REVIEW

"Anything you can do, I can do bigger?": the ethics and equity of growth hormone for small normal children

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This paper argues against the use of growth hormone (GH) for small normal children ("idiopathic" short stature) with the following considerations: ethical (philosophical) grounds, cost-economic implications, and the rationale for treating normal physiological variation with a potent pharmacological agent. The author would prefer to see health and economic resources being directed to correct nutritional and environmental deprivation among underprivileged groups in preference to providing GH injections for small normal children.

My objection to the use of GH in small normal children is based on four Es (endocrine, ethical, economic, and equity), on a profound philosophical objection to treating "normality", and on a rejection of the psychological arguments regarding smallness. Acceptance of one's height is part of being in harmony with one's self. Final adult height is the end-point of many physiological factors including familial genetic potential, racial origin, socioeconomic group, nutritional status, gender, and hormonal actions (GH, thyroxine, androgens, oestrogens, etc).

ENDOCRINE (PHYSIOLOGICAL)

Height in any population is distributed in a normal fashion, and is shown as the classical bell shaped or Gaussian curve (fig 1). We arbitrarily define below the third centile as small, recognising that most children below this line are "small normals". It is worth reiterating that:

- The 3rd centile includes 3% of children. Most children in this group are small because of genetic, racial, social, and nutritional factors.
- -3 SD below the mean includes 0.1% of children. Most children in this group have "pathological" short stature with a clinical diagnosis.
- -2.25 SD below the mean (the US indication for use of GH) includes 1.2% of the population.

The year 2005 was the 20th anniversary of the introduction of recombinant human growth hormone (GH), making available a safe, reliable, and efficacious preparation of GH for children with GH deficiency. The indications for GH have widened over the past 20 years and it is now licensed for use in Turner syndrome, Prader-Willi syndrome, chronic renal failure, and short stature in children who are small for gestational age.¹ In 2003 the FDA licensed GH for use in US children with "idiopathic" short stature,² generating a lively debate.³⁻⁵ It seems likely that a similar application will be made in the European Union (EU).

There is no doubt that GH will make small children, no matter what the aetiology of their smallness, bigger.⁶ Indeed it has been stated that "a rock will grow if one gives it enough GH".⁷ A recent EU multicentre study from 10 countries enrolled 239 children to receive two GH dose regimes with a planned follow up to final height.⁸ A height gain of 5-7 cm was found but curiously only 50 children finished the course, with a high dropout rate recorded for a variety of reasons.

Most paediatricians entered their particular profession of medicine in order to make children better. But does making small normal children bigger also make them better? That is the fundamental and simplistic question underpinning the use of GH in "idiopathic" short stature. Some simple truisms about growth are worth stating. Most children, especially boys, would like to be bigger than they are. Being bigger is perceived as being stronger, better, more successful. Tallness often leads to success in sports. Conversely is short stature a disability? Is short stature psychologically damaging? What is the evidence for the hypothesis that "bigger is better"? Do any of the studies show that making children bigger makes them psychologically happier?

The terminology used is important. The terms "small normal child", "short, otherwise normal children", "normal variant short stature", "familial short stature", and "constitutional growth delay" have traditionally been used to describe small children who, following appropriate auxology, physical examination, height chart interpretation, height velocity analysis, and clinical investigation have been found to have no apparent abnormality. These children do not have demonstrable growth hormone deficiency or end-organ growth hormone resistance. The term "idiopathic" short stature is a relatively recent concoction (which I could not find in the index of any of the large standard paediatric texts, UK or US) which seems to imply that these children may have some endocrine disorder not yet appreciated.

However one defines height, there will always be small normals. However big a population grows, or its mean height increases, there will always be 1% of children who will be eligible to receive GH if the EU follows the FDA's recommendation. The availability of a growth enhancing tool does not imply a responsibility to use it.

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Figure 1 Normal Gaussian curve for height distribution. Relation between centiles and standard deviations.

ETHICAL (PHILOSOPHICAL)

The traditional pillars of ethics are beneficence (do good), non-maleficence (don't harm), autonomy (freedom of will), and justice. Does giving GH to normal children conform to the norms of good, ethical clinical practice? Table 1 attempts to list the potential goods and possible harms of GH.

