REVIEW

Growth hormone therapy and Quality of Life: possibilities, pitfalls and mechanisms

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Abstract

The actions of growth hormone (GH) are not restricted to growth; GH modulates metabolic pathways as well as neural, reproductive, immune, cardiovascular, and pulmonary physiology. The importance of GH in most physiological systems suggests that GH deficiency at any age would be associated with significant morbidity. However, prior to the advent of recombinant GH, cadaver-derived GH was only used therapeutically to correct the height deficit, and thereby hypothetically improve quality of life (QoL), in GH-deficient children. Physicians now have access to unlimited, albeit expensive, supplies of recombinant GH, and are considering the advisability of GH replacement or supplementation in other patient populations. This paper analyses studies investigating the relationship between GH and QoL in GH-deficient children or adults, in GH-replete short children suffering from idiopathic short stature, Turner syndrome, or intrauterine growth retardation and in GH-deficient or replete elderly adults. Possible mechanisms by which GH might improve QoL at neural and somatic sites are also proposed.


Introduction

The actions of growth hormone (GH) are not restricted to growth; GH exerts pleiotropic effects on virtually every organ system. Indeed, immune, reproductive, neuronal, gastrointestinal, cardiovascular, bone, and muscular function have all been shown to be improved by GH therapy (see, for instance, Dorshkind & Horseman 2000, Hull & Harvey 2000a, Nyberg 2000, Simpson et al. 2002). The widespread beneficial effects of GH would imply that GH deficiency at any age would be associated with significant morbidity. Until the late 1980s, however, the scarcity of cadaver-derived GH restricted its use to correcting the height deficit, and thereby hypothetically improve quality of life (QoL), in GH-deficient children. Physicians now have access to unlimited, albeit expensive, supplies of recombinant GH, and are considering the advisability of GH replacement or supplementation in other patient populations. This paper analyses studies investigating the relationship between GH and QoL in GH-deficient children or adults, in GH-replete short children suffering from idiopathic short stature, Turner syndrome, or intrauterine growth retardation and in GH-deficient or replete elderly adults. Possible mechanisms by which GH might improve QoL at neural and somatic sites are also proposed.

QoL measurement

The definition of QoL is complex and has been the subject of numerous recent reviews (see, for instance, Eiser & Morse 2001). QoL has been defined by the World Health Organization as ‘the state of complete physical, mental, and social well-being and not merely the absence of disease or infirmity’ (World Health Organization 1947). The assessment of QoL could include objective measures, such as clinical indices of blood sugar or peak air flow and functional indices of the ability to climb stairs or walk.
a certain distance (Gill & Feinstein 1994). Perhaps of greater importance are more subjective aspects, reflecting the patient’s perception of his/her functional abilities and the gap between one’s attained and desired goals (Gill & Feinstein 1994). Excessive reliance on objective measures of QoL does not provide an accurate determination, since one cannot assume that abnormal clinical values or the inability to perform a normative task resulting from age, mental, or physical disability automatically reduces QoL (Leplege & Hunt 1997). Such assumptions would reinforce stereotypes that underlie discriminatory practices. For instance, while it is historically assumed that short stature (a clinical value) due to GH deficiency automatically impairs QoL, subjective analysis does not support this hypothesis (Pilpel et al. 1995).

Definitions of QoL have coalesced into a number of models. Health related QoL measures physical, psychological, and social functioning and the presence/absence of pain. This model can be used to quantify the cost–benefit ratio of treatment in quality-adjusted life years (QALYs) (Leidl & Stratmann 1998). The individualistic model emphasizes individual variations in the importance of different QoL aspects, defining QoL as ‘a person’s sense of well-being that stems from satisfaction or dissatisfaction with the areas of life that are important to him/her’ (Ferrans 1996). A third paradigm, the needs-based model, describes QoL as the ability of an individual to fulfill his/her needs – physical, emotional, and social. Employment, hobbies, and socializing provide means to fulfill these needs (McKenna & Doward 1999).

Researchers have quantified QoL in hormone-deficient patients in order to define the importance of the deficient hormone in determining QoL. However, patients with a chronic illness often adapt, matching their activities to their abilities. Since adaptation is not detected using conventional QoL instruments (Jorgensen 1999), the relevance of the deficient hormone to QoL is often underestimated by this investigative approach. Nevertheless, a number of different questionnaires (‘instruments’) have been used to quantify QoL in relation to GH status in adults (Table 1). Older studies have usually relied on well-validated, generic tests of overall health and psychiatric well-being, such as the Nottingham Health Profile (NHP) or the General Health Questionnaire (GHQ). These questionnaires have been criticized, however, for their lack of sensitivity to subtle changes in QoL (Gibney et al. 1999, McKenna & Doward 1999). In addition, generic tools do not address symptoms that are important to adult patients with GHD, and concentrate on areas that are of little relevance (McKenna & Doward 1999).

Some investigators have addressed these concerns by modifying generic questionnaires. For instance, a disease-specific ‘model’ incorporating the NHP and other tests has been developed for GHD by Wallymahmed et al. (1996), although its reliability and responsiveness have been questioned by other authors (McKenna & Doward 1999).

A specific module of the Questions on Life Satisfaction Modules-hypopituitarism (QLS(M)-H), and initial reports have demonstrated that questionnaire scores correlate well with GH status (Herschbach et al. 2001).

A third approach to the measurement of QoL in adult GHD is the development of disease-specific questionnaires, based on in-depth, relatively unstructured interviews of GHD individuals. The first GHD-specific instrument was the Quality of Life-Assessment of Growth Hormone Deficiency in Adults (AGHDA) (McKenna et al. 1999). This questionnaire addresses seven areas of common concern to GHD patients: body image and fat distribution, energy level, concentration and memory, irritability and temper, strength and stamina, coping with stress, and physical and mental drive. Patients answer yes or no to 25 statements such as ‘I have difficulty controlling my emotions’ (McKenna & Doward 1999). A high score indicates that the patient suffers from a large number of symptoms and thus has a lower QoL. The validity and unidimensionality of the AGHDA as a QoL instrument have been demonstrated by Rasch analysis (Wiren et al. 2000). In addition, the good scaling properties of the

### Table 1 Tests used to assess quality of life

<table>
<thead>
<tr>
<th>General Tests</th>
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<tbody>
<tr>
<td>Beck Depression Inventory (BDI)</td>
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<tr>
<td>Brief Symptom Inventory (BSI)</td>
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<td>Clinical Interview Scale (CIS)</td>
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<td>Comprehensive Psychological Rating Scale (CPRS)</td>
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<td>Disease Specific Questionnaire (DSQ)</td>
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<td>General Health Questionnaire (GHQ)</td>
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<td>General Well-being Schedule (GWBS)</td>
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<td>Hamilton Depression Scale (HDS)</td>
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<td>Hopkins Symptoms Check-list (HSCL)</td>
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<tr>
<td>Hospital Anxiety and Depression Scale (HADS)</td>
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<td>Kellner Symptom Questionnaire (KSQ)</td>
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<td>Life Fulfillment Scale (LFS)</td>
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<tr>
<td>Mental Fatigue Questionnaire (MFQ)</td>
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<tr>
<td>Mental Fatigue Scale (MFS)</td>
</tr>
<tr>
<td>Minnesota Multiphasic Personality Inventory-2 (MMPI-2)</td>
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<tr>
<td>Mood Adjective Check List (MACL)</td>
</tr>
<tr>
<td>Nottingham Health Profile (NHP)</td>
</tr>
<tr>
<td>Personality Assessment Schedule (PAS)</td>
</tr>
<tr>
<td>Profile of Mood States (POMS)</td>
</tr>
<tr>
<td>Psychological and General Well-being Schedule (PGWB)</td>
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<tr>
<td>Self Esteem Scale (SES)</td>
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<tr>
<td>Short Form 36 (SF-36)</td>
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<tr>
<td>Social Adjustment Scale (SAS)</td>
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<td>Social Relationship Scale (SRS)</td>
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<td>Symptom Check-list-90 (SCL-90)</td>
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<th>Disease-Specific Tests</th>
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<tr>
<td>Questions on Life Satisfaction Modules-hypopituitarism (QLS(M)-H)</td>
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<tr>
<td>Disease Specific Questionnaire (DSQ)</td>
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<td>Adult Growth Hormone Deficiency Assessment (AGHDA)</td>
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<td>Modified LFS (GHD-LFS)</td>
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<td>Modified Impact Scale (GHD-IS)</td>
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<td>Growth Hormone Deficiency Questionnaire (GHDQ)</td>
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questionnaire indicate that it can provide a quantitative, rather than all-or-none, measure of the degree of QoL. Impairment and that scores are independent of age or gender. A second questionnaire, the GH Deficiency Questionnaire (GHDQ) has been developed by Cuneo et al. (1998) to examine three common areas of dysfunction in GHD: energy, mood, and sleep. However, this questionnaire has not been rigorously evaluated nor extensively used.

Indices of social functioning, such as marital status, employment records, and independence (living alone, holding a driver’s licence), provide important adjuncts to quantitative QoL assessments of populations and of individuals. The use of health care resources (doctor and hospital visits) and health-related work absences (sick leave, disability pensions) can also indicate deficiencies in perceived QoL.

Short stature and QoL

The most phenotypically obvious effect of GH is in regards to height, and it has been suggested that the impact of GH on QoL relates solely to its influence on stature. Analysis of social parameters does not, however, reveal any impairment in physical abilities, self-esteem, school achievements, leisure activities, well-being, and relationships in short children (Erling et al. 1995, Pilpel et al. 1995) nor any reduction in marriage or employment status in short adults (Rikken et al. 1995). Similarly, Busschbach et al. (1998) failed to observe a direct relationship between QoL and short stature resulting from Turner syndrome, chronic renal failure, GHD, or idiopathic short stature, when QoL was measured by the time trade-off method and the NHP. The small sample sizes and the bluntness of the QoL measures may have obscured discrete changes in QoL; however, the general consensus is that short stature in itself does not significantly impair QoL.

