Lessons Learned from the hGH Era

David B. Allen
University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin 53705

Today, many medical interventions that begin as treatments for disease often expand into therapies that reduce disability, lessen disadvantage, or even confer advantage. Forces that propel profitable drugs, devices, and procedures dominate over considerations of efficient and equitable distribution of resources. This dominance is fueled by industry-physician collaborations often biased by prior assumptions, reliant on surrogate outcomes, and advantageous to marketing. Interventions are justified by “medicalization” of physiologic variations (e.g. short stature) as defects or disease, and nudged into “standard practice” by key opinion leaders. The story below of recombinant human growth hormone (hGH) treatment of short stature is one vivid example, but others (e.g. expansion of drug treatment to “optimize” cholesterol profiles, bone health, psychological well-being) can be found throughout medicine. In the new obesity era, lessons learned from the hGH era will be needed to keep the field of pediatric endocrinology empowered to make the key clinical decisions, and free of unintended consequences for patients and runaway health care inflation for society. ([J Clin Endocrinol Metab](http://jcem.endojournals.org/content/96/10/3042), 2011)

In 1985, the arrival of recombinant human GH (hGH) signaled a paradigm shift in pediatric endocrinology. Before then, the strategy was simple: deficient hormones were replaced, excess hormones suppressed. After the abrupt withdrawal of scarce pituitary-derived GH (pitGH), a mainstream narrative response to the challenge of hGH abundance arose from intuitive and deep-seated assumptions: 1) severe short stature (SS) in children is a disabling condition deserving of treatment; 2) hGH is safe for short children without GH deficiency (GHD) and at escalating dosages; and 3) hGH-induced height improvement would enhance quality of life. During the ensuing 20 yr, allure and acceptance of these assumptions swept us beyond physiological hGH replacement to pharmacological hGH height enhancement of children with idiopathic SS (ISS). Yet today, there is increasing uncertainty about the real benefits and potential risks of hGH therapy for many thousands of short, but healthy children (1). How did this happen?

In *The People’s History of the United States* (2), Howard Zinn illustrates how true history includes not only the mainstream story recorded by the wealthy, powerful, and influential, but also discounted, underappreciated, but no less “real” narratives. The history of hGH is an excellent example. It is dominated by a narrative of expansion of indications, escalation of dosage, and maximal height attainment that was generally accepted as valid, supported financially, and integrated into clinical practice. But it also includes an alternative narrative—fair but restricted access, efficient but restrained usage, and goals for nondisabling rather than maximal height attainment—that was generally suppressed, discounted, and not implemented into practice.

Three conditions preserved this imbalance in narratives: 1) a belief in SS as a disability and the ability of hGH to alleviate it; 2) confidence in the safety of pharmacological hGH therapy, both during and after treatment; and 3) shared vested interests of parents, prescribers, and industry, with support from payers. It is true that these conditions also advanced knowledge about height-increasing effects of hGH, facilitated treatment for many truly disabled children, and markedly increased the scope, size, and visibility of pediatric endocrinology—which is why the past 25 yr should be designated as the “hGH era.” But
our peculiar health care and policy environment allowed the creation of a “perfect storm” for expanded hGH use—patent protection advantages, absence of pricing competition, third-party payers willing to pay, and well-meaning physicians like myself willing to prescribe. This environment discouraged curiosity about reasons to restrain rather than expand hGH use and encouraged us to embrace the transition from hGH replacement to hGH enhancement therapy, to willingly partner with industry to expand the range of hGH recipients, to sustain height gain as the primary rather than surrogate outcome, and to neglect assessment of quality of life benefits and long-term posttreatment risks. The result is our current predicament: six U.S. Food and Drug Administration (FDA)-approved indications to increase height in non-GHD children with widespread off-label prescribing, but little evidence for measurable benefits of hGH-increased height to be weighed against potential risks, cost, and (if benefits actually do exist) potential unfairness to those without access to treatment.

This discussion is not about children who are clearly and severely GHD—we agree that these children need to be treated, many into adulthood—but rather it is about hGH-for-height treatment aimed at increasing stature and not at restoring hormonal normalcy. Herein, isolated GHD (IGHD) refers to short, otherwise healthy children who have low stimulated GH levels with normal magnetic resonance imaging scans and no other reason for GHD. ISS refers to short, otherwise healthy children distinguished from IGHD only by higher GH testing results.

Chapter 1: Primum Non Nocere—pitGH

The first event of any era signals the end of its predecessor. In late 1984, a 20-yr-old man who was previously treated with pitGH died from Creutzfeld-Jakob disease. When a possible pitGH/Creutzfeld-Jakob disease link was reported (3), many colleagues considered those responsible to be alarmists (4). But by April 1985, after other cases surfaced, the therapeutic use of pitGH in the United States was abruptly stopped. In July 1985 (when the author began fellowship training), the atmosphere was one of helplessness and foreboding as families of pitGH-treated children were notified by the FDA. But for almost all of these children who had profound GHD, pitGH “had to” be prescribed. What would it be like today to discover an unanticipated long-term serious adverse effect in children who really did not “have to” be treated?

