Growth Hormone (GH) Therapy as a Policy Analogue

Lainie Friedman Ross, MD, PhD
Carolyn and Matthew Bucksbaum Professor of Clinical Ethics
University of Chicago
Topics to be addressed

• The evolution of the clinical application of hGH in children
  – slippery slope
  – therapy and enhancement distinction
  – balancing of risks, benefits and uncertainties of using hGH in a traditionally protected population (children)
  – fairness, equity, and access in treating some “small normal” children with hGH.
History of GH Therapy until 1985

- Importance of the pituitary gland for growth was recognized in the late 19th century
- Although many hormones were made from animals (e.g., insulin) to treat human disorders, GH from animals did not work.
- Human GH (pituitary hGH) was made from human pituitary glands beginning in the late 1950s.
- In 1963, National Pituitary Agency to collect and distribute pituitaries in a logical and sensible manner
  - National Hormone and Pituitary Program (NHPP) funded by Department of Health, Education and Welfare (now Department of Health and Human Services (HHS)).
- 1963-1985: NHPP sent pituitary hGH to 100s of doctors in US.
  - ~7,700 children were treated
- 1985: 3 young men treated with pituitary hGH died of Creutzfeldt-Jakob disease (CJD)
- HHS immediately stops the distribution of the hormone
- [Update: 29 individuals all of whom received treatment prior to 1977—the year NHPP began producing hGH using a new purification step.]
  - Of note, France had 119 reported cases in 1,700 individuals treated and the UK had 75 cases of 1,849 individuals.
History of GH Therapy from 1985-2010

• 1985: A few months after hGH was removed from the market, FDA gave approval for recombinant human GH (rhGH).

• 1985-2010: Clinical trials supported primarily by manufacturers of rhGH to show that rhGH could improve growth rates and height in children without growth hormone deficiency (GHD) but who are short for other reasons.
  – (Huge expansion in the potential market: from treating GHD to treating short stature)
## Table 1. FDA-approved indications for human GH

<table>
<thead>
<tr>
<th>Year of FDA approval£</th>
<th>Indication</th>
<th>Recommended dosesb</th>
</tr>
</thead>
<tbody>
<tr>
<td>1985</td>
<td>GH deficiency</td>
<td>0.16–0.3 mg/kg · wk (up to 0.7 mg/kg · wk approved in pubertal patients)</td>
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<tr>
<td>1993</td>
<td>Chronic renal insufficiency</td>
<td>Up to 0.35 mg/kg · wk until renal transplantation</td>
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<tr>
<td>1996</td>
<td>Turner syndrome</td>
<td>0.33 mg/kg · wk; other approved doses are up to 0.375 or 0.469 mg/kg · wk</td>
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<tr>
<td>1997</td>
<td>Adult GH deficiency</td>
<td>FDA-approved starting dose, schedule for dose increase, and maximum doses vary£</td>
</tr>
<tr>
<td>2000</td>
<td>Prader-Willi syndrome</td>
<td>0.24 mg/kg · wk</td>
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<tr>
<td>2001</td>
<td>Small for gestational age (and failure to manifest catch-up growth by 2–4 yr)</td>
<td>0.33 mg/kg · wk; other approved dose ranges are 0.231–0.469 mg/kg · wk based on initial height and response to treatment and up to 0.48 mg/kg · wk</td>
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<tr>
<td>2003</td>
<td>Idiopathic short stature</td>
<td>Approved doses are up to 0.3 mg/kg · wk, 0.37 mg/kg · wk, and, and 0.47 mg/kg · wk</td>
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<tr>
<td>2003</td>
<td>Short bowel syndrome in patients receiving specialized nutritional support (no pediatric studies when approved)</td>
<td>0.1 mg/kg · d (0.7 mg/kg · wk), up to a maximum of 8 mg/d; administration for more than 4 wk was noted not to have been adequately studied</td>
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<tr>
<td>2003</td>
<td>HIV patients with wasting or cachexia (adults)</td>
<td>From 0.1 mg/kg · d (0.7 mg/kg/wk) if &lt;35 kg to 6 mg/d if &gt;55 kg</td>
</tr>
<tr>
<td>2006</td>
<td>SHOX (short stature homeobox-containing gene) deficiency</td>
<td>0.35 mg/kg · wk</td>
</tr>
<tr>
<td>2007</td>
<td>Noonan syndrome</td>
<td>Up to 0.066 mg/kg · d (i.e. 0.469 mg/kg · wk)</td>
</tr>
</tbody>
</table>

Unless otherwise stated, data in table refer to children with short stature. Current nonapproved uses of GH in children are cystic fibrosis, steroid-mediated growth failure, HIV, and inflammatory bowel disease.