Therapeutic possibilities: children

GH deficiency

GH-deficient children receive GH replacement therapy in order to increase final adult height and thus, allegedly, QoL. Due to this emphasis on the growth-promoting effects of GH, GH therapy is traditionally initiated at, or just prior to, the onset of growth failure, although Boersma et al. (1995) suggests that earlier treatment may increase final height. Existing data does not, however, support a link between height and QoL; thus, the current rationale for treating GH-deficient children may simply reflect societal bias against short stature. It is therefore imperative that QoL in GH-deficient children be assessed separately from stature. Unfortunately, the design of a QoL instrument for children is problematic, because needs vary according to age and thus QoL measures designed for GHD adults are not applicable. Although generic measures have been developed to quantify QoL in children (Eiser & Morse 2001), they have not been widely applied to GHD children. Questionnaires based solely on self-report (Wiklund et al. 1994, Pilpel et al. 1995) or on parental report (Haverkamp & Noeker 1998) have been developed, but have not been well-validated nor extensively used. The development of a GHD-specific module of the Pediatric Quality of Life instrument might be appropriate, since this questionnaire has been validated and works well for other chronic childhood conditions such as asthma or diabetes (Varni et al. 2001).

A small number of studies have correlated behavioral and academic indices of QoL with GH status in children. For instance, GH-deficient children show slight deficits in regards to academic achievement, alertness, mood and stability and an increased incidence of behavioral disturbances (particularly social phobia) (Stabler et al. 1994, 1996). GH therapy is partially successful at correcting these behavioral and mood disturbances (Stabler et al. 1998). Despite normal IQ scores, many GHD children repeat a school year and have difficulties with spelling and arithmetic, even in upper socioeconomic classes (Stabler et al. 1994, Sartorio et al. 1996). GHD children often have an immature self-concept, which may partially reflect the fact that they are treated as if they were younger than their actual age due to their small size and immature facial features (Sartorio et al. 1996). Inefficient problem-solving skills, impaired visual motor integration and impaired spatial orientation are also more prevalent in GHD children (Sartorio et al. 1996).

Bareille et al. (1999) discuss an additional consideration regarding GH therapy in children, particularly adolescents. GH deficiency is often associated with delayed puberty, whereas GH therapy accelerates puberty. While this acceleration is deleterious in terms of final growth attained, it may be advantageous psychologically by avoiding the problems of persistent sexual immaturity.

Idiopathic short stature

GH-replete children with idiopathic short stature (ISS) were early candidates for recombinant GH therapy, in the hope that GH would stimulate growth and thereby increase QoL during childhood and adulthood. Indeed, one-third of all GH-treated children in the US in 1996 had been diagnosed with ISS (Cuttler et al. 1996), and GH-treated ISS children often express satisfaction with their treatment (Rekers-Mombarg et al. 1998). However, studies by Downie et al. (1997) and Skuse and colleagues (Skuse et al. 1994, Gilmour & Skuse 1996) failed to identify any psychosocial deficits in short children, compared with age-, sex- and social class-matched controls, although Stabler et al. (1998) observed
an increased incidence in behavioral problems that was partially corrected by GH therapy. Measures of health-related QoL (NHP, Short Form-36 (SF-36)) also indicate that QoL is normal in children and young adults with ISS, and GH therapy does not induce any alterations in these indices (Downie et al. 1996, Rekers-Mombarg et al. 1998, Theunissen et al. 2002). Final adult height is increased only slightly (average 3–5 cm) (Mehta & Hindmarsh 2002) and may even be reduced by GH treatment in ISS, since GH shortens the duration of the pubertal growth spurt (Mehta & Hindmarsh 2002). The validity of the claim that GH therapy improves QoL, or even final adult height, in ISS children is thus questionable.

**Turner syndrome**

Turner syndrome is also associated with a significant decrease in final adult height (Tinklin & Betts 1999). GH therapy has been approved in numerous countries to treat the height deficit and ostensibly improve QoL in Turner syndrome girls (Tinklin & Betts 1999). GH, particularly self-esteem, life satisfaction, employment difficulties, and marital status, does appear to be impaired in individuals with Turner syndrome (Delooz et al. 1993). Nonverbal cognitive defects are more prevalent in Turner syndrome, but long-term GH therapy does not induce any changes in cognition (Ross et al. 1997). The relevance of their height deficit to their QoL impairment is also minor, since only 44% of patients would 'trade-off' longevity for height, and the number of years that they were willing to lose was very small (Buschbach et al. 1998). Moreover, long-term studies have questioned the impact of GH on final height in women with Turner syndrome (Donaldson 1997), although other studies show a significant increase in adult height, particularly if oxandrolone (an androgenic steroid) is co-administered (Rosenfeld et al. 1992). Girls with Turner syndrome are also more likely to report adverse side-effects resulting from GH treatment, particularly scoliosis and kyphosis (Mehta & Hindmarsh 2002). The increased incidence of side-effects and the lack of consistent improvements in growth and measured QoL resulting from GH treatment thus raise questions regarding the usefulness of GH therapy in Turner syndrome.

**Other disorders**

Partial GH insensitivity has been implicated in the short stature associated with a variety of childhood conditions (Table 2), including chronic renal insufficiency and intrauterine growth retardation (IUGR) (Mehta & Hindmarsh 2002). Preliminary results indicate that GH can induce a short-term height gain in these syndromes (Vance & Mauras 1999, Monson 1999), particularly in chronic renal insufficiency and IUGR (Vance & Mauras 1999). The influence of these short-term gains on final adult height has not been established, although an improvement in final height prognosis (based on height standard deviation scores for bone age) has been observed in IUGR (Hokken-Koelega 1999, Mehta & Hindmarsh 2002). Although QoL has not been measured in IUGR using specific tests, deficits in IQ, attention and self-concept (Hokken-Koelega 1999) have been documented, and attention, peer acceptance and self-worth have been shown to be improved by GH therapy (Van der Reijden et al. 1996, 1997). QoL has not been examined in most other childhood conditions associated with impaired growth.

**Side-effects**

Despite widespread use of GH in children, the absolute safety of long-term GH administration has not yet been established. Although the use of biosynthetic GH has eliminated the threat of Cruetzfeld-Jacob disease, the possibility that GH therapy may increase tumor formation, leukemia, insulin resistance, and glucose intolerance has not been ruled out (Bareille et al. 1999). Low-dose GH replacement may be particularly associated with problems in glucose homeostasis in children with Turner syndrome and IUGR (Bareille et al. 1999, Mehta & Hindmarsh 2002). A rare syndrome, benign cranial hypertension, is also associated with higher-dose GH therapy (Crock et al. 1998). Other rare side-effects include salt and water retention, pigmentation, pancreatitis, gynecomastia, and slipped capital femoral epiphyses (Vance & Mauras 1999, Mehta & Hindmarsh 2002).

**Conclusion**

Children with growth impairments are routinely treated with GH in order to improve height, on the assumption that short stature impairs QoL and thus requires correction. However, GH may only improve final adult height in GHD children, exerting only transient improvements in other cases of growth impairment, and data correlating short stature and impaired QoL are lacking. GH may, **Table 2 Target populations for childhood GH therapy**

| GH deficiency |
| Turner syndrome |
| Chronic renal failure |
| Intrauterine growth retardation |
| Idiopathic short stature |
| Hypophosphatemic rickets |
| Achondroplasia/hypochondroplasia |
| Skeletal dysplasias |
| Noonan’s syndrome |
| Prader Willi syndrome |
| Down’s syndrome |
| Spina bifida |
| Cystic fibrosis |
nevertheless, improve QoL in children by mechanisms unrelated to growth. Psychological testing may thus be an equally important determinant of treatment advisability as pre-treatment height and GH concentration, and improvements in psychosocial outlook, as well as in adult height, should be benchmarks of successful GH treatment (Allen et al. 1994).

**Therapeutic possibilities: adults**

**GH deficiency**

Extensive anecdotal evidence suggests that QoL is impaired in GH-deficient adults. Interviews reveal that poor body image and socialization, low energy, irritability, poor concentration and diminished memory often characterize GHD adults (Holmes & Shalet 1995a). Clinical studies have, in most cases, confirmed these claims (Table 3). Symptoms described above, as well as increased emotional stress, mental fatigue, social isolation, decreased self-esteem, and decreased life satisfaction (Table 4) appear to be more prevalent in the GHD population (Drake et al. 2001a). It must also be noted that a significant minority of GHD adults report an undiminished QoL (Drake et al. 2001a).

The advisability of GH replacement for GHD adults remains highly controversial. Indeed, debates were held about this issue at recent meetings of the Society for Endocrinology (London 2001) and the 5th International hGH Symposium on GH Deficiency in Adults (Copenhagen 1998), and many recent reviews are unabashedly partisan in favoring (Deijen & van der Veen 1999, Carroll et al. 2000, Simpson et al. 2002) or condemning (Barkan et al. 1999) et al. 2000) its use in adults. Economic reasons must also be considered, since GH therapy remains expensive despite the widespread availability of recombinant GH. The issue is further clouded by the heterogeneous nature of GH deficiency. Childhood onset GHD (COGHD) includes cases of isolated GHD (IGHD), usually resulting from congenital causes, and mixed pituitary hormone deficiency (MPHD), often secondary to pituitary surgery or radiation. COGHD is characterized by subtly different symptoms than adult-onset GHD (AOGHD), which is usually associated with MPHD. Psychological parameters also differ, in that COGHD patients have endured a childhood with short stature, daily injections, and frequent hospital visits and do not have a memory of GH-replete life (Chrisoulidou et al. 1998). Conversely, decreased QoL in AOGHD may reflect a deficiency or over-replacement of thyroid hormones, adrenal hormones, and gonadotropins (Burman et al. 1995, Chrisoulidou et al. 1998). Pituitary surgery, irradiation, or other side-effects of pituitary pathology such as visual impairment would also reduce QoL. It is thus generally accepted that COGHD should be treated as a separate disorder from AOGHD.