Chapter 2: Embracing Enhancement

With remarkable historical serendipity, hGH replaced pitGH within months. Orphan drug protection, conferred to treat the rare disease of GHD, not only provided 7-yr market exclusivity plus tax benefits, but also restricted competition, supported high pricing, and facilitated expansion of the market through off-label usage and additional FDA indications. For hGH manufacturers, this created opportunity for windfall profits. For prescribers, abundant hGH fueled emergence of this tempting concept: hGH-for-height treatment is a special endeavor that justifies hGH use beyond traditional goals of restoring physiological hormonal normalcy.

There were two ways this concept was explored. First, the diagnosis of GHD was made more inclusive by arbitrarily raising cutoff points for provocative testing (previously highly exclusive due to limited pitGH supply) and incorporating other GH secretion assessments (integrated serial sampling). And despite strong evidence that laboratory-diagnosed IGHD was transient in many children (5, 6), reexamination of the diagnosis was rarely practiced. The result was 14 times the frequency of children treated for GHD between the United Kingdom and United States (7). Secondly, prescribers and industry embarked on a joint pursuit of normalcy of stature itself as a new and valid hGH treatment goal, diversifying the hGH recipient pool and maximizing dose and duration of hGH use. With hGH trials in children with Turner syndrome, chronic renal disease, and ISS, we rapidly and readily moved from replacement to augmentation to enhancement therapy, from hGH as a physiological hormone to hGH as a drug.

At the same time, others began to challenge whether use of hGH to alter children in ways they or their parents desire to be changed was something medicine should do. Philosopher Norman Daniels argued that in a world where talents and appearances are not and ought not to be distributed equally, acquiescing to patient wants rather than needs for hGH departs from medicine’s proper role of helping people to be normal competitors, not equal competitors. Administration of hGH is treatment, and therefore it is deserved when it corrects disease and disability—defined as significant departures from normal function—and is not deserved when it merely lessens “unlucky” competitive disadvantage by enhancing performance or appearance (8). The charge to define such “departures from normal” that would constitute disability prompted, among us, a long-standing debate about criteria for GH insufficiency and hGH responsiveness (that generally expanded access to hGH) rather than studies of functional disabilities that could strengthen a case for treatment of SS.

A remarkably prescient 1989 editorial voiced concern about whether proper studies of hGH treatment effects on lessening psychological stress would be done and the use of height as a surrogate marker for success if the reason for treatment is perceived psychosocial morbidity (9). Soon
afterward, we argued that if the primary goal of hGH-for-height treatment is to alleviate psychological stress and social prejudice, it made sense for responsible prescribing of and reimbursement for hGH therapy to be guided by ongoing disability and responsiveness, and not simply by the diagnosis of GHD. A height less than the 1st percentile was proposed as potentially disabling enough to justify consideration of hGH treatment, and an adult height at the 5th percentile was proposed as nondisabling and a reasonable point at which subsidized hGH therapy should stop. This article concluded: “Whatever policy we develop, it will be easier to discuss it rationally before the expanded hGH era is on us. A billion-dollar industry will inevitably distort critical thinking, and it will be difficult to reverse practices after they have been established” (10).

Of course, back then, no one knew whether height promotion would make these patients happier or more productive. The mainstream hGH narrative’s perspective, “test growth effects first, assess rationale and value later,” was poignantly summarized by calls for “a moratorium on discussions concerning the ethical use of hGH in non-GHD children until more complete data are in” (11). With the focus deflected from distinguishing normal variation from disease and disability to simply determining how well hGH could increase height, the door to exploring and expanding hGH enhancement was opened wide.

**Chapter 3: Exuberant Expansion—Rational or Irrational?**

Pharmacological hGH therapy then became a paradigm of “expansive biotechnology” — wherein medical treatments for severely disabling conditions are found, with the encouragement of well-intended physicians and support of industry, to offer new benefits that do not so clearly belong in the health care system (12). The perfect storm for hGH expansion got a jump start as postmarketing safety surveillance studies (PMSS), mandated by the FDA and supported by hGH manufacturers, began exploring higher dosages and new indications for hGH. Prescribers of hGH (author included) became “investigators” whose institutions received per-patient compensation for tracking and reporting hGH-treated patients. How much such per-patient payments influenced prescribing of hGH is not known (by us), but it certainly satisfied cost/return analysis at the corporate level. What is known is that this physician–industry collaboration fostered an environment in which the availability of a growth-enhancing tool implied a responsibility to use it. After 1 yr, the largest PMSS already showed 14% of hGH-treated patients to be ISS, which rose to 19% by 2002, still before FDA approval for this indication (13).

