Growing Up Short

Synthetic growth hormone raises hopes—and ethical questions—in treating short children

By DEBORAH FRANKLIN

"Nobody's going to die from short stature," says Brian Stabler. "But you may feel like you wish you were dead."

Stabler, a psychologist at the University of North Carolina School of Medicine in Chapel Hill, studies the emotional bruises and scars that can start with an inability to reach door knobs, drinking fountains and elevator buttons, and extend to taint a larger world of social interaction and job choice. Synthetic growth hormone — the latest fruit of scientists' efforts to produce valuable proteins in bacteria — could provide new hope for some children never before expected to grow taller than four feet. Such children and their parents eagerly await approval by the Food and Drug Administration for widespread use of the new form of an old drug — expected early this year. Meanwhile pediatric endocrinologists around the world are watching with interest and some concern as the hows and whys of synthetic growth hormone treatment move from the controlled confines of academic medicine to the harsher pressures of the marketplace.

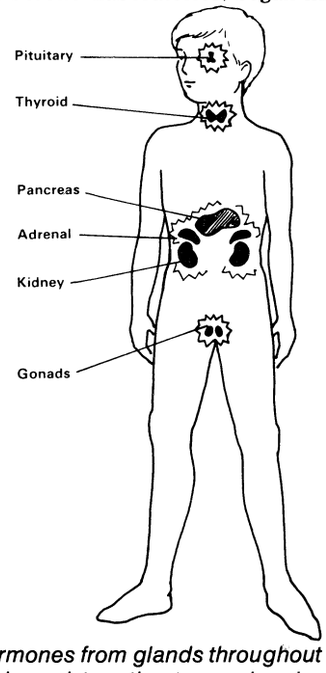
Mortimer Lipsett, director of the National Institute of Child Health and Human Development in Bethesda, Md., has called treatment with synthetic growth hormone, newly developed by Genentech of South San Francisco, Calif., "the key pediatric issue of this decade." James Tanner, director of the Institute of Child Health at the University of London, labeled the issue "a bombshell." Central to their concern is the still fuzzy understanding of why some children grow up short.

Genes inherited from parents, along with diet and environmental influences in the womb (SN: 10/15/83, p. 250) and a medley of chemical messengers from glands throughout the body, act synchronistically throughout childhood and adolescence to determine the speed of a person's growth and his or her ultimate height. Any misstep in the growth pathway, such as a malfunction in various hormone-producing glands, a bone defect or a missing or damaged chromosome, can lead to one of dozens of syndromes that retard growth.

Sometimes the source is readily diagnosed as a treatable medical malady. Since 1958, when a 17-year-old prepubescent dwarf more than quadrupled his growth rate after injections of a hormone gleaned from the pituitary glands of cadavers, each year from 1,200 to 2,000 children in the United States alone have benefited from similar injections. Hypopituitary dwarfs are perfectly proportioned, tiny people — often six to twelve inches or more shorter than others their age. Human growth hormone (hGH) treatment typically boosts their height by two to six inches each year of treatment until the long bones fuse at puberty. But a typical two-year treatment for one child requires hormone extraction from 50 to 100 pituitary glands — the pea-sized organ painstakingly removed from the base of the brain at autopsy. Unlike insulin, and other useful chemicals derived from the glands of cattle or swine, animal growth hormone is ineffective in humans.

The National Institutes of Health (NIH) carefully rations the limited supply of human hormone collected in the United States, by restricting its use primarily to "hypopituitary" children whose short stature can clearly be traced to a faulty or inadequate supply of their own growth hormone. The treatments are free to all children enrolled in NIH-sponsored studies of the drug but quantities allotted each patient are limited. Once a boy reaches about five feet six inches, and a girl reaches five feet four inches in height, treatments are discontinued.

When two European firms, KabiVitrum and Serono Laboratories, began harvesting growth hormone on a commercial scale and marketing it for profit in the United States in 1979 and 1980, the supply shortage eased somewhat. But the price of the commercial treatments (often $9,000 to $20,000 a year) is prohibitive for many families, and there certainly has been little to spare for non-hypopituitary children who might have benefited — not to mention burn victims, arthritics, and sufferers of the wasting disease cachexia.



Illustrations: Human Growth Foundation

Hormones from glands throughout the body work together to synchronize growth.

Pituitary insufficiency is not the only cause of short stature. In addition to those suffering from obvious physical abnormalities, some children are short for unidentified reasons. While endocrinologists are convinced that hormonal injections will not increase a child's height beyond genetically set limits or spur growth after puberty, a heterogeneous group labeled "constitutionally growth delayed," could probably benefit from treatment, says Selna Kaplan, a pediatric endocrinologist at the University of California at San Francisco. Kaplan and colleagues Guy Van Vliet, Dennis Styne, and Melvin Grumbach tested the synthetic hormone last year in 14 very short but otherwise normal children aged 4 to 16 years, and increased the growth rate in six of the children by an average of 1.2 inches a year.