£ Year of initial approval by the FDA for the designated indication. Subsequently, the FDA may have approved other GH products for the designated indication. The reader is referred to www.fda.gov/Drugs/InformationonDrugs (drug approvals and databases) for additional information.

b Doses shown are based on all GH products with FDA approval for the designated indication. Where there is a wide range of doses, the range is indicated. Data were provided by the FDA. Average wholesale price for most innovator brands of GH is approximately $76/mg and $55/mg for biosimilar GH (www.AmerisourceBergen.com; January 23, 2010).

c Issues related to dosing for adult GH deficiency are summarized in The Endocrine Society Clinical Practice Guideline (www.endo-society.org/guidelines/Current-Clinical-Practice-Guidelines.cfm (Evaluation and Treatment of Adult GH Deficiency).
GH as therapy or enhancement: A case study

- Johnny is a short 11-year-old boy with documented GH deficiency resulting from a brain tumor. His parents are of average height. His predicted adult height without GH treatment is ~ 160 cm (5’ 3”).
- Billy is a short 11-year-old boy with normal GH secretion according to current testing methods. However, his parents are extremely short, and he has a predicted adult height of 160 cm (5’ 3”).
- Allen and Fost: should we treat?
  - Both have a disease (Short stature)
  - They argue both should have an equal claim
    - They argue it should be a right and not a privilege (which would increase inequalities)
  - They reject the treatment (Johnny)/enhancement (Billy) distinction.
  - If clinical trials show efficacy in non-GH-deficient children, there would be no coherent ethical basis for defining access by GH deficiency. Rather, GH responsiveness should be the central criterion in considering candidates for treatment. Whatever percentile is considered "tall enough" for GH-deficient children should also apply to non-GH-deficient children.
  - Treat only if a serious handicap. But they would not treat because both are above the 1% for height (which is when short stature is a disease).
  - So it is NOT about whether you are or are not GH deficient, but if you have a “disease” (short stature)

Case Study Critiques: Is the disease GH deficiency or short stature?

• There is a difference between those who are short genetically (familial short stature) and those who are short due to a lack of GH.
  – Many studies indicate that a lack of endogenous GH is linked to other negative consequences besides a failure in growth including cognitive and behavioral difficulties.
    • (Brian Stabler, "General and Specific Psychologic Consequences of Growth Impairment in Children and Adults," in Access to Treatment with Growth Hormone: Medical, Ethical, and Social Issues, Special Proceedings Supplement to Growth: Genetics & Hormones 8, suppl 1 (May 1992): 24-26.)
  – In familial short stature, GH can add 1-2 inches; psychological benefits of this additional height have not been proven

• Allen and Fost are right to consider equity: If we allow families to buy this (without insurance), pressure to expand reimbursement.
  – What begins as a consumer issue becomes an issue of “fairness”
  – Useful critique if it is a treatment; less so if it is “merely” enhancement
The Critique of “Expansive Biotechnologies”

• “GH can be seen as a paradigm of “expansive biotechnologies” that begin as clear medical treatments and then are found to offer benefits that do not clearly belong in the health-care system.”
• “Although treatment for pituitary dwarfism [GHD] is clearly within the appropriate goals of medicine, newer uses of GH to produce marginal gains in height or to slow the aging process are less clearly appropriate uses of health care.”
• For Buchanan this is important because
  – if it fits within the medical paradigm, then there is the concern about equity and access issues and the physician’s role as gate keeper.
  – If it does not fit, we must ask whether to proscribe its availability or to permit it as an elective procedure, acknowledging the potential inequities that this “enhancement” may cause
  – “Even if a burgeoning market in biotechnology enhancements does not have an adverse effect on equal opportunity, it might erode society’s already shaky commitment to the right to an adequate level of care for all. Scientific talent and resources might be drained away...”

