*Endocrine Facets of Ageing.*
Novartis 242

Print ISBN 0-471-48636-1 Online ISBN 0-470-84654-2

# Effects of growth hormone and insulin-like growth factor 1 deficiency on ageing and longevity

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*Abstract*: Present knowledge on the effects of growth hormone (GH)/insulin-like growth hormone (IGF)1 deficiency on ageing and lifespan are reviewed. Evidence is presented that isolated GH deficiency (IGHD), multiple pituitary hormone deficiencies (MPHD) including GH, as well as primary IGF1 deficiency (GH resistance, Laron syndrome) present signs of early ageing such as thin and wrinkled skin, obesity, hyperglycemia and osteoporosis. These changes do not seem to affect the lifespan, as patients reach old age. Animal models of genetic MPHD (Ames and Snell mice) and GH receptor knockout mice (primary IGF1 deficiency) also have a statistically significant higher longevity compared to normal controls. On the contrary, mice transgenic for GH and acromegalic patients secreting large amounts of GH have premature death. In conclusion longstanding GH/IGF1 deficiency affects several parameters of the ageing process without impairing lifespan, and as shown in animal models prolongs longevity. In contrast high GH/IGF1 levels accelerate death.

*2002 Endocrine facets of ageing. Wiley, Chichester (Novartis Foundation Symposium 242) p 125–142*

In contrast to growth and development, ageing is a progressive process orchestrated by decreasing synthesis and secretion of numerous factors and hormones; among them growth hormone (GH) and its anabolic effector hormone, insulin-like growth factor 1 (IGF1). Therefore, ageing is often compared with growth hormone deficiency (GHD) (Toogood & Shalet 1998). This assumption is based on the evidence that pituitary GH secretion and serum IGF1 concentrations decline with increasing age (Gil-Ad et al 1984, Arvat et al 2000), reaching low levels in late adulthood, and have similarities to changes of body appearance, composition and function (Carroll et al 1998, Toogood & Shalet 1998) (Table 1). These findings led to trials of GH treatment in elderly people (Rudman et al 1990). The finding that GH increased lean body mass, decreased adiposity and improved apparent skin changes gave birth to an

**TABLE 1 Similarities between GH deficiency and ageing**

| |
|---|
| Thinning of skin (wrinkling) |
| Excess adipose tissue (obesity) |
| Rise in insulin resistance (tendency for diabetes) |
| Decline in $\beta$ cell function |
| Reduced lean body (muscle) mass |
| Reduced physical performance |
| Reduced mineral density (osteoporosis) |
| Lowered venous access |
| — — — — — — — — — — — — |
| Rise in serum cholesterol |

approved (Butterfield et al 1997) and non-approved administration of GH to ageing people, at 'so-called' rejuvenation clinics. These medical acts were reinforced by reports that GH deficiency increases the risk for cardiovascular disease (Rosén et al 1993) and leads to premature mortality (Rosén & Bengtsson 1990).

In order to analyse the present knowledge on the possible role of GH and IGF1 in ageing and lifespan, this paper reviews states of congenital (i.e. primary) GH and/or IGF1 deficiency in humans and animals. Attention is paid as to whether patients or animals with GH/IGF1 deficiency present early signs of ageing and effects on the duration of their lifespan.

## Congenital isolated GH deficiency (IGHD)

Previously called idiopathic GHD, modern laboratory technology has shown that this state can be caused by molecular defects of the GH releasing hormone (GHRH) gene or receptor, or the hGH gene (Laron 2001). These patients are presently diagnosed at an early age and treated with the unlimited amounts of available biosynthetic hGH. Therefore, there is little information on studies of adult patients with isolated GH deficiency (IGHD). In 1969 Merimee and colleagues reported 31 patients with hereditary IGHD, whose age ranged from 13–78 years (Merimee et al 1969). Among the clinical descriptions Merimee & Laron (1996) wrote that wrinkling of the skin often began early in life and these patients consequently looked prematurely old (Table 2). Ten out of 13 males and 9 of 18 females had wrinkled skin. Rimoin et al (1966) performed skin biopsies and found decreased soluble collagen in the dermis of two thirds of these patients. The histological changes found were probably the underlying cause of thinning and