**Adult onset**

Adult-onset GHD is generally, but not always, associated with decreased QoL and increased mental distress (Tables 3 and 4). For instance, the landmark study by McGauley (1989) observed a lower QoL in hypopituitary GHD patients in the areas of energy, emotional reaction, social isolation, general health, self-control, anxiety, vitality, mood, and sense of well-being using the NHP and the Psychological and General Well-Being Schedule (PGWB). Many AOGHD patients suffer from multiple endocrine deficiencies, and replacement of all hormones except GH does not normalize QoL (Rosen et al. 1994, Zenker et al. 2002). Disease-specific measures, as expected, show a much greater impairment in GHD adults. For instance, a study using the AGHDA showed decreased QoL in a large cohort of untreated GHD patients (144) compared with 1448 normal adult controls (Wiren et al. 2000). The increased sick leave and disability retirement in hypopituitary adults is also suggestive of a decreased QoL (Jonsson & Nilsson 2000). A number of studies have, however, failed to detect any difference in QoL between GHD individuals and the normal population (Table 3, Page et al. 1997, Baum et al. 1998). This may, in part, reflect the low sensitivity of generic tests to GH-dependent QoL indices, but also highlights the multifactorial nature of QoL. However, few studies have considered factors that modify the impact of GH deficiency on QoL. One determinant may be the duration of GHD, since Burman et al. (1995) has shown an inverse correlation between GHD duration and QoL. Conversely, the severity of GHD has not been shown to impact QoL, at least as measured by psychosomatic tests (Zenker et al. 2002).

Both generic and GHD-specific tests usually indicate that GH replacement therapy enhances QoL (Table 5). Quantitative indices of QoL are increased within 1–3 months in most patients (Drake et al. 1998, Wieren et al. 1998, Ahmad et al. 2001), although some individuals require a longer treatment duration (6 months) before improvements are noted (Wieren et al. 1998). Hernberg-Stahl et al. (2001) used health care usage as an indicator of QoL and found that sick leave and the number of doctor/hospital visits were significantly reduced with GH replacement in hypopituitary adults. Other recent studies fail to show any effect of GH supplementation on QoL (Table 5). The unchanged QoL observed in these studies may reflect the lower sensitivity of some generic tests to GH status, since some investigators observe QoL improvements using particular instruments but not others (e.g. Bengtsson et al. 1993). Patient selection also plays an important role, since QoL improvements in response to GH therapy would not be expected in individuals with normal pre-treatment QoL scores. For instance, Baum et al. (1998) did not observe any changes in QoL indices or cognition (NHP, PGWB, GHQ, and Minnesota Multiphasic Personality Inventory–2 (MMPI-2)) in an 18-month, double-blind placebo–controlled study of GH replacement in AOGHD. This negative result is not,
however, surprising, since the baseline scores of the GHD men were not different from the general population, with the exception of a small decrease in verbal learning and visual memory (Baum et al. 1998).

Table 3 Quality of life in growth hormone deficient adults

<table>
<thead>
<tr>
<th>Reference</th>
<th>Onset</th>
<th>n</th>
<th>Controls</th>
<th>Measurements</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sandberg et al. (1998)</td>
<td>CO</td>
<td>117 M 23 F</td>
<td>Same-sex siblings</td>
<td>SF-36, SRS, SAS, BSI</td>
<td>↓ general health = emotional and mental health BUT: GHD not confirmed</td>
</tr>
<tr>
<td>Page et al. (1997)</td>
<td>AO (hypopituitary tumors)</td>
<td>48</td>
<td>Mastoid surgery patients</td>
<td>GWBS SF-36</td>
<td>= QoL</td>
</tr>
<tr>
<td>Baum et al. (1998)</td>
<td>AO</td>
<td>41</td>
<td>Normal population</td>
<td>NHP PGWB GHQ MMPI-2</td>
<td>= QoL</td>
</tr>
<tr>
<td>Badia et al. (1998)</td>
<td>AO</td>
<td>356</td>
<td>Matched for age, sex, education (963 control subjects)</td>
<td>AGHDA</td>
<td>↓ QoL</td>
</tr>
<tr>
<td>McGauley (1989)</td>
<td>Mostly AO</td>
<td>24</td>
<td>Matched for age, sex, ethnicity, class and residence</td>
<td>NHP PGWB</td>
<td>↓ Qol: psychological distress (PGWB)</td>
</tr>
<tr>
<td>Rosen et al. (1994)</td>
<td>83 AO 3 CO</td>
<td>86</td>
<td>Matched for age, gender, marital status, socioeconomic class</td>
<td>NHP</td>
<td>↓ Qol: energy, ↑ emotional liability, ↓ sex life, ↑ social isolation</td>
</tr>
<tr>
<td>Stabler et al. (1992)</td>
<td>Multiple deficiencies</td>
<td>25</td>
<td>Matched for age, height, sex and socioeconomic status</td>
<td>Stress reactivity, psychometric testing</td>
<td>↓ openness, ↓ assertiveness</td>
</tr>
<tr>
<td>Wallymahmed et al. (1999)</td>
<td>AO</td>
<td>23 M 34 F</td>
<td>Age-matched diabetics</td>
<td>HADS SES MFQ LFS</td>
<td>↓ Qol: depression, fatigue, anxiety ↓ self-esteem, life fulfillment</td>
</tr>
<tr>
<td>Burman et al. (1995)</td>
<td>MO</td>
<td>36</td>
<td>Yes</td>
<td>HSCL NHP</td>
<td>↓ Qol, proportional to duration of GHD</td>
</tr>
<tr>
<td>Wiren et al. (2000)</td>
<td>MO</td>
<td>111</td>
<td>Normal population (1448)</td>
<td>AGHDA</td>
<td>↓ Qol</td>
</tr>
<tr>
<td>Wiren et al. (2001)</td>
<td>CO</td>
<td>21</td>
<td>GH-sufficient COGHD</td>
<td>NHP MACL PGWB</td>
<td>↑ anxiety = cognition</td>
</tr>
<tr>
<td>Bjork et al. (1989)</td>
<td>CO</td>
<td>23</td>
<td>47 controls</td>
<td>NHP PGWB</td>
<td>↑ sleep problems, ↑ social isolation, ↑ physical mobility problems</td>
</tr>
<tr>
<td>Lynch et al. (1994)</td>
<td>33 AO 8 CO</td>
<td>41</td>
<td>41 diabetics</td>
<td>CIS PAS CPRS</td>
<td>↑ depression, personality disorders</td>
</tr>
<tr>
<td>Deijen et al. (1996)</td>
<td>31 MPHD 17 IGHD</td>
<td>48</td>
<td>41 controls, matched for age</td>
<td>HSCL POMS cognitive tests</td>
<td>↓ vigor, memory, IQ ↑ anxiety (MPHD)</td>
</tr>
</tbody>
</table>

QoL, quality of life; GHD, growth hormone deficiency; Onset, age of growth hormone deficiency onset; CO, childhood onset; AO, adult onset; MO, mixed onset; IGHD, isolated growth hormone deficiency; MPHD, multiple pituitary hormone deficiency; n, number of growth hormone deficient subjects; M, male; F, female; Measurements, test used to quantify QoL (test abbreviations are given in Table 1); ↓, reduced QoL parameter with respect to control population; ↑, increased QoL parameter with respect to control population; =, normal QoL parameter in respect to control population.

Childhood onset Before the advent of recombinant GH, GH therapy in children was terminated once they reached their adult height. The advent of readily available GH has presented the possibility of life-long GH replacement in...
order to improve QoL. However, COGHD does not always persist into adulthood. Tauber et al. (1997) observed that 71% of children with partial GHD and 36% of children with complete GHD were GH-replete as young adults. The GH status of COGHD patients must therefore be assessed in early adulthood, and studies using COGHD patients in which GH status was not reassessed must be viewed with caution.

Although most studies of QoL in GHD adults have emphasized AOGHD, analysis of social indices and psychological parameters suggest that QoL is also impaired in COGHD. For instance, COGHD adults are more likely to be unmarried and unemployed and less likely to have a driver’s licence and live independently (Deijen & van der Veen 1999, Stabler 2001). These individuals perceive that their health interferes with their work, hobbies, sex-life, holidays, and household tasks (Deijen & van der Veen 1999, Stabler 2001) and often have a lower level of education (Takano et al. 1994). These social indices are also reflected in quantitative indices, since Bjork et al. (1989) observed decreased QoL in COGHD using the NHP and PGWB, particularly in the areas of sleep problems, social isolation, and physical mobility. A greater incidence of low self-esteem, anxiety, depression, panic disorder, and obsessive-compulsive disorder has also been reported in COGHD (Sartorio et al. 1995, Stabler 2001). Social phobia is also more prevalent in COGHD adults than in short GH-replete adults (Nicholas et al. 1997). Other studies have demonstrated impaired QoL in mixed-onset GHD populations, which likely reflects decreased QoL in both AO and CO patients (Table 3) (Lynch et al. 1994, Burman et al. 1995, Wiren et al. 2000). The reduced QoL in COGHD patients of normal height calls into question the use of increased height as an indicator of successful GH therapy.

Other investigations do not suggest a link between COGHD and impaired QoL. For instance, Wiren et al. (2001) observed similar QoL scores in GH-replete and GH-deficient adults who had suffered from COGHD. Using unaffected same-sex siblings as a control group, Sandberg et al. (1998) similarly observed normal QoL scores in COGHD adults. The GH status in these individuals was not, however, reassessed; thus, a proportion of the individuals in the GHD group may have been GH-replete.

Few investigators have examined the effects of GH replacement therapy exclusively in COGHD. Murray et al. (2002) observed a significant increase in QoL in GH-treated but not placebo-treated COGHD patients using the PGWB instrument. Conversely, Deijen et al. (1998) did not observe any effect of GH on well-being, although memory was improved. Sartorio et al. (1995, 1996) determined that GH therapy of COGHD individuals resulted in ‘...greater openness and sensitivity towards the surrounding world, greater fluency of thought, improved emotional control and a better perception of time processes.’

