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Martin T. Stein, S. Douglas Frasier and Brian Stabler

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Parent Requests Growth Hormone for Child With Idiopathic Short Stature*

CASE

Cody was always a short child with stature at the 5th percentile of a standard growth curve since he was a toddler. His weight was between the 10th and 25th percentiles. Developmental milestones and early learning achievement were normal. He played in a youth soccer league from 8 to 10 years of age, but he was not enthusiastic about group sports. In middle school, Cody excelled in the sciences and enjoyed tennis and swimming with his friends. In the 7th and 8th grades, his parents reported that Cody was teased frequently about his short stature. When the pediatrician asked Cody about the teasing, he was evasive.

Cody's parents were concerned that experiencing adolescence as the shortest boy in the class would have a lasting negative effect on his self-esteem. His father, remembering his own painful childhood as a short boy who was bullied frequently by other children until late adolescence, read about growth hormone (GH) on the Internet and thought that it might help his son.

Cody's father was 5 ft 5 inches, and his mother was 5 ft 2 inches. His father recalled initiating puberty later than his friends. The paternal grandparents were also short (5 ft 2 inches and 4 ft 8 inches). At the 14-year-old health-supervision visit, Cody's height was now below the 5th percentile. Review of systems was negative, and he continued to do well in school. Genitalia showed 2.5 cm testes with minimal scrotal thinning, Tanner 2 pubic hair, and no enlargement of the phallus. The thyroid gland was not enlarged; blood pressure and neurological examinations were normal. A bone age was 12 years 6 months (chronological age: 14.0 years). The pediatrician ordered a complete blood count, erythrocyte sedimentation rate, chemistry panel, serum thyroxine, thyroid-stimulating hormone, insulin-like growth factor-1 (IGF-1), and IGF-binding protein-3 (IGFBP-3). All studies were normal for age. It was concluded that Cody had constitutional delay of growth and familial short stature.

His parents asked if Cody could be given GH to accelerate his growth during adolescence. The pediatrician found it difficult to engage Cody in a discussion about perceptions and feelings with regard to his growth. Without objective evidence of GH deficiency, the pediatrician considered the physiological and psychological risks, potential benefits, and cost of treatment with GH.

INDEX TERMS. *short stature, growth hormone.*

Dr Martin T. Stein

Recombinant DNA technology transformed the meaning of "idiopathic short stature" (ISS) for developmental-behavioral pediatricians, primary care clinicians, and (as this case highlights) some parents of short children. Prior to 1985, GH treatment was limited, because the only available source was from human cadavers; prescriptions were essentially limited to pediatric endocrinologists.

The most recent US Food and Drug Administration (FDA) approval for the use of GH in children with ISS has been widely publicized. Cody is 1 of 8 children with either constitutional short stature (a family history of delayed adolescent growth and a bone age less than chronological age) or familial short stature (short parents and other relatives with a bone age equivalent to chronological age) whose parents have asked me about GH in the past year. Even when parents and the child/adolescent are informed appropriately about the potential benefits and risks associated with several years of GH treatment, decision-making is a difficult process.

What are the benefits of GH therapy in a child like Cody? How much added height will be achieved? What will be the effects of daily hormone injections on his self-esteem? Who is orchestrating the consideration for treatment—Cody or his father? What is the evidence that short stature affects psychosocial development? Is psychological well-being affected by added inches that may be achieved with hormone therapy?

Two specialists who have studied these questions from different perspectives were invited to comment on this challenging case. **Dr S. Douglas Frasier** is Emeritus Professor of Pediatrics at the David Geffen School of Medicine at the University of California, Los Angeles. For many years, Dr Frasier, who is a pediatric endocrinologist, participated in pioneering work on the clinical use of both human and recombinant GH. **Dr Brian Stabler**, Professor Emeritus of Psychiatry and Pediatrics at the School of Medicine, University of North Carolina, Chapel Hill, is a clinical psychologist who has directed studies addressing the psychosocial outcome of children treated with GH.