**TABLE 2 Clinical characteristics of adult patients with untreated IGHD**

| *n = 31* | *13 males* | *18 females* |
|---|---|---|
| Age (years) | | 13–78 |
| Height (cm) | | 110–140 |
| Wrinkled skin | 10 | 9 |
| High pitched voice | 12 | 5 |

Based on data from Merimee & Laron (1996).

wrinkling of the skin, characteristic of GH/IGF1 deficiency, and these in turn are caused by the lack of anabolic effect on collagen and hydroxyproline of these hormones. The only other histological data on the skin have been obtained by Abramovici et al (1983) who studied the skin biopsies of 35 children and adolescents including 18 with IGHD. These latter investigators found that patients with IGHD lack elastic fibres in the skin papillary layer and an uneven distribution of elastic fibres in the reticular layer.

## Congenital multiple pituitary hormone deficiencies (MPHD) including growth hormone

In 1988, we had the opportunity to examine six out of 10 living dwarfed patients, part of 24 related patients recorded on the island of Krk in the Adriatic Sea. They belong to two villages near to each other, and were known to have existed since the end of the 19th century (Hanhart 1925). DNA from these patients revealed a mutation in the *PROP1* gene (a transcription factor) causing MPHD (thyroid-stimulating hormone, prolactin, luteinizing hormone, follicle-stimulating hormone and GH deficiencies) (Krzisnik et al 1999). They were treated by thyroxine, which some took irregularly. Only one 14 year old girl received GH. The five adult patients ranged from 47 to 68 years (3 males, 2 females). In addition to short stature (120–139 cm), they were obese, sexually immature and had a very wrinkled skin (Fig. 1). Notably the patients did not have any grey hair despite their advanced adult age. This was also seen on a picture of a 70 year old patient found on his tombstone (Fig 2). The information obtained for four deceased patients revealed that they had died at ages 68, 77, 83 and 91.

## Laron syndrome (primary GH resistance)

The following describes adult patients with primary IGF1 deficiency due to primary GH resistance or insensitivity (i.e. Laron syndrome). In 1966 and in 1968 our group described a new hereditary syndrome resembling IGHD, but

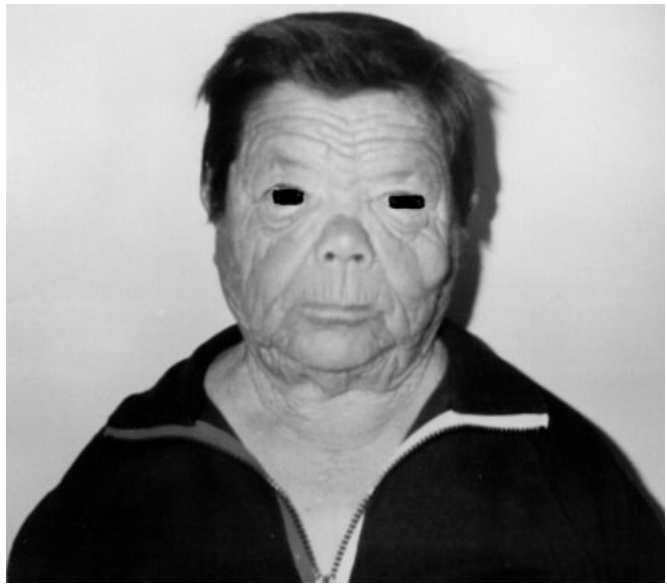

FIG. 1. Appearance of a 58 year old patient with GH deficiency due to a *PROP1* gene mutation. Note wrinkled and loose skin.

FIG. 2. Appearance of a 70 year old patient with GH deficiency due to a *PROP1* mutation. Note absence of grey hair and loose skin. For details see text. Reproduced with permission from Krzisnik et al (1999).