The available data would therefore suggest that QoL is affected by GH status in COGHD individuals, although the data are not extensive. Murray et al. (1999b) observed that levels of perceived distress are higher in AOGHD than in COGHD, suggesting that COGHD patients may have developed effective mechanisms for coping with their disorder. The high scholastic achievement and employability of many COGHD patients have been attributed to the inclusion of psychological counselling in their treatment regimen (Sartorio et al. 1996). Nevertheless, patients with COGHD have an equal or greater increase in QoL following GH treatment compared with AOGHD individuals (Murray et al. 1999b).

Therapeutic possibilities: the elderly

The somatopause

Ageing is often associated with the development of physiological GH insufficiency, since the amplitude of nocturnal GH spikes begins to drop after age 40 due to GH releasing hormone (GHRH) hypoactivity and somatostatin (SRIF) hyperactivity (reviewed by Janssens & Vanderschueren 2000). By the age of 60, secretion rates over a 24-h period are often indistinguishable from those of younger hypopituitary patients (Savine & Sonksen 2000). It has been suggested that this age-related decline in somatotropic function may, like AOGHD, impact QoL, since many elderly show symptoms of GHD such as muscle atrophy, central obesity, sleep disturbances, and depression (Cummings & Merriam 1999). Indeed, GH status in older adults is positively correlated with fitness, body composition and lipoprotein levels (Jorgensen 1999) and inversely correlated with frailty (Toogood et al. 1996, Cummings & Merriam 1999). The putative causal relationship between declining GH secretion and QoL measures in the elderly has led investigators to coin the term ‘somatopause’ to...
Table 5 Effects of GH therapy on quality of life in adults

<table>
<thead>
<tr>
<th>Reference</th>
<th>Onset</th>
<th>n</th>
<th>Dosage (per day)</th>
<th>Duration</th>
<th>Controls</th>
<th>Measurements</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baum et al. (1998)</td>
<td>AO</td>
<td>40</td>
<td>4 ± 2 µg/kg</td>
<td>18 m</td>
<td>PCDB</td>
<td>NHP, PGWB, GHQ, MMPI-2, Cognition tests</td>
<td>= cognition, QoL</td>
</tr>
<tr>
<td>Attanasio et al. (1997)</td>
<td>CO</td>
<td>99</td>
<td>12·5 µg/kg</td>
<td>18 m</td>
<td>6 m PCDB, 12 m Open</td>
<td>NHP</td>
<td>= mobility, energy (6 m)</td>
</tr>
<tr>
<td>McGauley (1989)</td>
<td>Mostly AO</td>
<td>24</td>
<td>0·07 U/kg</td>
<td>6 m</td>
<td>PCDB</td>
<td>NHP, PGWB, GHQ</td>
<td>= QoL (PGWB)</td>
</tr>
<tr>
<td>Whitehead et al. (1992)</td>
<td>6 AO</td>
<td>14</td>
<td>0·07 U/kg</td>
<td>6 m</td>
<td>PCDB, crossover</td>
<td>PGWB</td>
<td>= QoL, but no ↑ IGF-I</td>
</tr>
<tr>
<td>Bengtsson et al. (1993)</td>
<td>AO</td>
<td>10</td>
<td>13–26 µg/kg</td>
<td>6 m</td>
<td>PCDB, crossover</td>
<td>CPRS, SCL-90</td>
<td>↑ QoL (CPRS)</td>
</tr>
<tr>
<td>Beshyah et al. (1995a)</td>
<td>32 AO</td>
<td>40</td>
<td>0·04 U/kg</td>
<td>18 m</td>
<td>6 m PCDB, 12 m Open</td>
<td>CPRS, GHQ</td>
<td>↑ QoL at 12 m (CPRS)</td>
</tr>
<tr>
<td>Burman et al. (1995)</td>
<td>Mostly AO</td>
<td>21</td>
<td>2–4 U</td>
<td>9 m</td>
<td>PCDB</td>
<td>NHP, PGWB, HSCL, Spousal report</td>
<td>↑ QoL in GH-treated group (HSCL)</td>
</tr>
<tr>
<td>Gibney et al. (1999)</td>
<td>MO</td>
<td>11</td>
<td>0·025 U/kg</td>
<td>10 y</td>
<td>Control</td>
<td>NHP</td>
<td>↑ QoL (NHP): ↑ energy, emotional reaction</td>
</tr>
<tr>
<td>Drake et al. (1998)</td>
<td>AO</td>
<td>50</td>
<td>Normal IGF-I</td>
<td>6 m</td>
<td>Open</td>
<td>AGHDA</td>
<td>↑ QoL (3 m, 6 m)</td>
</tr>
<tr>
<td>Wiren et al. (1998)</td>
<td>MO</td>
<td>71</td>
<td>6 µg/kg/day</td>
<td>20–50 m</td>
<td>Open</td>
<td>NHP, PGWB</td>
<td>↑ QoL</td>
</tr>
<tr>
<td>Wallymahmed et al. (1997)</td>
<td>Mostly AO</td>
<td>32</td>
<td>0·018 U/kg (1 m), 0·035 U/kg (5 m)</td>
<td>12 m</td>
<td>6 m PCDB, 6 m Open</td>
<td>GHD-LFS, GHD-IS, NHP, HADS, SES, MFS</td>
<td>↑ self-esteem, ↑ energy and emotional reaction (transient)</td>
</tr>
<tr>
<td>Verhelst et al. (1997)</td>
<td>Mostly AO</td>
<td>148</td>
<td>0·035 IU/kg</td>
<td>24 m</td>
<td>6 m PC, 18 m Open</td>
<td>NHP, Social history</td>
<td>↑ QoL (also in placebo group): ↓ sick leave, hospitalization</td>
</tr>
<tr>
<td>Mardh et al. (1994)</td>
<td>AO</td>
<td>124</td>
<td>12–18 m</td>
<td>6 m PCDB, 6–12 m Open</td>
<td>NHP, PGWB</td>
<td>↑ energy, sleep (NHP)</td>
<td></td>
</tr>
<tr>
<td>Gilchrist et al. (2002)</td>
<td>MO</td>
<td>61</td>
<td>GH replacement</td>
<td>9 y</td>
<td>No replacement</td>
<td>NHP, PGWB</td>
<td>↑ vitality (PGWB)</td>
</tr>
<tr>
<td>Degerblad et al. (1990)</td>
<td>AO</td>
<td>6</td>
<td>0·07–0·09 U/kg</td>
<td>3 m</td>
<td>PCDB crossover</td>
<td>Mood questionnaires, psychometric testing</td>
<td>↑ vitality, mental alertness (5/6 patients)</td>
</tr>
<tr>
<td>Murray et al. (1999b)</td>
<td>MO</td>
<td>65</td>
<td>Normal IGF-I</td>
<td>8 m</td>
<td>Open</td>
<td>PGWB, AGHDA</td>
<td>Large ↑ in QoL on both scales</td>
</tr>
<tr>
<td>Carroll et al. (1997)</td>
<td>Not stated</td>
<td>42</td>
<td>0·024 (6 m) – 0·012 (6 m) µg/kg</td>
<td>12 m</td>
<td>6 m PCDB, 6 m Open</td>
<td>NHP, PGWB</td>
<td>↑ QoL on both scales</td>
</tr>
</tbody>
</table>

Continued
describe age-related hyposomatotropism (Toogood et al. 1996), although the physiological relevance of the somatopause is disputed by others. The somatopause was first implicated in the symptoms of frailty in the elderly by Rudman et al. (1985), who subsequently showed that GH therapy in elderly men improves insulin-like growth factor-I (IGF-I) levels, body composition and bone mineral content (Rudman et al. 1990). A subsequent, larger-scale placebo-controlled study also observed improved body composition in elderly men treated with GH for 6 months (Papadakis et al. 1996). Unfortunately, parallel improvements in functional capacity (strength, endurance, mood and mental status) were not observed (Papadakis et al. 1996). The patients used in this study were, however, in robust health and the lack of functional improvement may reflect a ceiling effect or the brief treatment regimen.

Alternatively, the somatopause may serve an adaptive role, protecting the elderly from adverse effects of GH. GH replacement in this population might thus be detrimental to QoL. This possibility is supported by the decreased life-span in GH transgenic mice, which would not experience a somatopause (Carter et al. 2002). Carter et al. (2002) have postulated that the stimulatory effect of GH on cellular metabolic activity (glucose oxidation and oxygen consumption) increases oxidative damage, resulting in pathological changes in tissues and death. The somatopause might also protect against certain malignancies, since Chan et al. (1998) observed a linear relationship between IGF-I levels and prostate cancer risk. Colorectal cancer is similarly more prevalent in acromegals (Colao et al. 1997, Jenkins et al. 1997, Orme et al. 1998). The overall cancer mortality rate is not, however, elevated (Orme et al. 1998), leading other investigators to conclude that long-term hypersomatotropism is not associated with an increased cancer risk (Cohen et al. 2000). The age-related reduction in GH levels post-puberty and particularly in the elderly may thus be adaptive, balancing the beneficial and detrimental effects of GH.