MARTIN T. STEIN, MD
Professor of Pediatrics
University of California
Children's Hospital San Diego
San Diego, California

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Dr S. Douglas Frasier

Twenty years ago, the use of human GH, which was extracted from human pituitary glands, was limited to the treatment of GH deficiency. Supplies were scarce, diagnostic criteria were rigid, and most treatment was investigational. A sea change occurred in 1985 with approval for therapeutic use of human GH manufactured by recombinant DNA technology. With the application of this technology, the supply of GH became unlimited.

The FDA has approved treatment with recombinant human GH for growth failure due to GH deficiency, Turner syndrome, chronic renal insufficiency, Prader-Willi syndrome, small-for-gestational-age babies who do not show catch-up growth, and patients with non-growth-hormone-deficient ISS. Parents and patients have become aware of this most recent development through newspaper, magazine, and television reports as well as the ubiquitous Internet. This widely circulated information has prompted Cody's parents to raise the possibility of GH treatment.

The first question to consider is whether Cody has 1 of the conditions approved for GH treatment. The answer is clearly "no" for a diagnosis of GH deficiency, which is not supported by normal serum concentrations of IGF-1 or IGFBP-3. With 1 exception, the other approved conditions and specific syndromes are ruled out by history and physical examination. The remaining category that might be treated is ISS. ISS is not a specific diagnosis but rather is a file drawer containing several conditions that affect growth. These include both familial short stature and constitutional delay in growth and adolescence. Although one could quibble about diagnostic categories, ISS is an appropriate label for this discussion. Treatment of Cody with GH would not be "off-label." Such treatment is within FDA-approved guidelines. The next considerations are the efficacy, safety, and cost of GH in patients with ISS.

A relatively large number of ISS patients have received GH. The most extensive review of such treatment was a meta-analysis published by Finkelstein et al¹ in 2002. Ten controlled trials (434 patients) and 28 uncontrolled trials (655 patients) were evaluated. After 1 year of treatment, patients enrolled in controlled trials grew 2.8 cm (1.1 in) more than untreated patients did. In uncontrolled trials, the difference in growth between pretreatment and the first year of GH administration was +0.53 SD of height or 3.18 cm (1.25 in). These results suggested an average gain in adult height of 4 to 6 cm (1.6 to 2.4 in). In this analysis, GH treatment was minimally efficacious in treating short stature in ISS patients.

The results of 2 extensive pharmaceutical-company-sponsored GH trials in ISS patients have now been published and/or submitted to the FDA. The Genentech study appeared in the *New England Journal of Medicine* in 1999.² The investigators treated 121 ISS patients with GH for 2 to 10 years. Eighty children reached adult height as defined by a bone age of 16 years in boys and 14 years in girls. The mean (\pm SD) difference between predicted adult height

prior to treatment and adult height achieved was 5.0 ± 5.1 cm (2.0 ± 2.0 inches) for boys and 5.9 ± 5.2 cm (2.3 ± 2.0 inches) for girls. Results were variable, and no significant response was observed at 6 months in 30% of treated patients.

The Lilly study, which led the FDA to approve GH for ISS patients, provides the most recent information. The highest dose employed in the Dutch arm of the Lilly study, which is comparable to the dose used in patients with GH deficiency, resulted in an average increase of 7.0 cm (2.8 inches) in adult height.³ However, the number of patients was small, and the variability of response cannot be ascertained from the material presented. Similar results were found in the overall Lilly trial, where there was an average improvement in final height compared to initial predicted height (mean \pm SEM) of 7.2 ± 1.2 cm (2.8 ± 0.5 inches).⁴ Again, the number of patients treated was small, and results were variable.

From these studies and numerous others not cited, it seems clear that GH treatment of children with ISS does increase growth in many, but certainly not all, patients. An average increase of 2 to 3 inches may be expected after several years of treatment but is not guaranteed. The best results are observed in children whose height is at least 2 SD below the mean and who are younger than 9 to 10 years of age.

GH treatment appears to be associated with minimal risk. Side effects are few, and it is very unusual to stop treatment because of such problems. Nevertheless, a thorough history and physical examination should be performed prior to starting therapy to rule out any silent chronic illness.

GH therapy is very costly. At current prices, this has been estimated to be as high as \$35000 for every inch attained above predicted height. Insurance coverage for the treatment of ISS is problematic.