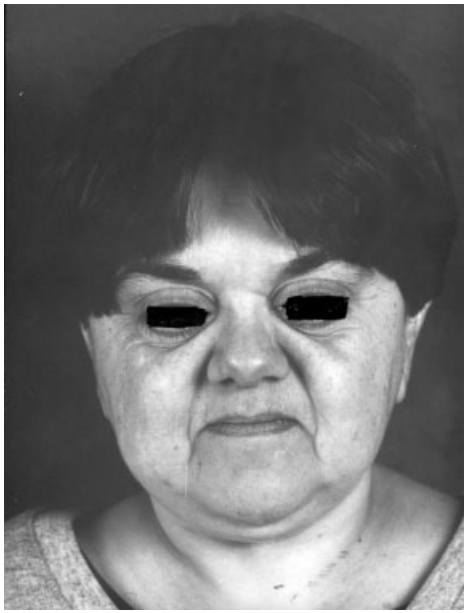

FIG. 3. Early ageing appearance of a 39 year old female with Laron syndrome.

with very high serum hGH levels (Laron et al 1968). Since then we have been following in Israel a cohort of 51 patients from infancy to adulthood (Laron 1999a, Laron & Parks 1993). Since the first description several hundred patients, or their descendants, have been described with Laron syndrome, mainly in Mediterranean and Mid-Eastern populations (Rosenfeld et al 1994, Laron 1999a). This syndrome is caused by deletions or mutations in the GH receptor or postreceptor pathways (Godowski et al 1989, Amselem et al 1996, Laron 1999a, 1999b), leading to an inability by the liver and possible other tissues to generate IGF1 (Laron et al 1971), the anabolic effector hormone of GH (Laron 1999c). Studying adult patients with Laron syndrome (Laron & Klinger 1993, 1994, Laron 1999b) we observed that these patients remain very short (females, 108–136 cm; males, 119–142 cm; adult height), have an early ageing appearance (such as a wrinkled face at an early adult age; Fig. 3), and relatively thin skin on their hands. Abramovici et al (1983) performed skin biopsies in six children and late adolescents and found that patients with Laron syndrome had bundles of thickened elastic fibres in the upper dermis.

Even young adult patients presenting with Laron syndrome develop marked general and visceral obesity (Fig. 4), high cholesterol levels (Laron & Klinger 1993), reduced muscular strength (Brat et al 1997), insulin resistance (Laron et al

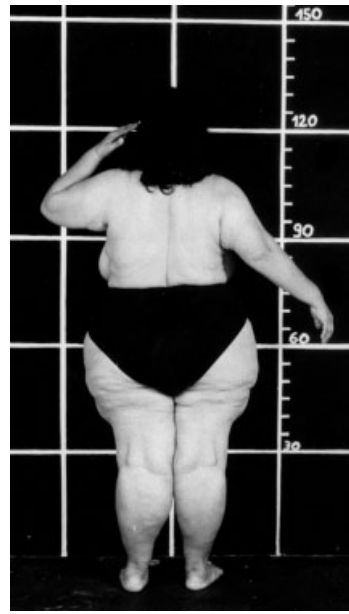


FIG. 4. Marked obesity in a 41 year old female with Laron syndrome.

1997), osteoporosis (Laron & Klinger 1994), and/or suffer from psychological deficiencies (Galatzer et al 1993), all features characteristic for normal ageing and usually apparent at a later age. The oldest patient followed by us is a 73 year old male; one lady examined by us only once and suspected (but not proven) to have Laron syndrome died at age 53. She had suffered from asthma and coronary heart disease (Laron 1999b). Also, adult patients in the large Ecuadorian cohort of Laron syndrome patients have been reported to have reached ages of 70 years or more (Rosenbloom et al 1999). It is of note that with one exception none of our adult patients has grey hair. However, they have a tendency for baldness (in males) and thin hair (in females) (Laron et al 2001).

In conclusion, the relatively small number of adult patients with IGHD or MPHD never previously treated with GH, as well as patients with primary IGF1 deficiency (Laron syndrome) not treated by IGF1, show a series of early developing characteristics compatible with ageing such as thinning and wrinkling of skin, obesity, muscle weakness, osteoporosis and hyperlipidermia.

