Appendix B – The Synthetic Human Growth Hormone (hGH)

Medical Indications

Since their introduction in 1985, the list of FDA-approved indications for synthetic human growth hormone has been expanded from classical human growth hormone deficiency in children to include, among other things, renal failure and Turner Syndrome. Pediatric endocrinologists have used synthetic hGH for several other off-label indications such as intrauterine growth restriction (IUGR) and Prader-Willi Syndrome.[1] Chronic renal insufficiency causes kidneys to fail, leading to an accumulation in the child's blood of toxins that hamper the normal growth process. As such, chronic renal insufficiency does not affect the production of hGH, yet treatments with this hormone have proven effective. Approximately 3,000 children yearly are affected by chronic renal insufficiency.[2] IUGR is also a clear case of a physiological dysfunction. IUGR is associated with abnormal growth in the uterus. (Affected children are said to be small for gestational age.) Just like chronic renal insufficiency, IUGR does not impair the production of the hGH; nevertheless, administering this hormone has been shown to help. Turner Syndrome is caused by a genetic defect that affects only girls. Symptoms include shortness and a failure to fully develop ovaries. Girls are on average only 4'8" tall, versus 5'5" for the average female.[3] Girls with Turner Syndrome do not have an hGH deficiency, yet when treated with hGH, they too display a faster growth rate. Prader-Willi Syndrome is another genetic defect that stunts growth. It is rare, affecting only 1 in 10,000 to 12,000 newborn babies. Children with the Prader-Willi Syndrome tend to be obese and of short stature, and have small hands, small feet, a small mouth, and small genitals. In these children, hGH treatment can add several inches to their stature, reduce their body fat, and even improve their physical activity.

The FDA decision to approve the use of synthetic hGH for idiopathic shortness represents a significant departure from earlier practice in that this condition may be described as a cosmetic use of hGH. Idiopathic short stature (ISS) has no clear or obvious physiological cause. The pharmaceutical industry has been trying to identify the causes of idiopathic shortness for many years, without success. Many ISS children have levels of hGH well above what is considered normal. On the other end, some children of normal stature have been shown to have growth hormone levels at or below the norm. This shows that the relationship between levels of hGH

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1 Hormone Foundation, "Get the Facts: Growth Hormone Issues in Children and Adults," (Chevy Chase, MD: The Hormone Foundation, 2003); Mary Lee Vance and Nelly Mauras, "Growth Hormone Therapy in Adults and Children," *New England Journal of Medicine* 341, no. 16 (1999).

2 Dieter Haffner et al., "Effect of Growth Hormone Treatment on the Adult Height of Children with Chronic Renal Failure," *New England Journal of Medicine* 343, no. 13 (2004).

3 Paul Saenger, "Turner's Syndrome," *New England Journal of Medicine* 335, no. 23 (1996).

secretion and height is far more complex than normally assumed. To complicate matters further, there is no agreed-upon definition of short stature. In some studies, children in the third percentile for their age and sex are considered short; in others, the threshold is the fifth or tenth percentile; in still others, all children below two standard deviations from the mean are characterize as short.

That one should be careful in diagnosing idiopathic shortness was demonstrated by a recently conducted study in which approximately one-third of both idiopathic short boys and girls eventually reached a normal stature.[4] This result indicates that growth velocity may vary considerably over time: In other words, a significant fraction of ISS children are simply growing at a speed slower than average for their age at the time of the measure, but their developmental velocity could accelerate significantly at a later point in time. These so-called ISS children not only are healthy, they are also not short. In sum, it is quite possible that ISS children are perfectly healthy, and often their shortness is only temporary.

Safety and Efficacy

Two key aspects of the debate over the use of synthetic hGH are safety and efficacy. The hormone may be effective, could critics argue, but should it be used to treat healthy children if there are any doubts about its safety? Alternatively, one may argue that it is not sufficient for this treatment to be safe. In order to justify the exorbitant costs of an hGH treatment, a treatment that usually lasts several years, the pharmaceutical company must be able to show clear and unambiguous evidence of effectiveness.

