality

? Low growth velocity

Record height and weight
Ideally, 2 observations over 6-12 months on Tanner and Whitehouse growth charts

Determine growth velocity and weight centile for age, by calculation, record height standard deviation score

Weight centile significantly less than height deficit

Consider: (A) Low calorie intake
(B) Malabsorption

Sweat test
Jejunal biopsy

Normal

Consider scanning pituitary fossa

Consider multiple trophic hormone deficiency

Combined pituitary function test

Normal

Abnormal

Consider replacement therapy

Growth rate poor (3rd centile)

Consider hypothyroidism

Measure basal TSH and record bone age

Normal

Consider hGH deficiency

Basal IGF-I

Normal

Low

? Small delay

Test for hGH deficiency, e.g. < 5 years, glucagon stimulation, > 5 years
Insulin induced hypoglycaemia or hGH sleep profile, raised hGH, low IGF-I
consider, receptor defects

FIGURE 7. A suggested protocol for the differentiation of hGH deficiency from other causes of restricted growth.

over the last 20 years (Rayner and Rudd, unpublished).

Baxter and Teale and Marks have reviewed the reported changes in IGF-I in a variety of diseases. Apart from patients with extensive liver disease, in whom hepatic function is the limiting factor in the synthesis of IGF-I, calorie or energy deficiency either primary or secondary to an underlying disease appears to be the major determinant of inadequate IGF-I synthesis and changes in levels of IGF-I. The observed poor growth in renal disease is associated with an interesting change in IGF-I-binding protein profiles, dominated by the appearance of low molecular weight forms. Children with chronic gastrointestinal diseases, notably coeliac disease, have low IGF-I levels which return to normal after a gluten-free diet. There are many rare conditions with a genetic basis for poor growth in which either IGF-I and/or IGF-I BP-3 is low. Patients with Turner's syndrome (XO and mosaic forms) have lower basal IGF-I concentrations with increasing chronological age than genetically normal females. Laron dwarfs in whom the primary defect is non-functional hGH receptors have, as predicted, low serum IGF-I concentrations. The poor growth in pygmies observed by Bakwin appears to be explained by inadequate hGH receptor and IGF-I synthesis at a critical time during puberty. Table 5 lists
Table 5. Factors which lower IGF-I

<table>
<thead>
<tr>
<th>Factor</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nutritional</td>
<td>Energy deficit (60%), protein deficit (40%)</td>
</tr>
<tr>
<td>Genetic</td>
<td>Gene deletion, e.g. isolated GH and IGF-I receptor defects</td>
</tr>
<tr>
<td>Hormonal</td>
<td>Corticosteroid excess, thyroid deficiency</td>
</tr>
<tr>
<td>Pathological</td>
<td>Acquired GH deficiency, Cushing's syndrome, hepatic damage, insulin deficiency</td>
</tr>
<tr>
<td>Environmental</td>
<td>Toxic agents, hypothermia, hypoxia, inhibitors linked to low calorie intake</td>
</tr>
</tbody>
</table>

some of the conditions in which serum IGF-I concentrations can be low.

IGF-II

The study of IGF-II in serum of patients with growth defects has been hampered by a lack of good quality reagents. An early report suggested little difference in IGF-II concentrations between hypopituitary and normal children but raised levels in acromegaly. Others, however, suggest that there is a difference in IGF-II concentrations between reference populations and hGH deficient patients, and that when IGF-II concentrations are combined with IGF-1 concentrations diagnostic accuracy is improved. Hardouin et al. observed that IGF-II appears to bind IGF BP-3 with a higher affinity than IGF-I and because IGF-I is low in patients with hGH deficiency, IGF-II may be preferentially bound. Thus, the combined measurement of IGF-I and II is likely to enhance the differential diagnosis of GH deficiency from other causes of poor growth.

Treatment with hGH

Bioengineered hGH is now available in unlimited supply for the treatment of GH deficiency. The assay of serum IGF-1 concentrations during hGH therapy should be a useful predictor of potential height in children because a positive correlation between an increase in height with age and basal IGF-I concentrations is demonstrable in normal populations. This has not been substantiated in a study of children with retarded growth, which failed to show a positive correlation between IGF-1 concentrations and growth rate following hGH treatment. Further, some children showed a good growth response to hGH, but a negligible rise in serum IGF-I levels. The situation is further complicated because hGH or IGF-1 receptor defects may be present in the heterogeneous population of patients under treatment with hGH.

Prior to the production of genetically engineered hGH, human pituitary extracts were the only suitable source of hGH for treatment. These preparations were shown to be biologically active, increasing calcium and hydroxyproline excretion, enhancing fatty acid synthesis, nitrogen retention and growth velocity. The preparations were withdrawn for treatment in 1985 because of the potential risk of contamination with slow virus. It is evident, therefore, that many of the earlier investigations on the therapeutic and biological effects of hGH require additional confirmation using bioengineered preparations. Studies in a recent review confirm the biological potency and benefits of these preparations. There remains, however, much to be discovered about the best treatment schedules and, at a biochemical level, about the effect of rhGH treatment on IGF-I and binding protein synthesis. Future studies will require the clinical and biochemical investigation of conditions such as primary or secondary malnutrition and other diseases associated with restricted growth before and during the therapeutic use of hGH.

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