In contradistinction to the postulation of Rosén & Bengtsson (1990) that hypopituitary patients have premature mortality due to cardiovascular disease (Rosén et al 1993), the patients with GH and IGF1 deficiency live a long life, despite the signs of early ageing. One big difference between our patients and

those reported by Rosén et al (Rosén & Bengtsson 1990, Rosén et al 1993) is that almost all of those reported by Rosén and colleagues had tumours, mostly pituitary adenomas, and were treated either by surgery or irradiation; all were MPHD and received a combination of hormone replacement treatments with the exception of GH. Therefore, those patients cannot be compared to the patients with IGHD and/or IGF1 deficiency, and the statement that GH or IGF1 deficiency shortens the lifespan seems incorrect.

A review of animal studies using models of GH or IGF1 deficiency also revealed that the lifespan in these animals is prolonged compared to intact animals.

## Ageing and lifespan in GH/IGF1-deficient mice

Several mouse models with GH/IGF1 deficiency are available to study the influence of these hormones on ageing and longevity (lifespan). Due to the IGF1 deficiency all homozygous affected mice are dwarfed and they divide as the human models into MPHD including GH (e.g. the Ames dwarf mice and the Snell dwarf mice) and primary IGF1 deficiency (the Laron mouse).

### *The Ames dwarf mice (df/df)*

These mice first described by Schaible & Gowen (1961) have a mutation in a transcription factor for all anterior pituitary hormones (GH, prolactin, thyroid-stimulating hormone and sex hormones) called Prophet of Pit.1 (Prop-1) (Sornson et al 1996), which is located on chromosome 11. Homozygous mice for the df/df mutation are dwarfed, and have a longer life span than control animals, which is not related to caloric intake or the reduced body temperature (Bartke 1998).

### *Snell dwarf mice (dw/dw)*

Described in 1929 this type of dwarfed mouse has been subsequently shown to be caused by a mutation of the transcription factor Pit-1 (Li et al 1990) which is involved in the differentiation of somatotrophs, lactotrophs and thyrotrophs (Sornson et al 1996). Phenotypically, the Ames and Snell dwarfed mice are very similar with the exception that in Snell mice the gonadal development is more advanced.

Snell mice have extremely low serum levels of IGF1 (van Buul Offers et al 1986). They have also been described to have delayed ageing and a longer lifespan than normal animals from the same strain (Bartke 2000).

The ageing symptoms of these two types of MPHD mice are their retarded sexual development, reduced activity (not in all), progressive obesity and hair

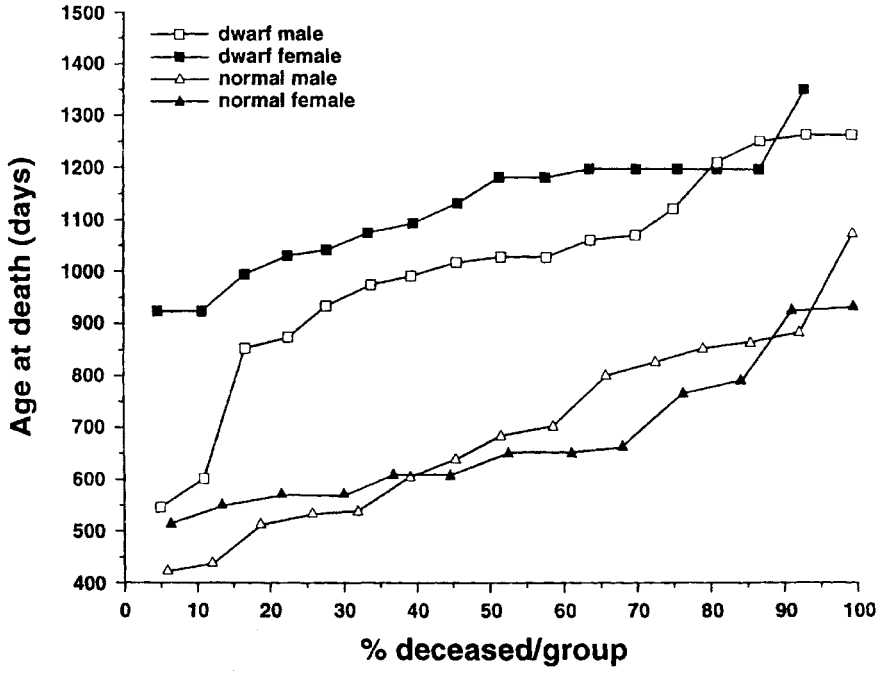


FIG. 5. Increased longevity in Ames dwarfed mice compared to normal controls of the same breed. Reproduced with permission from Bartke (2000).

loss (in part of the animals). Nevertheless, these animals appear to remain in excellent general condition for longer periods than their normal siblings (Bartke 2000). A group of Ames dwarfed mice outlived a control group of normal mice by more than one year (Bartke 2000) (Fig. 5). This extension of lifespan was longer in female mice.