I am very unenthusiastic about GH treatment for Cody. I would not expect a significant response in view of his age and height. Simply stated, he is too old and not short enough.

However, there is an effective and safe alternative therapy for his delayed adolescence.^{5,6} I assume that he is more troubled by his lack of pubertal development than he admits. He would benefit from a short (6-month) course of testosterone, which would result in additional secondary sex development. There are various ways to accomplish this. I recommend monthly injections of 50 mg of long-acting intramuscular testosterone. This would be followed by at least 6 months of observation without treatment. The effects are usually greatly appreciated by patients with delayed sexual maturation.

S. DOUGLAS FRASIER, MD
Professor Emeritus of Pediatrics
David Geffen School of Medicine
University of California
Los Angeles, California

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Dr Brian Stabler

Three things strike me as I read this case. First, the history of the family's height is so obviously shorter than average. Second, Cody appears to have no pathophysiological explanation for his relatively short stature. Third, Cody's parents may be in need of support more than Cody.

Our understanding of the causes of growth delay in children should inform our treatment decisions. There is a broad spectrum of possible growth-delay etiologies, ranging from multiple pituitary deficiencies such as panhypopituitarism, to constitutional growth delay. The factors to consider in a decision to treat include the degree of GH-production capability, height at or below the 3rd percentile on Tanner charts, and the amount of psychosocial stress reported by the child and others, preferably outside the family.

Studies of the psychological adjustment of short children differ in their findings. Some suggest that short stature per se does not constitute a psychosocial burden and therefore should not be treated with GH.¹ Others point to the wide range of psychosocial problems observed in many short children referred to endocrinologists and suggest that referral is the result of a self-selection process and, therefore, tends to include many children who experience social or emotional stresses related to their short stature.² Finally, in a large multicenter study, there appeared to be a high incidence of reported behavioral and achievement problems among short children referred for consultation.³ These findings pertained both to children with clinically significant GH deficiency and those who have minimal or no GH deficiency but who are short nevertheless.

We know that many clinically short children who are treated with GH do not go on to lead good quality of life. Many patients report being unhappy in young adulthood, have few friends, little formal higher education, do not marry, and may live with parents until late into their 20s or early 30s. Studies have shown that there may be an association between pituitary dysfunction and increased susceptibility to social anxiety, particularly the diagnosis of social phobia. This observation was first made by Uhde et al⁴ from their observation of hypopituitary pointer dogs that demonstrated marked signs of withdrawal and fright when approached by humans. Phenomenologically, the sociopathy of anxiety leads to isolation, withdrawal, and avoidance of social encounters or relationships, symptoms that closely re-

semble the reports of several investigators who have followed patients treated with GH in childhood and who, as adults, are no longer receiving GH therapy.⁵

Cody's condition is in the category of constitutional delay of growth, reflecting his family genetic predisposition. Hence, the quandary for clinicians: should GH be prescribed to accelerate Cody's growth rate, or is counseling for Cody and his parents (particularly his father) to accept and adjust to short stature a better alternative?

In my opinion, the most technically and ethically appropriate response must be the latter. Although studies on the value of GH therapy for non-GH-deficient short children suggest a minimal increase in adult height, the risk-benefit analysis is not encouraging. Thus, Cody's parents could benefit from education and counseling about the limitations of GH therapy for their son. Moreover, it is important that Cody be evaluated to assess the possibility that he harbors unrealistic expectations or misperceptions about his final height or experiences diminished self-esteem related to his stature. In my experience, it is never sufficient to manage such problems with a unitary approach, and rarely does a prescription for GH alone lead to a satisfying outcome.

BRIAN STABLER, MED, PHD
 Professor Emeritus of Psychiatry and Pediatrics
 School of Medicine
 University of North Carolina
 Chapel Hill, North Carolina

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Web Site Discussion

The case summary for this Challenging Case was posted on the Developmental and Behavioral Pediatrics Web site† (www.dppeds.org.list) and the *Journal's* Web site (www.lww.com/DBP). Selected responses are included.

Henry L. Shapiro, MD

"Oh brave new world, that has such people in it," said Miranda, daughter of the wizard Prospero in the *Tempest*, on seeing men for the first time.

