Pediatric Endo-Cosmetology and the Evolution of Growth Diagnosis and Treatment

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We find ourselves embarked on the fog-bound and poorly charted sea of endocrinology. It is easy to lose our bearings for we have, most of us, little knowledge of sea-faring and only a vague idea of our destination. In every profession, even ours, are to be found those who gather up bits of information of little intrinsic value which are exchanged for the property of credulous people as gullible as the natives of a new-found land. Thus do discoveries become exploited.[1]

This was Harvey Cushing's characterization of the practice of endocrinology in his presidential address in 1921 to the Society for Internal Secretions (which later became The Endocrine Society), founded in 1917 by a charlatan who specialized in selling glandular extracts by mail order. Elected without his knowledge a year earlier, Cushing nonetheless accepted, hoping to reform a field that he termed "endo-criminology," consisting largely of "poppycock."[1] The admonition remains relevant nearly a century later. The modern version of the practice that Cushing deplored can be described less pejoratively as "endo-cosmetology," specifically as it relates to growth therapy. This is appropriate because contemporary practice involves authentic biologic agents with unquestioned specific indications as physiological replacement therapy but with controversial extension to nondisease as pharmacologic intervention for cosmetic purpose.[2-10]

Background

Pituitary extract human growth hormone (hGH) distribution ceased in the spring of 1985 in the United States as a result of several cases of Creutzfeldt-Jakob disease ultimately traced to certain lots of hGH containing Creutzfeldt-Jakob disease infective material.[11] Fortunately, recombinant hGH (rhGH) had been in trial for several years, and Genentech received orphan drug approval from the U.S. Food and Drug Administration (FDA) for their biosynthetic methionyl growth hormone (GH) product in fall 1985.[12] Under the Orphan Drug Act of 1983, pharmaceutical companies received tax breaks and 7-year monopolies as an incentive to make drugs for rare diseases with potential markets of fewer than 200 000 patients.[13] The estimated market for the orphan indication of GH deficiency (GHD) for Genentech's GH, and the subsequently approved Eli Lilly non-methionyl rhGH was no more than 20 000 children.[14]

In addition to permitting more consistent treatment for children with GHD than had been possible with the limited supply of pituitary extract hGH, the unlimited supply made possible more exuberant dosing in GHD and the application to a broader range of indications by giving pharmacologic quantities of rhGH to individuals who had chronic disease or constitutional reasons for short stature (kidney failure, Turner syndrome, intrauterine growth retardation, and idiopathic short stature [ISS]). Also, the definition of the lower limit of normal for a serum GH concentration response to stimulation testing was arbitrarily increased from 5 to 10 ng/mL, resulting in a vast expansion of the number of children eligible for the approved indication for rhGH. Allen has noted that this history serves "as a paradigm of 'expansive biotechnology' wherein a biomedical technology, originally designed for treatment of disease, expands, with the encouragement of well intended physicians and support of industry, into treatment of conditions for which the conceptual boundary between disease and variation, and therefore between treatment and enhancement, is blurred."[15]

Problems with GH testing for the diagnosis of GHD, in addition to the nonevidence-based definition, included the frequent finding of deficient GH responses in normally growing prepubertal and early pubertal children, unless primed with sex steroids before testing[16]; poor responses without endocrine disease with obesity, subtle undernutrition, or cryptic chronic disease[17]; 2- to 3-fold variation in results depending on type of assay[18]; and variation in response in the same individual from one test to the next.[19]

In one study of 84 children who were growing normally, 100% of those at Tanner stage 4 or 5 met the criterion for normality of GH response >7 ng/mL, whereas 89% of those at Tanner stage 3 and only 39% of those at earlier stages

CDGM	Constitutional delay in growth and maturation
FDA	Food and Drug Administration
GH	Growth hormone
GHD	Growth hormone deficiency
hGH	Human growth hormone
IGF-I	Insulin-like growth factor I
ISS	Idiopathic short stature
rhGH	Recombinant human growth hormone
rhIGF-I	Recombinant human insulin-like growth factor I
SDS	Standard deviation score