*The GH receptor/BP gene-disrupted mice (the Laron mouse)*

A model of isolated IGF1 deficiency was created by disrupting the GH receptor (GHR) gene in mice (Zhou et al 1997). This model bears many similarities to the human primary GH resistance (GH insensitivity, i.e. Laron syndrome) (Kopchick & Laron 1999), such as high GH and low IGF1 and IGF binding protein (IGFBP)3 levels, dwarfism and organomicria, typical characteristics of Laron syndrome (Laron 1999b). Calculating average lifespans for each genotype (+/+, +/−, −/−) and gender, we observed that the homozygous mice for the GHR mutation had a significantly longer lifespan than the unaffected and heterozygote mice (Coschigano et al 2000) (Table 3).

**TABLE 3 Lifespan of GHR/BP gene-disrupted mice**

| *Gender* | *Genotype* | *n* | *Lifespan (days)** |
|---|---|---|---|
| Males | +/+ | 7 | $629 \pm 72$ |
| | +/− | 8 | $668 \pm 51$ |
| | −/− | 7 | $975 \pm 106$[a] |
| Females | +/+ | 13 | $749 \pm 41$ |
| | +/− | 19 | $701 \pm 36$ |
| | −/− | 11 | $1031 \pm 41$[b] |

*Mean SE.
[a]$P < 0.02$ compared to +/+.
[b]$P < 0.005$ compared to +/+.
Reproduced with permission from Coschigano et al (2000).

*GH transgenic mice*

In contrast to the previously described observations, prolonged elevation of serum GH, as occurs in GH transgenic mice, is associated with a reduced lifespan (Bartke 1998), which may reach half of that in normal mice of the same species. This is similar to findings in patients with acromegaly. Thus, the question arises whether high levels of GH increase mortality. In effect, treatment of rats with high doses of GH accelerates the death of the animals (Groesbeck et al 1987). Although the conditions may be different, one should remember that GH treatment of chronically ill patients in intensive care units was also found to increase mortality (Takala et al 1999).

At present it is not clear how GH/IGF1 deficiency prolongs the lifespan in mice. It is possible that certain genes are involved. Mutations of a recently described insulin receptor like-gene, *Daf2*, result in increased longevity (Kimura et al 1997). This receptor, possibly homologous to the mammalian IGF1 receptor, mimics primary IGF1 deficiency. Nor do we fully understand how GH excess shortens the lifespan. This may be partly due to the water and electrolyte retention induced by GH/IGF1 and/or by the well-documented cardiotrophic effects of these hormones.

Although it may sound anecdotal it should be mentioned that there is evidence that within species, lifespan is negatively correlated with body size. Thus dogs from small breeds live longer than dogs from large breeds and small mice live longer than large mice (Bartke 2000). Last but not least, food-restricted animals (which are smaller), live longer than those fed *ad libitum* (Masoro 1992), with the exception of Ames and Snell mice.

## The premature ageing syndromes

It was of interest to find out whether the rare genetic disorders known as premature ageing syndromes (Pesce & Rothe 1996) are related to a disorder in the secretion of GH or IGF1. All are characterized by marked growth retardation associated with early and fast ageing, various dermal changes (wrinkling, loose skin), hypotrichosis and early greying of the hair, and early death mostly by heart attacks due to atherosclerosis or congestive heart failure.

### *Progeria (Hutchinson–Gilford disease)*

First described in 1886 by Hutchinson, the incidence is estimated at 1 per million live births. The syndrome is characterized by increased hyaluronic acid excretion. We found only one report by Villee et al (1969) who studied two boys with classical progeria and found lack of GH response to insulin-induced hypoglycemia.