With regard to safety, there is very little evidence of risks or adverse effects associated with hGH treatments; very few adverse effects have been documented. Recently, the Growth Hormone Research Society reviewed approximately 200 peer-reviewed articles on this subject and concluded that the use of HGH for approved indications is safe.[5] The safety of synthetic hGH is not a concern for the FDA, which – at its June 10, 2003, meeting convened to review the pharmaceutical manufacturer's application for the non-medical uses of synthetic hGH – concluded with few reservations that hGH in general and Humatrope in particular are safe.[6]

Assessing the efficacy of synthetic hGH to treat ISS children is considerably more difficult. hGH treatments for children with a discernible physiological condition generally are considered very effective and can add several inches to these individuals' adult height, though these treatments usually do not entirely compensate for their shortness. Nevertheless, there is agreement in the medical community that hGH treatments are quite effective, if not in

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[4] Luigi Greco, Chris Power, and Catherine Peckham, "Adult Outcome of Normal Children Who Are Short or Underweight at Age 7 Years," *British Medical Journal* 310 (1995).

[5] Michael O. Thorner, "Critical Evaluation of the Safety of Recombinant Human Growth Hormone Administration: Statement from the Growth Hormone Research Society," *The Journal of Clinical Endocrinology & Metabolism* 86, no. 5 (2001).

[6] Briefings materials are available at http://www.fda.gov/ohrms/dockets/ac/03/briefing/3957b1.htm.

completely treating then at least in significantly mitigating the negative consequences of severe hGH deficiency. We were surprised to discover that the same treatment is far less effective in treating ISS children. In this case, the evidence is mixed. Opponents of the use of hGH for non-medical reasons have claimed that the efficacy of this treatment has not been demonstrated. Several recent studies seem to support this view.[7] Not surprisingly, supporters of legalizing hGH for treating ISS children point to other studies that seem to demonstrate precisely the opposite.[8] The literature on this issue is simply too large and too technical for us to offer an independent assessment, but it should be mentioned that researchers funded by the leading manufacturers of synthetic hGH tend to produce supportive studies, while the FDA, in reviewing the extant literature, including the studies conducted by pharmaceutical companies, is much less sanguine about the effectiveness of the treatment.

There are several reasons for these conflicting results. First, and perhaps most importantly, the non-therapeutic use of hGH remains controversial among medical practitioners. Medical doctors and scientists may read the available empirical evidence differently depending on their personal inclinations. Second, it is much easier to evaluate the efficacy of hGH treatments for traditional, medical indications, as these indications have been treated for a much longer period of time and the available empirical evidence is sizeable. Third, it is also important to recognize that a thorough evaluation of the efficacy of hGH treatments on final height requires conducting lengthy and costly longitudinal studies. Many studies on the efficacy of hGH for ISS children started in the mid-1990s and have not yet been concluded.

In sum, while the safety and efficacy of hGH treatments for traditional medical indications is not in dispute, the efficacy of these treatments for ISS children is debatable at best and inadequate at worst.

Social-Psychological Pathologies

In this section, we examine the possible negative psychological and social effects of shortness. We start by offering an obvious but important observation: The ethical questions raised by individuals of normal stature trying to gain a few inches are quite different from the concerns associated with parents trying to help their short children grow taller. Much of the debate surrounding the use of synthetic growth hormone is centered on treating short stature, but the abuse of synthetic hGH in individuals of normal stature is just as relevant to our discussion.

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[7] C.G.D. Brooks, "Growth Hormone: Panacea or Punishment for Short Stature?," *British Medical Journal* 315 (1997); Sharon E. Oberfield, "Growth Hormone Use in Normal, Short Children – a Plea for Reason," *New England Journal of Medicine* 340, no. 7 (1999).

[8] John G. Buchlis et al., "Comparson of Final Eights of Growth Hormone-Treated Vs. Untreated Children with Idiopathic Growth Failure," *Journal of Clinical Endocrinology and Metabolism* 83, no. 4 (1998); Beth S. Finkelstein et al., "Effect of Growth Hormone Therapy on Height in Children with Idiopathic Short Stature," *Archives of Pediatric & Adolescent Medicine* 156 (2002); Raymond L. Hintz et al., "Effect of Growth Hormone Treatment on Adult Height of Children with Idiopathic Short Stature," *New England Journal of Medicine* 340, no. 7 (1999).