Despite the lack of consensus regarding the beneficial or detrimental nature of the somatopause, GH is marketed as a ‘panacea of youth’ in private medical clinics and internet sites. The equivocal results of studies investigating GH

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**Table 5 Continued**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Onset</th>
<th>n</th>
<th>Dosage (per day)</th>
<th>Duration</th>
<th>Controls</th>
<th>Measurements</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Murray et al. (2002)</td>
<td>CO (cancer)</td>
<td>27</td>
<td>Normal IGF-I</td>
<td>18 m</td>
<td>Open</td>
<td>PBWB AGHDA</td>
<td>Large ↑ in QoL on both scales after 3 m</td>
</tr>
<tr>
<td>Giusti et al. (1998)</td>
<td>AO</td>
<td>25</td>
<td>0.5–1 U</td>
<td>6 m</td>
<td>Randomized PC</td>
<td>HDS KSQ</td>
<td>↑ QoL (HDS) compared with placebo = KSQ score</td>
</tr>
<tr>
<td>Florkowski et al. (1998)</td>
<td>16 AO, 4 CO</td>
<td>20</td>
<td>Up to 0.035 U/kg</td>
<td>3 m</td>
<td>Randomized, PC, crossover</td>
<td>DSQ SCL-90 SAS</td>
<td>↑ QoL in both GH-treated and placebo groups</td>
</tr>
<tr>
<td>Deijen et al. (1998)</td>
<td>CO (men)</td>
<td>48</td>
<td>1–3 IU/m²</td>
<td>2 y</td>
<td>PC</td>
<td>Psychological testing</td>
<td>= well-being ↑ memory</td>
</tr>
<tr>
<td>Hernberg-Stahl et al. (2001)</td>
<td>AO</td>
<td>304</td>
<td>0.125 IU/kg/day–0.25 IU/kg/day</td>
<td>12 m</td>
<td>Open</td>
<td>AGHDA Interviews</td>
<td>↑ QoL. ↑ physical activity ↓ sick leave, hospital/doctor visits ↓ assistance in daily living (men only)</td>
</tr>
<tr>
<td>Ahmad et al. (2001)</td>
<td>AO</td>
<td>24 M, 22 F</td>
<td>Normal IGF-I</td>
<td>3 m</td>
<td>Open</td>
<td>AGHDA</td>
<td>↑ QoL after 1 m, larger ↑ QoL after 3 m</td>
</tr>
<tr>
<td>Soares et al. (1999)</td>
<td>Not stated</td>
<td>9</td>
<td>0.035 U/kg</td>
<td>6 m</td>
<td>PCDB</td>
<td>HDS BDI Cognitive tests</td>
<td>↑ QoL, cognition</td>
</tr>
<tr>
<td>Cuneo et al. (1998)</td>
<td>Mostly AO</td>
<td>166</td>
<td>0.018 U/kg (1 m), 0.036 U/kg (11 m)</td>
<td>12 m</td>
<td>6 m PC, 6 m Open</td>
<td>NHP GHDQ Social history</td>
<td>↑ QoL (NHP; energy, emotional reaction) at 12 m = QoL (GHDQ)</td>
</tr>
</tbody>
</table>

QoL, quality of life; CHD, growth hormone deficiency; Onset, age of growth hormone deficiency onset; CO, childhood onset; AO, adult onset; MO, mixed onset; IGHD, isolated growth hormone deficiency; MPHD, multiple pituitary hormone deficiency; n, number of subjects; M, male; F, female; y, years; m, months; Normal IGF-I, dosage of GH was titrated to normalize IGF-I levels; PC, placebo-controlled; PCDB, placebo-controlled double-blind; open, open label; Measurements, test used to quantify QoL (test abbreviations are given in Table 1); ↓, reduced QoL parameter in GH-treated patients with respect to controls; ↑, increased QoL parameter in GH-treated patients with respect to control population.
supplementation during the somatopause may reflect the choice of subject group (very robust elderly), the short-term nature of the studies (6 months), the inapplicability of QoL instruments to the elderly, and/or the extensive side-effects of excessively high GH doses. QoL assessments after prolonged (more than 6 months) GH therapy, using doses that minimize adverse effects and QoL instruments validated for this age-group, are necessary before establishing the value of treating the somatopause in all elderly patients. A more plausible scenario is the selective use of GH therapy in patients with particularly low endogenous GH levels and particularly high degrees of QoL impairment. Short-term GH therapy may also be useful as an anabolic agent following surgery or injury. The diminished GH and lean body mass in many elderly patients renders them highly susceptible to postoperative catabolism, and a recent study by Weissberger et al. (2003) demonstrated that exercise performance following hip replacement declined in untreated elderly but increased in GH-treated patients.

GH deficiency
Organic GH deficiency in the elderly is distinct from the somatopause, since GH secretion rates in GHD elderly are 5–12% of those in age-matched control populations (Reutens et al. 1995, Toogood et al. 1997). It is generally accepted that elderly GH-deficient patients should receive the same consideration for GH therapy as younger GHD adults. Investigations by Toogood and Shalet (1999) and the KIMS study group (Monson et al. 2000) showed a significant increase in perceived QoL in GH-treated elderly patients with organic GH deficiency, as measured by the AGHDA. Although the increase was small, the decision of most patients to continue with GH therapy indicates that the improvement was perceived by the patient (Toogood & Shalet 1999). Other studies of GH-treated GHD elderly patients do not, however, show consistent increases in QoL indices (Li Voon Chong et al. 2002).

Adverse effects
The elderly appear to be more susceptible to adverse effects of GH therapy, particularly carpal tunnel syndrome, fluid retention and resulting peripheral edema, and arthralgias (Rudman et al. 1990, Holmes & Shalet 1995c). This increased susceptibility reflects enhanced GH responsiveness, since the elderly require a lower dose than younger patients to induce a similar IGF-I response (Toogood & Shalet 1999). The careful titration of GH dosage to normalize IGF-I levels is therefore extremely important in the elderly in order to avoid adverse side-effects (Savine & Sonksen 2000).

Therapeutic possibilities: conclusion
Despite difficulties in quantifying QoL, particularly in children and in the elderly, definite improvements in QoL have been observed following GH treatment in GH-deficient patients of all ages. The concordance between GH status and QoL is not, however, complete, and additional investigations into factors modulating the GH–QoL relationship are required. The ability of GH to increase final adult height in GH-replete children does not, however, appear to have any beneficial effect on QoL, and the advisability of GH therapy for physiological GH deficiency associated with ageing also remains speculative.

Therapeutic pitfalls
Determinants of treatment effectiveness
The data indicate that GH therapy does not improve QoL in every GHD individual. It is thus not advisable, for economic as well as ethical reasons, to subject every GHD individual to life-long GH replacement. Attempts have been made to identify which subjects would benefit most from GH replacement, but the determinants of GH replacement effectiveness have been difficult to identify. The severity of the GHD does not necessarily correspond with the severity of the QoL impairment, nor the effectiveness of the GH replacement (Burman et al. 1995). Thus, the decision to initiate (AOGHD) or continue (COGHD) treatment cannot be based upon tests of GH secretion and arbitrary diagnostic cutoffs (Allen 1999). Rather, if the goal of GH replacement in adulthood is to improve QoL, psychological testing and clinical interviews measuring QoL should be important determinants of the appropriateness of GH treatment (Shalet 1998).

The GH dosage is also an important determinant of treatment effectiveness, and it has proven difficult to determine the optimal dose based on weight or surface area. Insufficient GH would axiomatically be ineffective, and excess GH results in adverse side-effects that would obviously mitigate the improvement in QoL. A more recent approach is to titrate the GH dose to normalize IGF-I levels (see Table 5). Studies using this approach generally show a significant increase in QoL with few adverse events (Table 5, e.g. Drake et al. 1998, Murray et al. 1999a, 2002).

Difficulties with experimental design
Control populations The choice of control populations in studies of GH replacement can be problematic, because the lack of GH is not the only difference between GHD adults and the GH-replete general population (Johnston 1997). For instance, the childhood of GH-treated COGHD adults is characterized by frequent injections and
medical interventions and often a pre-treatment period of short stature. Adult-onset GHD, conversely, is usually associated with additional endocrine deficiencies and/or neurological deficits resulting from a tumor. Indeed, nearly one-third of GHD patients used by McGauley (1989) were GHD secondary to treatment for Cushing’s disease. The difficulty in differentiating generic effects of dealing with a chronic disease from specific effects of GHD thus renders healthy adults a poor control group for CO or AO GHD. Several studies have addressed this problem by using suffers of other chronic diseases as the control group. For instance, Page et al. (1997) compared hypopituitary patients with those who had undergone mastoid surgery. This study was unable to detect any difference either between the two patient groups or between the patient groups and the general population, using the SF-36 and the PGWS instruments. Other studies have used diabetics as the control group and obtained more significant results. Wallymahmed et al. (1999) detected a significant reduction in QoL (increased depression, mental fatigue and anxiety and decreased self-esteem and life fulfilment) in GHDA compared with diabetics using four different instruments (Hospital Anxiety and Depression Scale (HADS), Self Esteem Scale (SES), Mental Fatigue Questionnaire (MFQ) and Life Fulfilment Scale (LFS)). Lynch et al. (1994) similarly employed diabetics as the control group, and observed a significantly higher incidence of depression and personality disorders in the GHD group.

Other studies have attempted to control for surgery and radiotherapy, since hypopituitarism is often secondary to treatment for pituitary tumors. Conflicting data have been obtained. In AOGHD, radiotherapy, rather than GHD, has been implicated in impaired concentration and memory (Holmes & Shalet 1995a), but in a separate study impaired QoL was shown to be independent of radiotherapy (Page et al. 1997).

Study populations The choice of study populations is equally problematic. Investigators may differ in their definition of GHD, complicating interstudy comparisons. Moreover, study populations are rarely homogeneous, including patients with a variety of etiologies. Patients with different etiologies may respond differently to GH treatment and may have distinct QoL concerns. This heterogeneity would increase the variability within the study population, and could render results statistically insignificant. A few studies have, however, attempted to differentiate between different groups of GHD patients. Dejien et al. (1996) compared QoL and cognition between men with IGHD and men with MPHD, and concluded that cognitive changes reflected the lack of GH whereas vigor deficits were more closely associated with testosterone deficiency. However, other studies have observed that the degree of hypopituitarism does not relate to QoL (Burman et al. 1995) and that IGHD and MPHD impair marriage and employment prospects to the same extent (Rikken et al. 1995).