GH is usually a safe and efficacious intervention. Side effects, though infrequent, are real and potentially serious. The EU study⁸ showed a 1.3% discontinuation rate because of adverse effects. The major practical difficulty with GH is the need for hundreds to thousands (depending on duration of GH therapy) of subcutaneous injections or "gun therapies". Reduced insulin insensitivity and the emergence of diabetes mellitus on GH remain unquantifiable concerns from the available studies.⁹

There is undoubtedly a considerable amount of pain, inconvenience, and difficulty for any child self administering hundreds, or more likely, thousands of subcutaneous or intramuscular GH injections over a number of years. Are children of 8–12 years (the most likely "target" group) capable of understanding the implications, potential complications, and duration of GH therapy? Who should decide on informed consent—parents, doctors, society? Are the available studies of sufficient rigour and evidence base to permit GH use on children with no demonstrable pathology? How informed was informed consent in the trials submitted to the FDA? Were the studies free of conflicting interests?

One needs to demand the highest standards of ethical practice and clinical safety when treating children with no biological disorder with GH for several years. Parents consulting paediatricians about their short children seek information, medical evaluation as to possible causation, and correction of smallness where possible. While parents will usually accept the explanation of "small normal", their sympathy for the child and wish to make their child better (and bigger), may make them highly vulnerable to persuasion to try GH. Idealistically, one could argue that there should be no harm, definite good, and absolute autonomy

before any decision is made to start a "small normal" child on GH.

All the studies on GH have been sponsored by pharmaceutical companies with all of the inherent problems of such arrangements. None of the GH studies has understandably included a placebo group (receiving sterile water injections for years would be ethically difficult to justify). None has included a nutritionally supplemented comparison group.

Pharmaceutical companies seek to expand the indications for using GH in small children of diverse aetiologies. Paediatricians need to be conscious of their primary Hippocratic philosophies of firstly to do good and secondly to avoid doing harm. Making children bigger seems to be a good thing to do—but does it cure anything? Paediatricians are aware that education on GH issues is appropriate, but promotion, persuasion, and subtle coercion can be closely allied when all the information is delivered by the pharmaceutical industry. Concerns have been expressed in the USA at the manner in which the FDA was persuaded to licence GH for "idiopathic" short stature.

Parents of small children wish to receive informed, objective, professional, and child sensitive advice on indications for GH. Good clinical practice demands that paediatricians be as objective, evidential, ethical, and child focused as possible in deciding when or where to use GH, and most especially in small normal children whose only "abnormality" is to be at the lower end of what is arbitrarily defined as "normal".

All the information and physician education on GH use is likely to emanate from the pharmaceutical industry. Paediatricians need to be conscious of their independence and objectivity before accepting invitations to sponsored GH meetings and to critically question the studies, analyses, and conclusions drawn from small studies by committed investigators.

Is a height gain of 5 cm worth 1500 injections and an expenditure of approximately €50 000?

ECONOMICAL (COST BENEFIT)

GH is expensive.^{3 10} The estimated annual cost will depend on dose, frequency, and the proprietary preparation used. To treat a 50 kg, 10 year old boy with 1.5 mg GH daily would cost approximately €15 000 per annum. Making GH available to "small normals" makes GH subject to market forces. In the USA the cost of GH is paid for by private individuals or by insurers. In the EU the cost of GH is usually met by the Health Service, which is supported by income tax or by insurance levies.

- Annual cost of GH: €10–15 000
- Total cost of GH course (over 5–6 years): €50–75 000
- Additional height gained: 5–7 cm
- Cost per incremental cm: €10 000.

The current estimated EU population is approximately 450 million, including 100 million children. If one accepts the US precedent, some 1 million EU children would be eligible to receive GH. While it is highly unlikely that this number would receive GH, the potential costs of GH are enormous and, in theory, indefinite. The US definition of eligibility for GH would create a limitless market for GH since the smallest 1% of population will always fulfil the criteria for use of GH.

EQUITY (JUSTICE)

Is the prescription of GH for "small normals" an equitable and just use of health funds and resources? Many commentators would argue that economic poverty and nutritional inadequacies are a much more important cause of short stature than GH deficiency.¹¹ None of the studies of GH in

Table 1 Benefits and possible harms of GH

Benefits	Possible harms
Increased height 5–7 cm	Hundreds/thousands of injections
Psychological benefit?	Benign intracranial hypertension
Improved athletic performance	Slipped upper femoral epiphysis
	Reduced insulin insensitivity (diabetes mellitus?)
	Risk of leukaemia (data very inconclusive)
	As yet unknown biological effects?