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did. With estrogen priming, 100% of the prepubertal children had a normal response. When the commonly applied criterion of 10 ng/mL was applied, only 20% of these normally growing children at Tanner stage 1 and 2 had a "normal" response.[16] Thus, there is no value in GH testing of prepubertal children unless they are primed with sex steroids, a particularly salient consideration because constitutional delay in growth and maturation (CDGM) is by far the most common diagnosis in patients referred to pediatric endocrinologists for short stature. There have been no subsequent studies in normally growing or short-statured children that alter the conclusions of Marin et al.[16] The physiological rationale for sex steroid priming is to briefly establish an adolescent hormonal milieu, because preadolescent GH responses are physiologically low and no age-specific reference data have been generated. Nonetheless, 70% of pediatric endocrinologists in the United States and 50% of those in Europe do not do sex steroid priming of prepubertal or early pubertal patients undergoing GH stimulation testing.[20] Justification for this omission has been that such priming would lead to underdiagnosis of GH deficiency that might have benefited from GH treatment.[20] This hypothesis was unsupported in a study of 50 boys who failed unprimed tests but responded normally with testosterone priming; they eventually grew to their target heights without intervention.[21]

Isolated GHD is greatly overdiagnosed; three-fourths of individuals treated for this diagnosis are found to have normal GH responses when retested after adolescence.[22] When all children treated for isolated GHD who had normal or small pituitary glands on magnetic resonance imaging were studied as adults, 100% were found to be GH sufficient.[23] The magnitude of overdiagnosis of GHD in the United States is reflected in the remarkable 14-fold difference in frequency between the United Kingdom and the United States, 20/million versus 287/million total population.[24]

Development costs of rhGH for Genentech were $45 million and for Lilly $16 million. During the initial 6 years after approval, their U.S. sales totaled $730 million.[14] By 2006, they had 4 competitors but retained nearly 60% of the billion-dollar U.S. rhGH market, with combined U.S. sales of $580 million for the year.[25-27]

Orphan drug approval for recombinant human insulin-like growth factor I (rhIGF-I) was obtained in fall 2005, on the basis of studies in individuals who were unresponsive to rhGH because of GH receptor and postreceptor abnormalities or GH-inhibiting antibodies impairing the ability to synthesize IGF-I, a population of no more than a few hundred patients worldwide. This approval was immediately followed by promotional efforts based on the hypotheses that much, if not most, ISS was due to IGF-I deficiency as the result of GH insensitivity and that exogenous IGF-I was appropriate growth-promoting therapy.[28] These hypotheses were not data based and were disproven by the manufacturers' clinical trial data in which subjects had dubious IGF-I deficiency, normal GH sensitivity, and responses to rhIGF-I in relation to bone age advance which were no different than in control untreated subjects.[29,30]

The Concept of Endo-Cosmetology

The view of rhGH treatment in children without clear evidence of GHD as endo-cosmetology comes from reviewing usage data for a state-funded program, reviews of insurance claims, consideration of promotional strategies, discussions with colleagues concerned about the overuse of rhGH, experience with families seeking a second opinion or transferring care, and the lack of evidence of health or psychosocial disability from normal short stature or benefit from the modest, at best, gains in adult height in normal children without GHD.[31,32]

The Florida Department of Health program for children with special health-care needs, Children's Medical Services, provides rhGH for eligible children. The North Florida region accounted for 25% of the children covered by the program in 2004, but only 5% of the rhGH prescribed, whereas the South Florida area, with 18% of the Children's Medical Services population, accounted for 54% of the rhGH use. This 15-fold regional difference in rhGH use per capita reflects the magnitude of the variation in physician approaches to growth problems.[33]

Reviews of several insurance appeals in which pediatric endocrinologists indicated necessity for rhGH therapy included mostly claims for normal youngsters with CDGM and projected adult statures of –1.0 to –0.5 standard deviation score (SDS), between the 16th and 30th height percentiles.

Promotional Activities

With the introduction of the 2 brands of rhGH in North America in the mid 1980s, competing biennial conferences were provided to pediatric endocrinologists at resort locations with spouses welcome, along with other direct and indirect support. Off-label use was actively promoted by field representatives, although FDA policy, while supporting individual physicians' decisions about off-label use, eschewed drug manufacturers from promoting such use.[34]

One effort was industry support for community height screening programs that did not meet basic epidemiologic standards for such activity.[35] It had been shown years earlier that even true population-based height screening provided no information that was not already available to the families and medical community.[36] These same authors also identified socioeconomic class as the most important determinant of stature, as did Voss later.[37] If a true population-based screening program has the goal of identifying abnormally short individuals who might benefit from rhGH treatment on the basis of the unproven assumption that stature correlates with success and happiness, then it would be the obligation of society to identify those least likely to appear for voluntary screening to avoid elitist domination of the stature enhancement opportunities.[5,35] Such an endeavor could add more than $10 billion per year to health costs in the United States.[13]

Support for height screening was an early effort in the successful campaign by industry over the past 25 years to