† A bimonthly discussion of an upcoming Challenging Case takes place at the Developmental and Behavioral Pediatrics Web site. This Web site is sponsored by the Maternal and Child Health Bureau and the American Academy of Pediatrics section on Developmental and Behavioral Pediatrics. Henry L. Shapiro, MD, is the editor of the Web site. Martin Stein, MD, the Challenging Case editor, incorporates comments from the Web discussion into the published Challenging Case. To become part of the discussion on the Developmental and Behavioral Pediatrics home page, go to www.dppeds.org.

Stipulating that the boy probably does not have a disease causing short stature, it is very clear that contextual factors are causing a significant problem for him. If he were refusing to go to school, embarrassed to leave the house, and had panic episodes during the physical examination, we would diagnose an adjustment disorder related to how he and others perceived and responded to his stature.

Because of his short stature, it is also possible that his ability to participate in different activities due to his height could be a problem. It is likely that he is going to be repeatedly excluded because others judge his maturity based on his size. Already at a disadvantage compared to girls (who often are taller in early adolescence), this discrepancy will be substantially amplified. His parents may point to evidence that there is a relationship between height and earning ability.

His parents might also point out that it is a social norm to modify the natural course of life in a variety of ways (eg, providing better nutrition, delaying pregnancy, fluoridating water, straightening teeth, coloring hair, and correcting birth defects). Other examples of our cultural acceptance of altering biological variations include erasing wrinkles, straightening (or curling) hair, enhancing secondary sexual characteristics, tailoring clothes, and correcting vision. Specific pediatric examples are preventing chickenpox, providing education, providing "educational toys," and choosing certain parenting practices over others. If GH were cheap, easy to administer (like a nasal spray instead of an injection), and reliably effective, I am not sure that there would be much controversy.

Whether it is GH or some other future treatment (such as atherosclerosis reversing factor or neurofibrillary detangler), there are certain to be many future treatments for what we consider normal variations. However, while I would not encourage the parents to search for any doctor willing to treat their son, I think this is not a matter of principle ("don't fool with mother nature") as practicality. It probably won't do much good, it will probably be a very expensive out-of-pocket expense, and the long-term safety of recombinant GH is unknown.

Michael Cupoli, MD

I recently worked with several children and adolescents who were concerned about height, and their families requested GH. A 16-year-old boy with short stature due to chronic steroids associated with severe, nearly fatal asthma responded well to a few office visits where we discussed the potential benefits (none in this particular case) and risks of GH therapy. I think the opportunity to talk made the change in him. We had worked together in the management of his chronic asthma over a 3-year period, and we really liked/enjoyed each other. Nothing works as well as that.

The second case is a boy with short stature who had several losses in his life. He has a syndrome that may or may not respond to the GH. The treatment plan that he, his mother, and I developed is psychotherapy targeted at his losses and anger before even

addressing the short stature. Dr Shapiro said it well, we need to help children and their parents understand that to be perfect is not a goal but often a barrier to insight and greater self-awareness.

Dorothy Johnson, MD

I met a little Elf-man, once, Down where the lilies blow. I asked him why he was so small, And why he didn't grow. He slightly frowned, and with his eye He looked me through and through. "I'm quite as big for me," said he, "As you are big for you."

John Kendrick Bangs¹

There are problems being the shortest boy or the tallest girl, and at no time will it be worse for Cody than now, when the difference in age of onset of puberty causes the most disparity between the statures of early and later maturing youth. But this is not just an issue of height but also of different interests, muscle mass, and sexual maturation. The problem is compounded by the developmental insecurity seen in the early stage of adolescence, when, in desperation for acceptance, the desire is to be just like peers.

It is important to understand and validate the distress that Cody experiences. His pediatrician should determine whether any peers are intimidating or picking on him. Through embarrassment or fear, he may not volunteer these social experiences. It is important that Cody understands that his younger bone age (compared to his chronological age) means that he will grow when his peers have stopped growing, and so ultimately he will be much closer to their height than now.