"idiopathic" short stature includes a nutritionally supplemented comparison group. It is probably easier for doctors to prescribe GH for small normals than to initiate nutritional supplemental programmes for the underprivileged. Cogent and compelling arguments can be made for such programmes. It is known that higher socioeconomic groups are appreciably taller than lower socioeconomic groups. A UK study¹² showed differences of 4.5 cm for boys and 4.1 cm for girls. Similar differences have been reported from Poland and Sweden.¹³

It is not widely appreciated that 2 year old toddlers have achieved half of completed adult height. Early growth is largely driven by nutrition. The Dutch are now the tallest people in Europe, if not in the world. They attribute enhanced growth to early nutritional programmes, to child health initiatives, and to distribution of wealth across social groups.

DISCUSSION

GH was introduced to the paediatric market as a physiological replacement therapy for children with GH deficiency. We are now entering an era where it is being promoted as a pharmacological agent to enhance growth in a wide variety of conditions.¹⁻¹⁰ While many paediatricians would be empathetic to treating "pathological" (extreme) short stature, most would not want to treat "physiological" short stature with GH. Starting with the assumption that a normal small child is abnormal cannot be justified philosophically, ethically, or socioeconomically. The fundamental principle underlying paediatric practice is "in the best interest of the child". It is not in the interest of children to prescribe a painful, protracted, expensive, potent medication (of which they are not deficient) for a problem which is as much perception as reality.

Better by far to reassure of normality and leave alone. Among the small and successful celebrities one can cite Bono (U2), Tom Cruise, Brad Pitt, Kylie Minogue, and Gerry Halliwell. Who can define how big is big enough? Who can say with certainty when smallness becomes a disability? I have always been fond of the simple wisdom contained in this little poem:

I met a little Elfman once
Down where the lilies blow
I asked him why he was so small
And why he did not grow.
He slightly frowned and with his eyes
He looked me through and through
"I'm big enough for me" he said
"As you are big for you". (JK Bangs)

Many studies, particularly those of Voss *et al* have argued that individuals with short stature are largely indistinguishable from their peers, whether in childhood, adolescence, or adulthood.¹⁴⁻¹⁵ A *BMJ* editorial¹⁶ stated that the use of GH to increase the height of children who are of normal height should be considered abuse. A Dutch group¹⁷ suggested that the prevention of psychological and social problems attributed to short stature (and not merely enhancement of growth) should be the ultimate goal of medical treatment and research. Available evidence does not show that GH improves social adjustment, even when such treatment increases the final height of GH deficient children who have emotional problems.¹⁸ No data exist supporting a psychological benefit to GH therapy in otherwise normal short children.¹⁹

An interesting debate, discussion, and decision analysis was presented in a commentary Allen and Fost,¹⁰ who point

out inconsistencies and irrationality in paediatricians' response to smallness.

Paediatric endocrinologists, paediatricians, parents, and society need to engage in a profound medical, ethical, economic, and practical debate on the future uses of GH. The pharmaceutical industry should not be involved in this debate, for it can produce a limitless supply of GH and its responsibilities lie largely to its shareholders. The industry has a duty to ensure that its products are safe, efficacious, and used appropriately. Profit alone can never justify using GH in children, whatever the indication.

Portuguese are smaller than Swedes, Italians smaller than Danes, and Norwegians taller than Greeks. I assume the EU Commission does not wish to harmonise children's heights across the EU, but rather recognise national norms and international diversity. Northern European tall stature is based on genes, nutrition, economic prosperity, and good social welfare programmes.

The licensing of GH for "small normal children" in the EU will hopefully be resisted by the EMEA. The FDA's approval of GH for "idiopathic" short stature has generated great concern and considerable resistance among endocrinologists in the USA.²⁰

Tanner, the father of British study of growth stated some years ago: "from an ecological point of view, smallness has its advantages. It must not be thought that bigger or faster (growth) is necessarily better".²¹

Competing interests: none declared

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