Heterogeneity in the study population may thus result in an underestimation of the role of GH in QoL. Conversely, selection bias in the GHD population used in GH replacement studies may exaggerate the importance of GH in determining QoL. Individuals that participate in GH replacement studies usually have a lower QoL than other GHD adults, whereas individuals without a perceived deficit in QoL are less likely to volunteer (Holmes & Shalet 1995a). Moreover, individuals that do not perceive an improvement in QoL in GH replacement trials are less likely to continue GH replacement therapy than individuals who do perceive an improvement (Holmes & Shalet 1995b).

Placebo effect The act of enrolling in a study protocol can result in improvements in QoL; thus, open-label protocols demonstrating enhanced QoL subsequent to GH therapy (Table 5) must be interpreted with caution. Indeed, a placebo effect on QoL has been observed using the Symptom Checklist-90 (SCL-90), the Social Adjustment Scale (SAS) (Florkowski et al. 1998), the NHP (Burman et al. 1995, Verhelst et al. 1997), and the PGWB (Carroll et al. 1997). Double-blind, placebo-controlled protocols have been developed to overcome the placebo effect, but the overt physical changes resulting from GH therapy render a true ‘double-blind’ protocol virtually impossible (Mardh et al. 1994). The placebo effect cannot, however, account for the continuous improvements in QoL between 6 and 12 months following GH therapy (e.g. Attanasio et al. 1997).

Therapeutic mechanisms

Before the advent of recombinant GH, the rationale for GH replacement therapy was to improve QoL in COGHD children by correcting their height deficit. However, this rationale is no longer valid, since height and QoL are not tightly linked and many prospective recipients of GH therapy have completed their linear growth. Despite intensive studies attempting to quantify GH-induced changes in QoL, few investigators, with the exception of Chrysoulidou et al. (1998), have discussed possible mechanisms by which GH improves QoL. GH may act directly at neural sites, modifying mood, memory and cognition, or may affect subjective well-being via somatic changes in body composition, cardiovascular health, reproductive function, and/or skin.

Therapeutic mechanisms: neural effects

GH may affect QoL by altering mental function at central nervous system (CNS) sites. GH may induce mental changes via increased production of hepatic IGF-I, since
IGF-I is actively transported across the blood–brain barrier (BBB) (Coculescu 1999). However, the presence of immunoreactive GH in the human brain and cerebrospinal fluid (CSF) suggests that GH may also act directly on neurons and/or glia (Nyberg & Burman 1996). This GH may be of peripheral origin, since peripheral GH therapy increases CSF GH concentrations in a dose-related manner (Burman et al. 1996). Although the BBB is generally considered to be impermeable to GH, peripheral GH may access the CNS by non-specific mechanisms during development and stress, when vascular permeability is increased. The presence of abundant GH-binding activity in the human choroid plexus (Lai et al. 1991) also suggests that specific, receptor-mediated GH uptake may occur at the circumventricular organs (Coculescu 1999). CNS GH immunoreactivity may also reflect local synthesis, since GH mRNA has been detected in the rodent and avian brain (Harvey & Hull 2003). This finding has not, however, been replicated in humans (Castro et al. 2000).

Regardless of the source of the GH, direct neural actions of GH are suggested by the presence of GH-binding sites in the human hippocampus, putamen, thalamus, hypothalamus and pituitary gland (Lai et al. 1991) and by GH receptor (GHR) immunoreactivity in the fetal brain (Hill et al. 1992). The hippocampal GH-binding activity is of particular interest, since this region plays a significant role in posulated GH-dependent processes (memory, motivation, and attention) (Nyberg 2000). Data regarding the distribution and regulation of GHR mRNA in the human brain are sparse, although considerable data have been collected in rats and chickens (Harvey & Hull 2003). Preliminary reports in humans note that GHR mRNA has been detected in the choroid plexus (Nyberg 2000), in glioblastoma cells and in normal embryonic brain tissue (Zogopoulos et al. 1996, Castro et al. 2000). GH-binding activity in the choroid plexus, hippocampus, putamen, pituitary gland, and hypothalamus declines with advancing age (Lai et al. 1993) and GHR mRNA declines in the choroid plexus (Nyberg 2000). This decline, in concert with the decline in circulating GH levels, may contribute to impaired mood and cognition in the elderly.

Neuromodulation GH may modulate mood, and thereby QoL, by modifying neurotransmission. Long-term GH replacement in GHD men decreases dopamine turnover, as indicated by reduced CSF concentrations of homovanillic acid (a dopamine metabolite) (Johansson et al. 1995, Burman et al. 1996). The concomitant increase in CSF aspartate concentrations and N-methyl-D-aspartate (NMDA) receptor activation implicates excitatory amino acids in this reduced dopamine release (Burman et al. 1996). Free concentrations of thyroxine are also reduced in the CSF of GH-treated GHD men (Burman et al. 1996). These GH-induced modulations in neurotransmitter levels may be responsible for the positive effect of GH on mood, since similar changes are observed following successful treatment with anti-depressives (Risby et al. 1987, Burman et al. 1996). Increased beta-endorphin levels have also been observed in the CSF of GH-treated patients in some (Johansson et al. 1995) but not all (Burman et al. 1996) studies. Beta-endorphins are produced in regions containing GH-binding activity (pituitary and hypothalamus) and are involved in exercise-induced changes in mood (Goldfarb & Jamurtas 1997).

Brain growth and development GH may enhance cognition, and thereby QoL, by stimulating brain growth and development. This possibility is strongly supported by animal studies, since brain growth, glial and neuronal proliferation, and myelination are impaired in GH-deficient dwarf mice, and brain size is increased in mice expressing the GH transgene (Harvey & Hull 2003). Microcephaly and abnormal skull development are similarly prevalent in patients with GH insensitivity (Laron syndrome, LS) and GHD (Laron & Klinger 2000, Kornreich et al. 2002) and have been implicated in the delayed psychological and motor development in LS children (Galatzer et al. 1993). Diffuse parenchymal loss and occasionally cerebellar atrophy are also observed in LS, and the severity of the structural changes often parallels the degree of intellectual impairment (Kornreich et al. 2002). The ability of IGF-I to improve head circumference in LS patients to the same extent as GH in GHD patients suggests that GH effects on brain growth may be IGF-I dependent (Laron & Klinger 2000). Conversely, GH effects on motor neuron morphology appear to be IGF-I independent (Chen et al. 1997, Scheepens et al. 2000). Curiously, Tan (1995) observed an inverse relationship between GH levels in umbilical cord blood and neonatal brain size, suggesting an inhibitory effect of prenatal GH on brain growth, although support for this hypothesis is limited.

Neural repair GH may play a particularly important role in neural function during periods of brain injury, maintaining neuronal viability, normal cognition, and thereby high QoL. Studies in rats demonstrate that GH (i.e.v.) can prevent cell loss in the hippocampus, but not the striatum, following hypoxic-ischemic brain injury (Scheepens et al. 2001). GH-binding sites are similarly found in the hippocampus but not in the striatum, suggesting that GH itself is modulating glial activity via receptor-mediated mechanisms. The inability of IGF-I to mimic this effect suggests that it is IGF-I independent (Scheepens et al. 2001) although other investigators have obtained conflicting results (Frago et al. 2002). The physiological relevance of neuroprotective actions of GH is shown by the upregulation of neural GH and GHRs following hypoxic/ischemic injury (Scheepens et al. 1999, 2001). GHRs are initially upregulated in the choroid plexus and endothe-lium, indicating the importance of CNS uptake of
peripheral GH, and subsequently in glia surrounding the injured area (Scheepens et al. 1999).

**Cognition and memory** Subtle effects of GH on cognitive abilities, mediated by hippocampal GHRs, may contribute to QoL. Although IQ scores are normal or low-normal in GH-resistant (Galatz et al. 1993, Kranzler et al. 1998) and GH-deficient (Sartorio et al. 1996) children, GH status and performance in a visual motor test are strongly correlated in children (Andronikof-Sanglade et al. 1997). Deijen et al. (1996) similarly observed impaired IQ and perceptual-motor performance in GHD adults, and cognitive dysfunction is prevalent in hypopituitary women (Bulow et al. 2002). In support of the hypothesis that GH enhances cognition, Soares et al. (1999) observed improved scores in a number of cognitive tests examining attention, verbal fluency, and cognitive efficiency following GH treatment in GHD males. Memory may also be influenced by GH, since memory deficits (particularly short-term and iconic) are common in GHD adults (Deijen et al. 1996) and are ameliorated by GH replacement therapy (Almqvist et al. 1986, Deijen et al. 1998). GH may enhance memory by acting as a neuromodulator, since GH-induced improvements in memory in rats are associated with increased expression of NMDA receptor subunits in the hippocampus and increased synaptic plasticity (Le Greves et al. 2002). Altered SRIF levels have also been postulated to mediate GH effects on memory and cognition (Schneider-Rivas et al. 1995).

The role of GH in cognition may be particularly important in the elderly, since the decline in cognition is associated with the decline in endogenous GH secretion in ageing men (Aleman et al. 2000). Although marked improvements in cognition have not been detected following GH administration to elderly men, GHRH administration to elderly rats prevents age-related losses in spatial reference memory by chronically elevating circulating GH (Thorton et al. 2000). However, Schneider-Rivas et al. (1995) observed an improvement in memory following GH treatment in young but not old rats, which may reflect age-related downregulation of GHRs (Lai et al. 1993).

Some investigations do not support a cognitive role for GH. For instance, Baum et al. (1998) did not observe any effect of GH deficiency or GH treatment on performance in cognitive tests in AOGHD men, including tests of memory. Degerblad et al. (1990) and Wirén et al. (2001) also failed to observe any correlation between GH status and cognition. Curiously, GHR-knockout mice do not experience an age-related loss in memory skills, which would suggest that the complete absence of GH action enhances memory (Kinney et al. 2001).