Accordingly, one should distinguish between the (mostly positive) effects of above-average stature on individuals (mostly men), and the (largely) negative effects of shortness on children and adults well below normal height.

Tallness – a Requisite for Success?

Popular wisdom holds that taller-than-average individuals – especially men – are more successful than the average population. Surprisingly perhaps, in this case popular wisdom seems indeed to be correct. A recent study of the relationship between stature and socioeconomic status in the former West Germany – defined as a composite of educational level, occupational types and of occupation and income – has shown that men of average social status are 1.7 cm (0.67 inches) taller, and men enjoying a higher status are 3.9 cm (1.54 inches) taller than men of a lower social status. A similar pattern emerges for citizens of the former East Germany and for women.[9] Two factors that could explain these results – limited access to health care and poor nutritional habits – are most likely not responsible for the study results, as Germany has an excellent health care system and high standards of living.

Height is not only associated with status and income. It also affects the reproductive chances of males. According to a recently conducted survey, taller men are much more likely to have children, even after controlling for residence (compared to the urban population, the rural population is shorter), health (hGH deficiency and other conditions can have a dramatic impact on final height), and education – all factors that have been shown to affect stature.[10] The size of the sample – 3,000 individuals – does not leave any doubts about the robustness of this conclusion. Height has also been shown to account for the differences between males and females in status and income.[11] According to another study, career chances seem to be considerably higher for taller-than-average individuals.[12] The study analyzed homogenous groups of professionals (nurses, individuals in clerical positions, and craftsmen) and found that height correlates with seniority – even after controlling for education level and socioeconomic background.

It doesn't stop here. It is a well-documented empirical fact that there is a significant – albeit weak – correlation between height and IQ. One may have serious doubts about the adequacy of IQ tests as indicators of cognitive performance, but it would be hard to ignore available empirical evidence. In one study, the authors assembled a very large, representative sample of the entire U.S. population.[13] These children were examined twice, between 1963 and 1965, and again

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[9] J. Komlos and P. Kriwy, "Social Status and Adult Height in the Two Germanies," *Annals of Human Biology* 29, no. 6 (2002).

[10] B. Pawlowski, R.I.M. Dunbar, and A. Lipowicz, "Tall Men Have More Reproductive Success," *Nature* 403 (2000).

[11] Paul V. Crosbie, "The Effects of Sex and Size on Status Ranking," *Social Psychology Quarterly* 42, no. 4 (1979).

[12] A. Schumacher, "On the Significance of Stature in Human Society," *Journal of Human Evolution* 11 (1982).

[13] Darrell M. Wilson et al., "Growth and Intellectual Development," *Pediatrics* 78, no. 4 (1986).

between 1966 and 1970. The longitudinal sample consisted of more than 2,000 children ages 8 to 11. Each sample included approximately 14,000 children. The study found a small but significant correlation between height and IQ in both cases. The correlation persisted even after controlling for socioeconomic status (i.e., family income), and race (black versus white).

These findings have been repeatedly replicated, suggesting that the relationship between stature and IQ, while not strong, is indeed real. For example, a recently completed study of physical, psychological, and cognitive aptitudes of a nearly complete cohort of more than 38,000 18-year-old Swedish young men showed that taller men perform significantly better than average on a variety of cognitive tests and are psychologically more stable.[14] A Danish study of 76,000 young men confirmed these results.[15] However one decides to account for this evidence, it is hard to ignore the fact that on the whole, taller and good-looking men (for women tallness is often a handicap) seem to be considerably more successful than their average peers.

Shortness as a Psychological and Social Impairment?

The question of whether short individuals are at a disadvantage compared to individuals of normal height is analytically distinct from the question we have discussed in the preceding section, i.e., whether individuals taller than average enjoy (undeserved) benefits. One can easily imagine passing a ban on the use of synthetic hGH for individuals of normal height on the ground that the ubiquitous use of hGH in this case could trigger a costly arms race with no discernible benefits for the participants. The rationale for administering synthetic hGH to extremely short children is rather different. In this case, it is presumed – and parents have argued to the FDA – that children of idiopathic short stature suffer from low self-esteem and are at a significant disadvantage compared to their peers. Determining whether these claims are justified is therefore of some import to this discussion.