Height is about individuality, not perfection. Let's help Cody think about the possible advantages of being Cody. If he's a thespian, he'll be able to take the part of younger children with the skill of his greater maturity. If an equestrian, he'd be ideal for a jockey without needing to starve himself. If he enjoys boating, he'd be sought after as coxswain, and if a gymnast or cheerleader, he'd be the first choice for the top of a human pyramid. (In general, throughout schooling he should be directed to sports such as wrestling and gymnastics in which competition is by weight rather than age.) If into technology, consider the necessity of small stature to fitting into the confines of narrow spaces often required for installing internet connections, telephone, or satellite cables. In travel he'll fit the seats of commercial carriers without being cramped. If a surgeon, his slither hands would more readily traverse small spaces.

The point is not that his stature defines him, but that it can be among his gifts that he can use to advantage.

This is a time to identify and nurture what Robert Brooks refers to as "islands of competence"² so that Cody and his peers define him by his gifts, not by his stature. To buffer the embarrassments of always being looked down upon by peers, it may help Cody to have responsibility helping students who are sufficiently younger and who would "look up to him" literally as well as figuratively.

It may be helpful to find adult role models who are short (eg, celebrities, other family members, teachers, etc). It may be worthwhile to spend some time with

the parents (particularly the father) apart from Cody, discussing not only their own experiences of short stature but also looking for short relatives whom they have enjoyed and/or admired. The father's negative experience of late development and short stature needs to be addressed so that he does not project it onto his son.

Most of all, it is more important to identify meaningful adults (in addition to his physician and parents) who regard him with the respect appropriate for his chronological age. For all of us, what matters most as we cross the minefields of adolescence is that someone believes in us.

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Martin T. Stein, MD

Medical ethicists have expressed concern following the approval of GH for children with ISS. Dr Arthur Caplan of the University of Pennsylvania, commenting on the use of GH for children with ISS, observed: "We will start to treat the normal as a disease. Whenever you take people on the low end of a distribution curve and say they have a disorder, you're starting down a slippery slope."¹ In contrast, Dr Shapiro pointed out the pervasive use of contemporary medical therapies to change our biological endowment. I was struck by many of his examples that are acceptable treatments. Bioethicist Caplan would likely disagree with the use of many of those treatments.

Side effects occur in approximately 3% of patients when using daily subcutaneous injections of GH. The most common side effects, joint pain, edema, local reactions, and bruising, are usually reversible by lowering the dose or temporarily discontinuing therapy. Less common side effects include pseudotumor cerebri, slipped capital femoral epiphysis, gynecomastia, and carbohydrate intolerance in children with compromised insulin secretion.²

Dr Johnson provided a gem when she observed: "Height is about individuality not perfection." I suggest that this may be the mantra for pediatricians who are asked by parents about GH treatment for ISS. Height as a child and as an adult is only 1 element of an individual that comprises a sense of

self. No doubt that tall stature is associated with specific areas of achievement in many cultures. Dr Johnson's examples of the value of shortness in certain occupations may be useful when talking to patients and parents. More important is to catalogue a child's strengths through a careful developmental and psychosocial history. This is the source of each child's individuality—the resources that support resiliency during adolescence and adult life.³ Dr Cupoli expressed the preferred clinical method in a direct manner ("... the opportunity to talk ... nothing works as well as that").

Cody's bone age (1.5 years below his chronological age) means that he will enter his adolescent growth spurt later than most children. Although his midparental height predicts a final height below the 5th percentile, knowledge that he will continue to grow, perhaps later than other boys in his class, may be helpful.

Teasing needs to be addressed. Is it occasional? How does he respond to it? Can he be taught to ignore moments of teasing? Or is the teasing a reflection of being bullied by 1 or a few boys? A recent study demonstrated that victims of bullies had significantly higher risk for depression and psychosomatic symptoms compared with children not involved with bullying behavior.⁴ Cody's father's memory of a childhood bully is important to address as a factor influencing his father's perceptions about short stature. It would also be important to learn about Cody's mother's perceptions about his height.

There will be some children with ISS for whom treatment with GH will be appropriate. Pediatricians can begin the discussion about the child's and parents' expectations for adult height and the child's self-esteem and educational and social achievements. In most cases, consultation with a pediatric endocrinologist and pediatric psychologist will provide the most comprehensive care.

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