In addition to direct, receptor-mediated effects on memory and cognition at neural and glial sites, studies in animal models suggest that GH may enhance neural function by enhancing cerebral blood flow and intercellular communication. For instance, GH may improve intercellular communication via gap junctions, since it stimulates connexin–43 synthesis in the rat brain (Aberg et al. 2000). The cerebral microvasculature, which determines cerebral blood flow and therefore function, is also a putative GH-target site, since GH has angiogenic properties (Corbacho et al. 2002). This hypothesis is supported by the parallel decline in GH secretion and the quality of the cerebral microvasculature in aged rats (Sonntag et al. 2000). Moreover, GH administration has been shown to increase vascular density in the ageing rat cortex (Sonntag et al. 2000). The effect of exogenous GH can be mimicked by caloric restriction, which prevents the age-related decline in GH (Lynch et al. 1999). Cerebral IGF-I is increased whereas peripheral IGF-I is decreased following caloric restriction (Sonntag et al. 1999), suggesting that local IGF-I may mediate cerebral angiogenic actions of GH.

GH may also affect QoL by improving sleep and appetite, both of which affect subjective feelings of well-being and are often abnormal in the elderly and other GHD individuals. For instance, Nyberg (2000) reports that some GHD children have poor appetites and eating habits, both of which are improved by GH therapy. Beta endorphin, which is a known appetite stimulant and is increased in the CSF of GH-treated patients (Johansson et al. 1995), may mediate the effect of GH on food intake, although other neurotransmitter systems (neuropeptide Y) have also been implicated (Nyberg 2000, Harvey & Hull 2003).

The concomitant decrease in slow wave sleep and GH secretion during ageing implies that GH may play a role in normal sleep generation (Van Cauter et al. 2000, Anawalt & Merriam 2001). Although this relationship may reflect increased GH secretion during slow-wave sleep, a small number of preliminary studies suggest that GH enhances sleep. For instance, Aström & Lindholm (1990) observed decreased deep sleep, increased total sleep time and a decreased percentage of rapid eye movement (REM) sleep in GHD adults. The changes in total sleep time and REM sleep were reversed by GH treatment, and patients also reported enhanced well-being (Astrom et al. 1990). In addition, a small study observed sleep disturbances, particularly in REM sleep, in two of three GHD girls that were improved following GH therapy (Hayashi et al. 1992). Other investigators have, however, questioned the importance of GH in sleep generation (Kern et al. 1993, Feinberg 2000).

**Neural mechanisms: conclusion** The brain is now considered to be a site of GH production and action. Documented effects of GH on neural function in children and adults may account for the dependency of some QoL indices, particularly mood and cognition, on GH status.
Therapeutic mechanisms: somatic effects

Unlike the possibility of GH-induced neurological changes, little controversy exists regarding the sensitivity of somatic indices to GH therapy. GH exerts well-defined effects on body composition, bone, cardiovascular function, metabolism, pulmonary function, and skin that may impact QoL. Indeed, GH-induced improvements in the physical mobility (Attanasio et al. 1997, Gilchrist et al. 2002) and energy (Wallymahmed et al. 1997) subsections of QoL indices would likely be mediated at somatic sites. The relevance of somatic actions of GH to QoL is not, however, accepted by all investigators (Barkan et al. 2000).

Body composition

The importance of GH status in the determination of body composition is well-accepted, since both CO and AO GHD are associated with a 7–10% increase in adiposity, particularly in the abdominal region (Salomon et al. 1989, Attanasio et al. 1997). The resulting increase in the waist-hip ratio is considered a risk factor for heart disease, diabetes and hypertension. GH therapy reduces visceral fat to a greater extent than peripheral fat (Bengtsson et al. 1993), at least in AOGHD (Attanasio et al. 1997), which would reduce morbidity and mortality and theoretically improve QoL. The increased adiposity in GHD is associated with a reciprocal reduction in lean body mass (LBM), particularly in COGHD. This reduction is largely the result of decreased skeletal muscle volume, which is corrected by GH treatment (Bengtsson et al. 1993).

The reduction in LBM also reflects the GH dependency of fluid homeostasis. Alterations in fluid volume may have a significant impact on QoL, since resulting changes in tissue hydration, blood volume, and muscle size and function would impact cardiac output and exercise capacity. Total body water, particularly extracellular water, is reduced in GH deficient individuals, and total blood volume and plasma volume are correspondingly reduced (reviewed by Verhelst & Abs 2002). GH rapidly (<1 month) normalizes extracellular water and plasma volume, and this effect persists for the length of the treatment (Hanukoglu et al. 2001). The mechanism by which GH improves fluid homeostasis may involve increased tubular absorption of sodium (Herlitz et al. 1994) and perhaps activation of the renin–angiotensin–aldosterone system (RAAS) (Hanukoglu et al. 2001), although some studies do not observe any effect of GH on RAAS activation (Ekman et al. 2002).

Energy levels and self-esteem could theoretically be improved by GH-induced changes in body composition. However, a relationship between body composition and QoL has not yet been demonstrated (Chrisouliou et al. 1998). Indeed, Ahmad et al. (2001) did not observe any correlation between changes in QoL and changes in body fat percentage in GH-treated GHD adults. Bengtsson et al. (1993), however, associated GH-induced changes in body composition with improved QoL scores using the Comprehensive Psychological Rating Scale (CPRS).

Bone

GH may play a critical role in maintaining skeletal health and decreasing the risk of bone fractures. Bone fractures, particularly of the lower limbs and pelvic girdle, would axiomatically limit physical mobility. Physical mobility is explicitly examined in some QoL instruments (e.g. NHP) and would impact other QoL indices such as physical drive (AGHDA). Skeletal effects of GH may thus impact QoL, particularly in the elderly and other patient groups more susceptible to fractures. GHD is associated with decreased bone mineral density (BMD) in GHD children, COGHD adults and AOGHD adults, reflecting decreased bone accretion and/or reduced bone turnover (reviewed by Monson et al. 2002, Verhelst & Abs 2002). The reduced BMD in AOGHD is associated with an increased incidence of fractures, particularly in men (Rosen et al. 1997). Osteoporosis is similarly prevalent in untreated GH-resistant LS patients (Laron 2001).

The effects of GH replacement therapy in hypopituitary patients are influenced by gender. Markers of bone turnover are increased more rapidly in females than in males, resulting in a short-term reduction in BMD for the first 6 months following the initiation of GH therapy in both genders (Drake et al. 2001b). However, BMD in men is significantly improved after prolonged therapy, whereas BMD values in women with similar baseline values remain stable (Johansson et al. 1999, Drake et al. 2001b). Conversely, an earlier study by Johansson et al. (1996) observed lower baseline BMD values in women than in men and a correspondingly larger improvement following GH replacement in women. Both gender and baseline BMD values are thus important determinants of bone responses to GH replacement therapy. Indeed, both Vandeweghe et al. (1993) and Johansson et al. (1996) observed that some patients do not show any improvements in BMD following 24 months of GH therapy. Additional studies elucidating the role of gender and other factors affecting GH responsiveness would be beneficial in determining which
patients can expect a significant increase in skeletal health following GH therapy.

**Skin** GH is associated with a number of detrimental changes in skin, including thinning (Attanasio et al. 1997), decreased body hair (Blok et al. 1997), and reduced sweating (Juul et al. 1993), that may impair self-esteem and physical mobility aspects of QoL. The reduction in sweating ability may be particularly relevant to exercise-related parameters of QoL, since GHD adults are unable to adequately dissipate heat by sweating during exercise (Juul et al. 1993), that may impair self-esteem and physical mobility aspects of QoL. The reduction in sweating ability may be particularly relevant to exercise-related parameters of QoL, since GHD adults are unable to adequately dissipate heat by sweating during exercise (Juul et al. 1993). GH replacement corrects these deficiencies, increasing skin thickness (Attanasio et al. 1997), sweat production (Pedersen et al. 1989), and hair growth (Blok et al. 1997). The increased hair growth is observed in the facial and axillary regions, which may enhance masculine appearance and thereby enhance self-esteem. These effects on skin may be mediated directly at GHRs, since sweat glands in human skin and hair follicles in rat skin contain GHR immunoreactivity (Lobie et al. 1990).

**Metabolic disturbances** The importance of GH in carbohydrate, fat, and protein metabolism would suggest that metabolic disturbances would be more prevalent in GHD individuals. For instance, GH replacement increases protein synthesis (Beshyah et al. 1993), which may enhance muscle growth and fat oxidation (Vahl et al. 1997), thereby reducing adiposity. More subtle changes, such as reduced fasting blood glucose, non-esterified fatty acids and ketones may also affect QoL by altering mood upon awakening and before meals (Al Shoumer et al. 1996). In GHD patients also suffering from diabetes, GH replacement decreases hypoglycemic episodes (Christ et al. 2003). However, GH replacement exacerbates, rather than corrects, the hyperinsulinemia and resulting insulin resistance observed in GHD adults (Simpson et al. 2002).

GH is also associated with decreased whole body resting energy expenditure (REE), even when expressed in relation to lean body mass, and GH replacement dramatically increases REE (Salomon et al. 1989). This action likely reflects the stimulatory effect of GH on thyroid function (Salomon et al. 1989).

**Cardiovascular system** GH-dependent aspects of cardiac performance may influence energy levels and exercise capacity, two important determinants of QoL.

Early studies suggested that cardiac changes associated with GHD may be dependent upon the age of onset (Colao et al. 2001). Cardiac output is impaired in COGHD adults, reflecting decreased myocardial contractility, reduced left ventricular mass and reduced ejection fraction (Amato et al. 1993). Early studies of mixed onset or AOGHD adults did not reveal any abnormalities in cardiac morphology or function (Cuneo et al. 1992, Beshyah et al. 1995b), suggesting that GH is only important in prepubertal heart development. More recent studies by Cuneo et al. (2000), however, have detected abnormal diastolic and systolic function at peak exercise in AOGHD patients aged up to 60 years, suggesting that GH also plays a role in post-pubertal heart function. Longobardi et al. (1998), comparing CO and AO GHD adults with closely age-matched controls, also observed impairments in left ventricular systolic and diastolic function regardless of the age of onset.