The prevailing wisdom until the late 1980s was that short children are indeed at a disadvantage. According to some studies, they frequently experience teasing and bullying, they have poor social skills, they are isolated, they are plagued by low self-esteem, and their academic performance is poor.[16] Similar conclusions were reached for adult short individuals. Among the most frequently cited concerns are education,[17] employment, romantic relationships, and friendships.[18] In more recent times, however, the prevailing view has begun to shift. New,

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[14] Torsten Tuvemo, Björn Jonsson, and Ingemar Persson, "Intellectual and Physical Performance and Morbidity in Relation to Height in a Cohort of 18-Year-Old Swedish Conscripts," *Hormone Research* 52 (1999).

[15] T.W. Teasdale, David R. Owen, and T.I.A. Sørensen, "Intelligence and Educational Level in Adult Males at the Extremes of Stature," *Human Biology* 63, no. 1 (1991).

[16] David E. Sandberg, Amy E. Brook, and Susana P. Campos, "Short Stature: A Psychosocial Burden Requiring Growth Hormone Therapy?," *Pediatrics* 94, no. 6 (1994), p.832.

[17] Teasdale, Owen, and Sørensen, "Intelligence and Educational Level in Adult Males at the Extremes of Stature."; Melissa Wake, David Coghlan, and Kyle Hesketh, "Does Height Influence Progression through Primary School Grades?," *Archives of Disease in Childhood* 82 (2000).

[18] F. Ulph et al., "Personality Functioning: The Influence of Stature," *Archives of Disease in Childhood* 89 (2004), p.17.

methodologically more rigorous studies and larger samples suggest that short children do indeed experience stress as a result of teasing and bullying, but that these experiences have very little impact on their psychological well-being and on their ability to cope with these problems. Studies conducted in the UK[19] and in the United States[20] found that boys of idiopathic short stature differed only moderately from peers in the control groups on a variety of psychological tests such as self-esteem, self-perception, and behavior. Girls of idiopathic short stature, for their part, were nearly indistinguishable from their normal counterparts.

These results have been corroborated by other studies. A Dutch group analyzed the impact of short stature on the quality of life of five different groups of short individuals: individuals affected by classic hGH deficiency, individuals suffering from renal failure, women with Turner Syndrome, individuals of idiopathic short stature, and individuals presumed to be idiopathically short. (The latter group is a reference group of short individuals who had not been referred to an endocrinologist.)[21] According to the study, all participants experienced difficulty in finding a partner. In other respects, however, the picture is far more nuanced. Only women with Turner Syndrome reported problems with job applications, and normal short individuals did not report any reduction in their quality of life.

Surprisingly, individuals of idiopathic short stature who were referred to an endocrinologist did report reductions in their quality of life. They also reported a range of psychological and social problems.[22] This result has been confirmed by other studies[23] and has been attributed to the failure of the hGH treatment to produce the expected results. It is not entirely clear whether the failure should be interpreted in physiological terms, i.e., as an ineffective treatment, or whether it should be attributed to the realization by the subjects in question that increased stature alone was unlikely to have a significant impact on their quality of life. Either way, this finding suggests that the medical treatment of what is ultimately a psychological and a social problem could exacerbate rather than mitigate the problem.

In sum, the available empirical evidence suggests that there is no basis for the claim that children of idiopathic short stature are psychologically impaired, that their chances of success in life are limited, or that their quality of life is poor. Short children do report experiencing bullying and teasing, but this does not seem to have a significant impact on their well-being.

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[19] Bruce A. Dowdney et al., "Are Short Normal Children at a Disadvantage? The Wessex Growth Study," *British Medical Journal* 514 (1997); A.B. Downie et al., "Psychological Response to Growth Hormone Treatment in Short Normal Children," *Archives of Disease in Childhood* 75 (1996); Ulph et al., "Personality Functioning: The Influence of Stature."

[20] Sandberg, Brook, and Campos, "Short Stature: A Psychosocial Burden Requiring Growth Hormone Therapy?."

[21] J.J.V. Busschbach et al., "Quality of Life in Short Adults," *Hormone Research* 49 (1998).