### *Werner's syndrome (adult progeria)*

First described in 1904 this disease is clinically characterized by short stature, skin changes (soft tissue wasting ulcerated hyperkeratosis, pigmentation) fine hair and alopecia; early greying of hair and a tendency to malignancies and insulin-resistant diabetes. There is only one report on GH deficiency in Werner syndrome (Rubin & Reed 1996).

### *Cockayne's syndrome*

Reported in 1936 and 1946 by Cockayne, it is characterized by dwarfism associated with retinal atrophy and deafness as well as skin atrophy. Endocrine function in a group of patients revealed normal GH response to stimulation tests in eight patients, decreased response in four, and an exaggerated response in three children (Nance & Berry 1992).

### *Bloom syndrome*

Bloom syndrome is a rare autosomal recessive disorder characterized by growth deficiency, skin changes, photosensitivity, variable degrees of immunodeficiency, predisposition to malignancies, type 2 diabetes and early death. It is caused by mutations in the gene BLM. Growth retardation is a major characteristic of Bloom syndrome but GH deficiency has so far not been documented.

*Rothmund–Thomson syndrome*

This disease first described in 1986 is a rare autosomal recessive disorder characterized by short stature, skin changes (consisting of atrophy and telangiectasis) and hair loss (Kaufmann et al 1986). The skin changes resemble Bloom syndrome. Kaufmann et al (1986) reported GH deficiency in an 11 year old girl when tested by arginine, L-Dopa and GH-releasing hormone (GRF 1–44). No similar reports have come to our attention.

In summary, the finding of only very few patients with GH deficiency among the patients with 'premature ageing syndromes' of genetic origin, the majority of whom have normal pituitary functions, indicates that their accelerated ageing and various complications are not related to GH or IGF1. The rare instances of GH deficiency must be considered coincidental.

## Conclusion

From the clinical and experimental studies reviewed it ensues that longstanding GH/IGF1 deficiency of genetic origin does not shorten lifespan. On the contrary, it may prolong it, as is clearly evident from animal models. This occurs simultaneously with the development of some characteristic changes of early ageing (thinning of skin, wrinkling, obesity, reduction in lean body mass) but arrest of other signs, such as greying of hair. It has also been shown that high levels of GH accelerate death. How exactly GH and IGF1 affect the ageing process and duration of life remains to be established.

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## DISCUSSION

*Shalet:* Just a point of fact. Elderly patients with pituitary disease are very different in their GH secretion when compared with age-matched controls. Just

to equate a so-called somatopause with pituitary tumour patients that have organic GH deficiency is incorrect. The difference in the 24 h profile is some 90%. The patients with pituitary tumours and organic GH deficiency have a GH reduction of 90%, mainly consisting of a decrease in the amplitude of the GH pulse. This needs to be stated up-front.

I was surprised at the way you were pushing us at the end into thinking it is better to be IGF1 and GH deficient. I find that puzzling for a man who has spent so many years of his life fighting to get IGF1 replacement for patients with GH insensitivity. It is a curious contradiction in terms of your policy. Does this mean that you will no longer replace GH and IGF1 in children who are GH-deficient or insensitive, respectively, for fear of reducing their potential life expectancy?

*Laron:* You don't have to exaggerate. If you have muscle weakness, short stature and osteoporosis, this should be treated. What I wanted to point out is the following. (a) The general statement that hyperpituitarism reduces the lifespan is not true, unless you analyse the precise nature of the hyperpituitarism. (b) Too much GH is dangerous. We should learn how to administer GH replacement in order to prevent its negative effects. I am not saying we shouldn't treat true GH/IGF1 deficiency. However, the dose one should use in ageing adults is still controversial.

*Giustina:* I have a couple of points. The parallelism between greying hair and longevity is not proven. I am not sure there are data showing that people with no grey hair live longer. Moreover, acromegalic patients do not have very early greying of hair. This fact raises some doubts in the relationship with GH. When you quote the data from Rosén and Bengtsson on lifespan, if you look at the real data, there is no big difference between control and population studies. This means that when you study a very small population such as yours, and say that lifespan is not reduced, statistically this is not correct. This is because GH-deficient subjects do not die at a very young age. However, they have been proven to have a reduced lifespan with respect to a comparable population in the same country in the same registry. If you want to demonstrate what you are saying you need to look at the comparable population in your territory and see whether on a statistical basis there is a reduction or not in lifespan. Otherwise, what you are saying is that these people may sometimes live long and sometimes not. This is a descriptive concept that has to be proven on a statistical basis.