Along the way, an additional outcome of PMSS was facilitation of hGH use beyond labeled indications. A PubMed search for Genentech’s “National Cooperative Growth Study (NCGS)” reveals 34 articles about positive effects of hGH treatment (compared with 13 about safety), often for conditions not approved by the FDA at the time (14). When favorable industry-sponsored studies are reported by key opinion leaders, education, promotion, and persuasion become intertwined, reinforcing off-label prescribing that led, for instance, to over 8000 children being treated for ISS in the NCGS before the FDA approval for ISS treatment occurred (15).

Expansive hGH biotechnology also benefits by preserving treatment of SS as a qualified health care service. One approach has been to identify SS today (and obesity tomorrow) as a maladaptive condition that is rooted in biology, whether in genes or an abnormal pituitary gland. By referring to biological underpinnings of SS collectively as physiological defects rather than variations or alterations (16), we imply that the use of costly hGH to overcome them is a medically necessary endeavor.

In addition, expansion of hGH treatment dominated over restraint because exploration of new therapeutic endeavors is the natural desire of curious and well-meaning physicians. For hGH, the symbiotic prescriber–manufacturer relationship overwhelmed usual constraints—limited research funds, barriers to using investigational drugs, or a lack of willing study patients—with plentiful industry-sponsored substudies, reimbursement for participation, and funding and study drug for investigator-initiated trials. This resource-abundant environment, however, was too good to be all good. Most studies were noncontrolled, observational, focused primarily on increased short-term growth rate and predicted height, and lacking analysis of growth rates and final heights of participants who dropped out. Acceptance of standard practice under mined recruitment for randomized, controlled trials. Clinic volumes and relative value units increased, and for many of us, leadership positions, lecture invitations, and publications advanced academic careers. Thus, expansion of hGH-for-height treatment was swept along not only by opportunities to help patients, but also by benefits for our careers and specialty.

**Chapter 4: Necessary or Discretionary Treatment of SS**

The environment that has favored hGH expansion more than restraint is changing as funds to cover treatment of
otherwise healthy short children shrink, uncertainty about poorly defined benefit and possible long-term adverse effects grows, and we are forced to return to unanswered questions from the dawn of the hGH era.

Why does SS deserve treatment?

The mainstream narrative—that distress in short children is due to their shortness—is forged from long-held assumptions, early studies of mostly GHD children, and our own experiences with worried parents and anxious children. The alternative narrative’s search for data supporting these beliefs suggests that the more this is examined, the less is found. For instance, 250 consecutively referred short children demonstrated only minor difficulties of behavioral adaptation in boys (17), and subjects who only reached a mean adult height SD of −2.62 showed no associated cognitive and psychological difficulties (18). Although these and other studies showing similar findings (19, 20) may not exemplify all severely short children coming to our clinics, we must accept that psychological morbidity, while possible, is not a predictable consequence of SS. Moreover, with regard to longevity, a growing body of evidence suggests that, within generally healthy environments, shorter people may actually live longer (21).

Is hGH effective at correcting a problem due to shortness?

With regard to ISS, the FDA was persuaded that a 3.7-cm (22) to 5.5-cm (23) increase in adult height was effective. In contrast, similar improvements in adult height are described in the United Kingdom as having “little short- or long-term effects on height” (24). A U.S. meta-analysis (25) questioned whether a 2-inch gain should be considered effective in light of the $35,000 per inch cost. A Cochrane review (26) then concluded that evidence for a clinical benefit was insufficient without more randomized controlled trials, such as a 2010 report of high-dose prepubertal hGH treatment in children with ISS showing no difference in adult height between hGH-treated vs. nontreated controls (27). Even with these results, the mainstream narrative is revealed in the investigators’ focus on how study design might have compromised benefit, rather than the finding that hGH was not effective.

If hGH therapy yields a measurable height increment, does it improve psychosocial well-being?

The mainstream hGH narrative equates maximum height gain with expected and commensurate improvements in quality of life. The alternative narrative asks whether hGH treatment makes children better off, not just bigger. Again, it is difficult to validate prior assumptions. Among GH- and estrogen-treated young women with Turner syndrome, height was not related to psychosocial parameters (28). And in young adults who were ISS or small for gestational age, neither hGH treatment nor untreated SS led to long-term positive or negative psychosocial effects (29). Psychosocial studies following hGH treatment are thus far few in number and limited by small sample size. But available evidence suggests that hGH does not predictably improve psychosocial well-being for most children, even when such treatment increases the surrogate measure of final height—cautions that should be included in the informed assent process for hGH treatment.

What should be the end-point of hGH-for-height treatment?