[22] H.-C. Steinhausen et al., "The Behavior Profile of Children and Adolescents with Short Stature," *Journal of Behavioral Pediatrics* 21 (2000); L.E. Underwood, "The Social Costs of Being Short: Societal Perceptions and Biases," *Acta Paediatrica Scandinavica*, no. 377 (1991).

[23] Sandberg, Brook, and Campos, "Short Stature: A Psychosocial Burden Requiring Growth Hormone Therapy?."

Patterns of Use

Could the medical profession contribute to discourage parental demands for treatments with synthetic hGH, or is it more likely that it will actually support and amplify questionable parental desires? Should the government trust the medical profession not to indulge demands for what may be cures of dubious effectiveness? To explore this question, in this section we examine prescription patterns for synthetic hGH among medical specialists.

A fairly recent, comprehensive survey of prescription practices among pediatric endocrinologists and their views on numerous questions pertaining to the prescription of synthetic hGH provides several important insights.[24] The survey was sent to the members of the Lawson Wilkins Pediatric Endocrine Society, the largest professional organization of pediatric endocrinologists. The response rate was very high: 81 percent, or 434 out of 534 physicians, returned the survey. A first important conclusion emerging from this survey is that pediatric endocrinologists do not treat ISS children very often. According to this survey, 58 percent of the patients were treated for classical hGH deficiency, 15 percent for Turner Syndrome, 11 percent for neurosecretory disorders, and 2 percent for renal insufficiency. Of the remaining 14 percent, 5 percent were treated for other, non-endocrine medical conditions and 9 percent for familial, constitutional, or unknown causes of short stature. In other words, only approximately one out of 10 treated patients were ISS children.

Based on this initial observation, one might conclude that pediatric endocrinologists are generally cautious in prescribing hGH for the treatment of idiopathic short stature. This conclusion would be premature. Asked whether short children in the third to fifth percentile for their age are likely to be psychologically impaired, 83 percent of pediatric endocrinologists answered that this is either "sometimes" or "often" the case. This percentage rises to 91.5 percent for children in the third percentile. An analogous pattern emerges for adults in the same height intervals. The survey also shows that pediatric endocrinologists are more likely to recommend a treatment the shorter the child is, the slower his or her growth rate is, and the more advanced bone age is.[25] These patterns of prescription again are inconsistent with the medical literature: Shortness is a poor indicator of responsiveness to treatment, and so are slow growth and bone age.[26] This data suggests that the decision to recommend treatment is based on two equally unwarranted perceptions – that shortness causes psychological impairment, and that shorter children are more likely to respond well to a human GH treatment.

These observations indicate that if an increasing number of ISS children were to be referred to pediatric endocrinologists, the total number of prescriptions for hGH treatment would increase significantly. We do not have recent data on this question, but the aforementioned study offers

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[24] Leona Cuttler et al., "Short Stature and Growth Hormone Therapy: A National Study of Physician Recommendation Patterns," *Journal of the American Medical Association* 276, no. 7 (1996).

[25] Bone age is a measure of skeletal maturation, and its used to evaluate a child's remaining potential for growth.

[26] Cuttler et al., "Short Stature and Growth Hormone Therapy: A National Study of Physician Recommendation Patterns," p.535.

some clues. The survey reports that 68 percent of respondents believed that the rate of prescription for ISS children had increased either "somewhat" or "significantly" in recent years.[27] Anecdotal evidence indicates that parents are indeed likely to refer their short but otherwise healthy children to an endocrinologist,[28] so much so that insurance companies have found it necessary to clamp down on prescriptions for hGH.[29]

Perhaps the strongest evidence that making idiopathic short stature a medical condition would lead to an unprecedented increase in the non-therapeutic use of hGH comes from Australia. In 1988, the Australian government decided to eliminate mandatory testing for hGH deficiency as a condition for the prescription of hGH. The number of children receiving hGH treatment increased by a factor of four, and the annual cost for these prescriptions went from $1 million to $45 million in three years. Alarmed by this trend, the Australian government decided to reverse its decision, and in 1995, the total cost was reduced to $16 million.[30] The situation in the United States differs from the Australian case in that the FDA has merely included idiopathic shortness in the list of approved medical uses. A prescription by a pediatric endocrinologist is still required. Nevertheless, the Australian experience clearly suggests that regulatory agencies should be very cautious in indulging societal tendencies that may be both ethically questionable and very costly.