*Laron:* One thing is clear. The animal models with isolated IGF1 deficiency or multiple hormone deficiency, including GH, live longer. In humans, having 'congenital GH or IGF1 deficiency' does not shorten the lifespan, as stated by Rosén & Bengtsson (1990). The population they studied were patients after operation or irradiation for pituitary tumours.

*Giustina:* But you didn't prove it.

*Laron:* Their statements have been cited in many papers and even textbooks.

*Giustina:* You need to prove that in your control population in that territory, the lifespan is the same. Otherwise you are not proving the concept. You are just describing the fact that some of the patients may live a long time. There is no statistical evidence supporting your concept.

*Laron:* With regard to cancer and IGF1, there was a meeting in Halle in September 2000 which had a clear message. People genetically susceptible to cancer are very susceptible to IGF1, as they are to sex hormones. In those who are not genetically susceptible, IGF1 does not induce cancer.

*Monson:* Concerning the comparison of different populations, the Lund series (Bülow et al 1997) and the Gothenburg series (Rosén & Bengtsson 1990) examined patients from the mid-1950s, when the concept of lipid lowering and healthy lifestyle was less defined. So these were observational, epidemiological studies in patients who by current standards may have had suboptimal care. We are superimposing on that background a group of patients who by virtue of small size may not have sufficient power to show a difference in mortality, and who also by virtue of one's interest in their clinical problem, are likely to have had more interventions. It is therefore very difficult to be certain that lifespan is reduced.

We talk about the Lund study and the Gothenberg study as demonstrating increased mortality related to GH deficiency, but these patients were predominantly pan hypopituitary. This is a demonstration of increased mortality in hypopituitary populations, who may have had variable quality of cortisol replacement. We know that GH deficiency itself alters the relationship between cortisol and cortisone conversion. This is likely to be accentuated in hepatocytes and adipocytes. Arterial intima–media thickness is increased in hypopituitary patients and this is partially reversed by GH replacement. Nonetheless, we should be wary about concluding that GH of itself has any true impact on atherogenesis and that there is reversibility in terms of GH replacement. Having said this, I agree with you that the animal data are extremely compelling in terms of the effect of GH and IGF1 on longevity.

*Handelsman:* I would add that in several of those studies they did not have adequate reproductive hormone replacement, either.

*Laron:* In view of the alleged neuroprotective and neurotrophic actions of IGF, in people with Laron syndrome there is a decline in the central nervous system (CNS) function and when they are treated with IGF there is amelioration, as observed in the treated children. We have not treated adults long enough, but we have recently found, by MRI, changes in the brains of IGF1-deficient adult patients, and no defect whatsoever in patients treated from childhood onwards. The longest treatment in paediatric patients is 10 years. It is difficult to compare adults with children, but judging by the size of the head (which indicates brain growth; Laron et al 1992) and by psychological tests (Galatzer et al 1993), the

intrauterine and perinatal IGF1 is of great importance for its neurotrophic effect. This seems to be preventable by treatment.

*Riggs:* Are individuals with congenital IGF1 or GH deficiency truly susceptible to osteoporosis? Outside of the bone field it is not always appreciated that what is measured by dual-energy X-ray absorptiometry (DEXA) is areal bone density and not volumetric density. There will be a built in error if you have small bones. It is possible to correct this through formulae. It would be interesting to see whether you could do this. I guess the compelling question is, is there enough follow-up on these patients with regard to whether or not they develop vertebral fractures?

*Laron:* There aren't vertebral fractures, but there is cervical stenosis which develops in adulthood. In children who have been treated for a long time we don't see these changes. We know that IGF1 is an anabolic hormone that influences the connective tissue. I wish to mention one more important issue that relates to GH or IGF replacement therapy, namely quality of life. This is a difficult subject to study.