To the child in front of us, we feel a duty to provide the best possible height outcome (30). But because social and economic height benefits of hGH therapy are relative, occurring at the expense of another (now shorter) person, the individual’s interest in greater height does not necessarily correlate with societal interest (31). Although it is untenable to expect titration of hGH treatment to avoid passing nontreated children, it is possible to balance duties to one child and to all children when it comes to the ultimate therapeutic goal. In the absence of unequivocal GHD, continuing treatment until (FDA-allowed) maximum height assumes the child needs treatment to that point (usually perceived to be a medical question) and is entitled to it (an ethical question).

Because a significant percentage of children diagnosed with IGHD later show normal GH secretion, observation off hGH therapy at onset of puberty (never promoted by the mainstream hGH narrative) would often save years of unnecessary and expensive treatment. Second, it is difficult to defend that children with any SS-associated diagnosis are entitled to medical care beyond a normal adult height. Putting parental disappointment aside and adhering to a statistical “normal opportunity range” therapeutic goal coincides with healthcare-with-justice aims to provide opportunities to achieve generally accepted benefits of life in our society. Although families could use their own resources to pay to maximize height attainment above other (presumably nondisabled) persons with heights in the lower part of the normal adult range, there is no coherent claim to communal resources for such treatment.

Chapter 5: Primum Non Nocere—hGH?

Although PMSS affirm a remarkable record of on-hGH-treatment safety (32), they do not follow children after hGH treatment. By analyzing the historical cohort as a
Concluding Thoughts

The hGH era, despite its pitfalls, has been 25 yr of positive advancement for pediatric endocrinology, but conditions that favor hGH expansion over restraint are weakening. Uncertainties about true benefits of hGH-aided height gain and conceivable long-term risks are undermining the height-promotion enterprise and emboldening voices of hGH restraint: “The story of treating stature is ultimately the story of temptation; the temptation of parents trying everything to secure their child’s current and future happiness and success; the temptation for doctors who want to help children grow and believe that they can alleviate suffering, even of the social variety, with a prescription; the temptations of industry, not just in the form of consulting fees but also the more general offer to provide a medical fix for social problems” (1).

The era of height enhancement as the primary driving force sustaining research, education, and growth in physician number in pediatric endocrinology will, and should, soon come to an end. However, helping children who cannot grow normally to do so will always be a central and immensely satisfying part of our specialty—so the end of the hGH era will not, and should not, be the end of hGH therapy. Given modest effects on increasing height and still unproven benefits for quality of life, third-party support for open-ended hGH to maximum height is likely to diminish rapidly, and categorical exclusions of hGH therapy could follow. A credible defense against endocrinology (36) is to direct hGH-for-height treatment to extremely short children truly impaired by stature, to use it judiciously and cost-effectively in those that are, and to not ask for insurance support for discretionary treatment of normal-adult-statured patients, regardless of etiology.

Affordable hGH will not solve the conundrum of responsibly prescribing it because supraphysiological hGH therapy cannot be considered so free of potential long-term effects to recommend its elective use in healthy children. In addition, whereas we have addressed what we can do with hGH-for-height treatment and the minimal ethical question about what we may do, we still haven’t settled on the moral question about what we ought to do (37), particularly in an environment that doesn’t provide access to basic health care for all. The alternative hGH narrative strives to show how, by adhering to treatment of severe SS and resisting enhancement of normal stature, it is possible to “push back” against ever-expanding hGH use and minimize our contribution to society’s perception that to be taller is to be better.

The next era for pediatric endocrinology has arrived. Type 2 diabetes and other obesity-related metabolic disorders are challenges of daunting, if not horrific, proportions. The advent of innovative, expensive, and controversial treatments for these disorders will fuel another convergence of concerned parents, well-meaning physicians, and enterprising industry to explore to what extent drugs, devices, and procedures will displace healthy lifestyle treatment and parental responsibility (38). Compared with hGH-for-height treatment, the patient numbers, the economic stakes, and the importance to the nation’s health will be magnitudes higher than SS treatment. A strong finish by our generation and a valuable legacy for the next would be to embark from the outset of this new era, in contrast to the hGH era, on a path that balances better the narrative of therapeutic expansion with narratives of efficiency and restraint.

Acknowledgments

The author wishes to thank Norman Fost and Brittany Allen for their thoughtful assistance in the preparation of this paper.

Address all correspondence and requests for reprints to: David B. Allen, M.D., H4/448 CSC–Pediatrics, 600 Highland Avenue, Madison, Wisconsin 53792-4108. E-mail: dballen@wisc.edu.
This review is taken from the Pediatric Endocrine Society Presidential Address given by D.B.A. at the Pediatric Academic Society Meeting in Denver, 2011.

Disclosure Summary: The author has no conflict of interest to declare.

References

21. Samaras TT 2009 We are too tall. Public Health Nutr 12:439