The admittedly limited data demonstrates that pediatric endocrinologists are likely to share with parents and children inaccurate and misleading views of the relationship between shortness and psychological impairment. These views may translate into supportive attitudes toward parents demanding costly cures for non-existent conditions. More importantly, they also facilitate the creation of a powerful coalition of medical professionals, pharmaceutical companies, and patient groups dedicated to advancing what ultimately are the narrow interests of a few societal groups.

The Market for Human Growth Hormone

Reliable figures about the size and growth of the market for synthetic hGH are very difficult to come by. Repeated inquiries with the leading pharmaceutical manufacturers such as Pfizer, Genentech, and Ely Lilly produced very limited results. The lack of reliable data notwithstanding, there is no doubt that this market is both lucrative and rapidly expanding. In 1996, a group of medical practitioners estimated the cost of an hGH treatment at $13,000 to

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[27] Remember that the survey was conducted in 1996, so this trend might well have accelerated since then.

[28] Rick Weiss, "Growth Hormone's Downside; Use on Healthy Children Raises Ethical Concerns," *The Washington Post*, May 10, 1995.

[29] Rick Weiss, "Are Short Kids 'Sick'? Doctors and Drug Makers May Be Overpromoting a Profitable Hormone That Makes Children Taller," *The Washington Post*, March 15, 1994.

[30] G.A. Werther, "Growth Hormone Measurements Versus Auxology in Treatment Decisions. The Australian Experience," *Journal of Pediatrics* 128, no. 5 (1996).

$16,000 per year, for several years.[31] More recent figures range between $20,000 and $30,000 per year. The aforementioned study estimates the number of children in the United States affected by severe hGH deficiency at approximately 14,000. Based on this number, in the mid-1990s, market size was between $182 and $224 million – a sizeable but not a huge market.

Every new therapeutic use of synthetic hGH approved by the FDA has of course expanded the size of this market. With the recent decision by the FDA to add idiopathic short stature to the list of approved indications, the potential size of the synthetic hGH market has grown dramatically. Estimates of the number of ISS children range from 400,000 to 1,7 million.[32] The lower estimate, by Eli Lilly, can be attributed to a more conservative definition of short stature, in this case below 2.5 standard deviations. Leona Cuttler, by contrast, defined ISS children as those in the third percentile for their sex and age. In the latter case, the market for hGH would expand to a very attractive $22 billion. Another way to appreciate the economic significance of the FDA decision to declare idiopathic short stature a medical condition is to note that children with classical hGH deficiency constitute only between 0.82 and 3.5 percent of the population of ISS children, depending on how idiopathic short stature is defined.

The actual market size for synthetic hGH is even larger if one includes off-label prescriptions and illegal uses of hGH. Anecdotal evidence suggests that aging baby-boomers are beginning to rely on hGH treatments to combat age-related symptoms.[33] It appears that in modest amounts, hGH can indeed be beneficial, and the side effects are minimal. A new, more recent trend has been observed among women seeking "eternal youth."[34] It is also well-known that some athletes have used hGH to boost their performance.[35] Finally, there is some evidence that adolescents are abusing hGH.[36] In sum, the synthetic hGH is on its way to becoming a major source of revenue for several large pharmaceutical companies – a point that federal regulators and most bioethicists have failed to adequately acknowledge.

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[31] Cuttler et al., "Short Stature and Growth Hormone Therapy: A National Study of Physician Recommendation Patterns."

[32] Ibid.

[33] Sabin Russell, "Aging Baby Boomers Turn to Hormone: Some Doctors Concerned About Growing 'Off-Label' Use of Drug," *The San Francisco Chronicle*, November 17, 2003.

[34] Katrina Beikoff, "New Body-Drugs Shock Seeking Beauty in Bottle," *Hobart Mercury*, February 12, 2000.

[35] Sabin Russell, "Growth Hormone an Expesive Garnish: Drug Used to Treat Dwarfism in Young Appeals to Athletes," *The San Francisco Chronicle*, October 22, 2003.

[36] Jeannette M. Smith, "Human Growth Hormone: A New Substance of Abuse among Adolescents?," *Journal of the American Medical Association* 269, no. 11 (1993).

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