*Shalet:* Adults with childhood-onset GH deficiency are as a group significantly osteopaenic. Middle-aged subjects with adult-onset GH-deficiency are also osteopaenic, but less so. The elderly-onset GH-deficient patients are not significantly different in terms of bone mineral density measurements from age-matched controls.

*Monson:* Should we really be using the term osteoporosis in relation to childhood-onset GH deficiency? Isn't this a peak bone mass issue?

*Riggs:* Osteoporosis can arise from lack of developing optimal peak bone mass. But the point is that even though DEXA is universally used, it is not widely appreciated that if the size of the bone is different from normal, the normative values are not useful.

*Monson:* I was thinking about structure, also. A similar bone mineral density deficit in a child that has failed to reach peak bone mass, compared with a 60 year old with hypopituitarism, will be associated with quite different bone morphology in terms of what will have happened to the struts.

*Riggs:* That is correct.

*Ruiz-Torres:* From a gerontological point of view, there are two contradictory facts that are apparent. On the one hand, GH deficiency is not related to short life. Furthermore, there are experiments, such as those of A. V. Everitt in Australia, which show that hypophysectomy has lifespan-prolonging effects similar to those of dietary restriction. On the other hand, the opposite point is that well being is related to GH concentration, as we have seen in healthy people in agreement with your GH deficiency results.

*Laron:* Patients with Laron syndrome are short and have reduced muscle mass, which contributes to the development of osteoporosis. They are hindered in normal life to varying degrees. These patients also have varying deficits in mental

abilities. They should be diagnosed prenatally, and ideally start treatment prenatally — and certainly no later than at birth.

*Veldhuis:* Do they tend to have a slightly low core body temperature? We heard yesterday how fasting tends to reduce mean core temperature. Does anyone know whether the mice deficient in mitochondrial uncoupling protein are also thermogenic? This would test the theory of thermogenesis, which is painfully broad.

*Handelsman:* To avoid therapeutic nihilism about the use of GH, what about using IGF1 as a way of dose titration? How important is this?

*Laron:* It is used as a marker for acromegaly. We use IGF1 as a marker for testing whether the dose of IGF1 is sufficient.

*Shalet:* Remember that 50% of middle-aged hypopit patients start with a normal IGF1 level. In adult patients we keep the IGF1 between −2 and +2 SDs. We don't give them supraphysiological doses of GH because we would then exceed the IGF1 SD score of +2. Clearly, at the other end, for a patent starting with a low IGF1 level, monitoring the IGF1 level helps assess compliance. Otherwise, in terms of optimizing GH replacement therapy, IGF1 SD score doesn't really help.

*Laron:* There is debate concerning whether one has to look at both IGF1 and also IGF binding protein 3. The consensus now is that IGF1 suffices, and only in early infancy when IGF1 is low should IGFBP3 be measured.

*Elahi:* I have reviewed the literature and been unable to find a consistent number for what is considered a low IGF1 at any age. Professor Shalet, what number do you use? We use $\leqslant 135$ pg/mol as our low value.

*Shalet:* There is no number. We have a service provided by a pharmaceutical company that makes the GH. Our patients are in an international surveillance program. We take blood, the sample is sent off to that particular lab and they have normative data that are decade based and gender based, and they then issue a standard deviation score that takes into account the normal age-matched value.

*Haus:* The circadian peak in plasma GH decreases in the elderly and some suggestions have been made that the functional state of elderly subjects could be improved by GH substitution. This clearly is not supported by Professor Laron's observation on the life expectancy of subjects with genetic and/or acquired conditions of habitually high or low GH concentrations. In this context, an observation on the correlation of the circadian means and amplitudes in plasma GH concentrations with the functional state of the subjects may be of interest. Comparing the circadian mean and amplitude of plasma GH (obtained in 279 profiles in 149 subjects, 77 8 years of age with 6 measurements over a 24 h span) with the functional state of the subjects as evaluated by the Index of Independence in Activities of Daily Living (ADL, Katz) and the Mental Status Index (MSI) we found a statistically significant positive correlation of the growth hormone levels

and amplitudes with functional impairment rather than with functional capacity (Haus et al 1989).

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