History of GH Therapy after 2010

• **National Cooperative Growth Study (NCGS)** is the largest observational database in the U.S. of children with growth disorders.
• Started in 1985, NCGS was a long term longitudinal study following patients undergoing GH treatment in North America (the U.S. and Canada).
• The study was closed in 2010.
• At that time it had over 200,000 patient-years of statistical data collected.
• The related iNCGS (the "i" standing for "International") database is ongoing in Europe, collecting data in the United Kingdom, France, Germany, Italy, Spain and other European Union member countries.
• Why does it matter?
What are the risks and benefits of GH in non-GH deficient children?

**Risks**
- Increased risk of type 2 diabetes
- Benign intracranial hypertension
- Slipped capital femoral epiphysis
- Scoliosis
- Features of acromegaly
- Pancreatitis
- ? Leukemia (esp. in those who were formerly treated for cancer)
- Sudden respiratory death in children with PWS (and marked obesity) leading to greater pretreatment evaluation
- Psychosocial meaning of needing to “be fixed”
- Hundreds/thousands of injections
- ~$30,000/inch
- Attendant benefits of increased height have not been shown to accrue

**Benefit**
- Increased height 5-7 cm
- In children with PWS, GH can decrease body fat; increase respiratory muscle function, physical strength, agility and bone mineral density;
- No consistent psychological benefits
Is GH in the child’s best interest?

• “The Best Interest of the Child”
  – Long-term risks are still unknown
  – The increased height does not improve psychological well-being

• “Growth hormone therapy may be motivated more by parental hopes and aspirations than by any concern for the child”

• “While parents may rear their children as they choose, they cannot insist that the medical profession cooperate with whatever plan they may have.”

• Short term versus long-term best interests
The Expanded Use of GH: The Ethical Issues of Access and Consent

• If GH is a treatment and benefits >> risks, justice requires that all have access
  – GH deficient short stature, Prader-Willi,
• If in some populations, benefits modestly outweigh risks, no moral right to access.
  – Non GH deficient short but otherwise healthy children
  – Should it be permitted as an enhancement not covered by insurance?
• Parents must give consent (children often too young to provide active assent). What are the limits of parental autonomy?
  – If GH is a treatment
  – If GH is enhancement (endo-cosmetology)
  – If GH is truly dangerous...
Primum Non Nocere: Why we still need a longitudinal database

  – “When Laura was growing up in a small New England town, her parents and doctors worried that her predicted adult height threatened her future happiness. Laura’s tall mother had been teased and embarrassed about her own height at school. When the local paediatrician mentioned that a specialist might be able to stunt Laura’s growth and spare her the social pain of towering over boys as an adolescent and men as an adult, her family agreed. A paediatric endocrinologist affiliated with a prestigious US academic medical centre confidently prescribed the synthetic oestrogen diethylstilbestrol in doses 100 times greater than the oestrogen found in today’s high-dose oral contraceptives.
  – Laura obediently took the little coated pills, now commonly known as DES, for about 2 years.
  – But they made her sick and when she reached adulthood and married, she experienced miscarriage after miscarriage that denied her what she most wanted in life—children.
  – When doctors also diagnosed her with a condition that put her at risk of breast cancer, Laura wondered what effects the little pills might have had on her adult health.
  – She didn’t know at the time that other tall girls also went on to have reproductive problems after taking diethylstilbestrol and other high-dose oestrogens to stunt their growth, or that there had been concerns about the drug’s potential effects on fertility and cancer even at the time her physician prescribed it. Laura didn’t know because none of the physicians she consulted as an adult had heard of the treatment she had received as a child; there had been hardly any follow-up studies of these girls once they became adults.”

• Yes we have 25 years of rhGH data, but we have increased the dose and the frequency and we have changed the inclusion criteria and yet we have no long term data for newer cohorts.
Concluding Remarks

• The slippery slope of “expansive biotechnologies”
  – From the treatment of growth hormone deficiency to the provision of GH to enhance the height of those with short stature.
    • (and it doesn’t work very well; 1-2 inches for 6 years / $50k)

• Safeguards:
  – Longitudinal databases
    • Especially because the impact on children may be decades downstream!
  – Clear safety and efficacy endpoints for use
  – On-going consent process with parents (and eventually with the children themselves)