GH replacement increases ventricular mass and/or performance in COGHD patients (Amato et al. 1993, Sartorio et al. 1997, Ter Maaten et al. 1999). The cardiac hypertrophy may be transient, since it subsides after 2 years of continuous treatment, but improvements in cardiac performance persist for up to 10 years (Ter Maaten et al. 1999). Other studies using AOGHD patients (Nass et al. 1995) did not observe any improvement in cardiac morphology or function following GH treatment. Curiously, although Valcavi et al. (1995) observed impaired diastolic function but normal left ventricular mass and systolic function in AOGHD patients, all three parameters were improved following GH treatment.

In addition to morphological cardiac changes, decreased plasma volume (Moller et al. 1996, Christ et al. 1997) and increased peripheral resistance resulting from reduced systemic nitric oxide (Boger et al. 1996) may also contribute to the reduction in cardiac output in AOGHD. GH replacement normalizes fluid volume and decreases peripheral resistance (Boger et al. 1996, Moller et al. 1996, Christ et al. 1997).

GH also stimulates erythropoiesis and thereby increases red blood cell mass (Christ et al. 1997). The hemoglobin concentration is unchanged following GH treatment (Cuneo et al. 1991b), since plasma volume is augmented to a similar extent, but the oxygen carrying capacity of the blood is improved (Christ et al. 1997). The increase in oxygen carrying capacity could theoretically enhance energy levels and exercise capacity.

GH may also enhance QoL by protecting against cardiovascular morbidity and mortality, since atherosclerosis and cerebrovascular disease are more prevalent in GHD adults than in the general population (Simpson et al. 2002). Well-accepted cardiovascular risk factors, including altered lipid profiles, are common in GHD adults, and GH replacement therapy usually improves these parameters (Table 6) (Simpson et al. 2002). Although GH exerts beneficial effects on lipid profiles during higher and/or longer treatment regimens (Christ et al. 1999), low-dose GH therapy can improve some risk factors (vascular reactivity and sialic acid levels) without altering lipid profiles (Christ et al. 1999a,b). Hypertension, reflecting increased diastolic blood pressure, is also observed in many GHD adults as a result of dramatically elevated sympathetic nerve activity (Sverrisdottir et al. 1998), and GH therapy can lower diastolic blood pressure (Caidahl et al. 1994). It must
also be emphasized that many individual GHD adults have entirely normal lipid profiles and cardiac function (Bengtsson et al. 2000).

**Exercise capacity** The involvement of GH in numerous body systems would suggest that GH status would determine exercise capacity. Although the relationship between QoL and exercise capacity has not been explicitly examined, most QoL instruments evaluate energy level, which would reflect submaximal exercise capacity (i.e. AOGHD; McKenna et al. 1999). Indeed, low energy and fatigue are common complaints in GHD, and are often alleviated by GH replacement therapy (Wallymahmed et al. 1997, Woodhouse et al. 1999). Moreover, Hernberg-Stahl et al. (2001) used the amount of physical activity and patient satisfaction with activity level as markers of QoL, and determined that both parameters were significantly increased in AOGHD following 12 months GH replacement.

Laboratory studies also reveal that GH deficiency severely compromises exercise capacity. For instance, the maximal exertion level, as measured by VO₂ max, is reduced in GHD adults to levels observed in patients with congestive heart failure (Woodhouse et al. 1999) and is improved by GH replacement (Cuneo et al. 1991b). A measure that may be more relevant to QoL in GHD patients is the ventilatory threshold (VeT), which reflects submaximal exercise performance and is an indicator of the effort required to undertake basic everyday activities (Woodhouse et al. 1999). The VeT/VO₂ max ratio is significantly improved by GH therapy; thus, daily activities, like walking, can be performed at a lower perceived exertion level (Woodhouse et al. 1999).

Improvements in LBM, both in fluid volume and muscle mass, play a major role in GH-induced enhancements of exercise capacity, since VO₂ max values are virtually constant following GH therapy when expressed in proportion to LBM (Cuneo et al. 1991b). Improved pulmonary function may also be involved, particularly in COGHD, since indicators of pulmonary function (lung volumes and respiratory pressures) are impaired in GHD and improved by GH replacement (Merola et al. 1996). Impaired ventricular filling (Caidahl et al. 1994) and abnormal EEG readings (Shahi et al. 1992) during exercise suggest that normal exercise capacity may also depend upon cardiovascular actions of GH. Erythropoiesis, cardiac output, and sweating are additional GH-dependent parameters that would influence exercise capacity.

**Reproduction** The involvement of GH in sexual performance may explain why GHD patients often report a decreased QoL with respect to sex life (Rosen et al. 1994). GH may be involved with erection, since GH in vitro can induce relaxation of corpus cavernosum tissue and elevate cGMP (Becker et al. 2000). The importance of GH in vivo in erectile function is suggested by the elevation of GH in cavernous and peripheral blood during the tumescent phase in normal men (Becker et al. 2000) and in men with psychogenic erectile dysfunction (Becker et al. 2002). Conversely, this elevation does not occur in men with organogenic erectile dysfunction (Becker et al. 2002). The ability of GH to enhance fertility (Hull & Harvey 2000b, 2001) may also impact QoL.

**Somatic mechanisms: conclusion** The impact of GH status on clinical indices such as height, body composition, metabolism, and cardiovascular and bone health is well-established, and may be responsible for the GH dependency of QoL indices such as energy and the ability to carry out everyday functional tasks. Heterogeneity in some responses to GH therapy, particularly skeletal and cardiovascular aspects, has been documented and may contribute to individual variation in QoL impairment and GH responsiveness.
Table 7 Putative mechanisms by which GH improves quality of life

<table>
<thead>
<tr>
<th>Mood</th>
<th>Cognition and memory</th>
<th>Energy and exercise performance</th>
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<td>Improved sleep and appetite</td>
<td>Improved sleep and appetite</td>
<td>Increased sweating</td>
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<tr>
<td>Altered dopamine metabolism</td>
<td>Increased cerebral blood flow</td>
<td>Increased LBM, decreased fat</td>
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<tr>
<td>Increased endorphin production</td>
<td>Increased intercellular communication</td>
<td>Increased cardiac output</td>
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<td>Increased NMDA receptor expression, synaptic plasticity</td>
<td>Increased pulmonary function</td>
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<td>Altered SRIF production</td>
<td>Increased erythropoiesis</td>
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**Therapeutic mechanisms: conclusions**

QoL instruments indicate that GH induces improvements in a number of subscales, including energy, mental performance, and mood (Table 5). These improvements can be explained on the basis of documented effects of GH on metabolism, body composition, skeletal, neural, cardiovascular, and reproductive function (Table 7) and reflect the actions of pituitary and possibly neural GH.

**Summary**

The ability of GH to improve body composition, cardiovascular, and metabolic function, and metabolism is well accepted, and GH may also improve neural function and reproductive performance (Hull & Harvey 2000a, Simpson et al. 2002, Harvey & Hull 2003). These myriad effects of GH are reflected in the impaired QoL in many GHD patients and the improved QoL following GH replacement (Tables 3 and 5). QoL remains, however, difficult to quantify, and many GHD individuals do not perceive an impairment in QoL and/or do not respond favorably to GH replacement therapy. Factors influencing the relationship between GH status and QoL have not been adequately elucidated, although gender, age of GHD onset, duration of GHD, and GHD etiology have been proposed as possible determinants. A relationship between the severity of the original QoL impairment and the magnitude of GH-induced QoL improvements has also been documented. The high cost of GH therapy and the heterogeneity of QoL impairments and GH responsiveness necessitate that GH replacement therapy in GHD adults be considered on a case-by-case basis. The ability of GH to improve QoL in GH-replete syndromes, including idiopathic short stature, IUGR, and Turner syndrome, remains highly speculative. Similarly, the advisability of GH supplementation in the non-GHD elderly remains unsupported by scientific study. Further epidemiological investigations into long-term effects of GH supplementation in GH-replete patient groups, greater insight into mechanisms by which GH improves QoL, and the elucidation of factors that modify the relationship between GH status and QoL are required to adequately determine which patients will derive the most benefit from GH therapy.

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**References**


Allen DB 1999 Issues in the transition from childhood to adult growth hormone therapy. *Pediatrics* 104 1004–1010.


Astrom C & Lindholm J 1990 Growth hormone-deficient young adults have decreased deep sleep. *Neuroendocrinology* 51 82–84.


Attanasio AF, Lamberts SW, Matranga AM, Birkett MA, Bates PC, Valk NK, Hiinset J, Bengtsson BA & Strasburger CJ 1997 Adult


Cummins DE & Merriam GR 1999 Age-related changes in growth hormone secretion: should the somatopause be treated? Seminars in Reproductive Endocrinology 17 311–325.


Dörschkind K & Horsman ND 2000 The roles of prolactin, growth hormone, insulin-like growth factor-I, and thyroid hormones in lymphocyte development and function: insights from genetic models of hormone and hormone receptor deficiency. Endocrine Reviews 21 292–312.
stature and in a pseudohypopaldosteronism patient with a mutation in epithelial sodium channel alpha subunit. Journal of Steroid Biochemistry and Molecular Biology 77 49–57.
Li Voon Chong JS, Groves T, Foy P, Wallymahmed ME & MacFarlane IA 2002 Elderly people with hypothalamic-pituitary


Schneider-Rivas S, Rivas-Arancibia S, Vazquez-Pereyra F, Vazquez-Sandoval R & Borgonio-Perez G 1995 Modulation of long-term memory and extinction response induced by growth hormone (GH) and growth hormone releasing hormone (GHRH) in rats. Life Sciences 56 L433–L441.


Thornton PL, Ingrain RL & Sonntag WE 2000 Chronic [-Ala2]-growth hormone-releasing hormone administration attenuates age-related deficits in spatial memory. Journal of Gerontology A: Biological Sciences and Medical Sciences 55 B106–B112.