All 14 had shown a slow growth rate prior to treatment (less than 1.5 inches per year), but had normal levels of growth hormone in their blood. The study cracked open a door to a new treatment group, though Kaplan and co-workers are concerned that the crack not be misread as a floodgate.

"Only long-term follow-up will establish whether sustained treatment with growth hormone will increase the final height of these short normal children," they caution in the Oct. 27 New England Journal of Medicine. Until more information has been gathered on the long-term effects and possible side effects in normal children, and researchers can clearly define who might be helped, "the extrapolation of these findings to support indiscriminate treatment of short normal children with this potent hormone is premature and unwarranted," they warn.

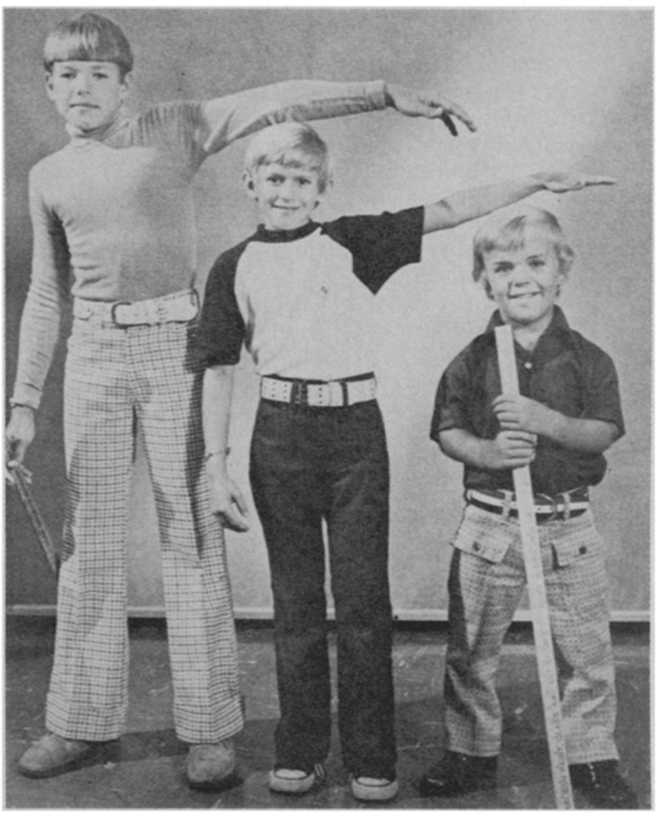
What are the risks? Published data are skimpy, but possible side effects of very large doses include gigantism and acromegaly — an abnormal enlargement of the bones. These problems, as well as a mild form of diabetes, occur in children

with pituitary tumors whose bodies produce too much growth hormone. Researchers are concerned that injecting large amounts of extra hormone into children whose levels are already normal could prompt similar effects. A more probable side effect—though still unlikely, researchers say — is a build-up of antibodies in the recipient's bloodstream that could inactivate both injected and native hormone. No significant side effects of any kind have appeared in children treated thus far. The synthetic hormone has one more amino acid than the substance made by the pituitary, but the disparity seems to make no difference in function.

Perhaps the most intriguing question to arise from the Kaplan study is why some children grew, while others did not. Many researchers have cited low blood levels of the growth mediator somatomedin C as a good indicator of children who were likely to respond to therapy. But in Kaplan's study, children with normal somatomedin levels also benefited.

Once the medical questions surrounding the new drug have been answered, the ethical quandary begins. The risk of raising a child's—and parents'—expectations beyond realistic limits has been a problem for 25 years in the treatments of some hypopituitary children. That problem could balloon, Stabler says, as use of the synthetic hormone expands.

A short child may adapt by becoming a "mascot" to friends and family, says Stabler. Exceptional shortness could even boost rather than hinder self confidence. But even the most successful hormone treatment only raises a child's height by several inches. As he or she grows to the short side of average, the mascot becomes less visible, and may develop what Stabler calls "an invisible handicap."



Three 12-year-old boys illustrate growth maladies that shorten stature. The child on the left is average, while the center boy has a pituitary deficiency treatable with growth hormone. The child on the right has achondroplasia, an inherited abnormality of cartilage and bone.

Diane Rotnem, an assistant professor of social work at The Yale Child Center in New Haven, Conn., recently documented the psychological problems that developed when 11 children with malfunctioning pituitaries were treated with growth hormone, and failed to grow to their own expectations. "Before hGH treatment, the short children were immature and dependent and were treated like much younger children whom they resembled physically," she says. "In spite of accelerated growth with hGH, children and parents perceived the treatment to be a failure relative to their expectations. The children became angry, pessimistic, guilty, and negativistic, and felt unacceptable as they were."

When he first began treatment, one nine-year-old child Rotnem calls "C" was shy, insecure and much shorter than his shortest classmates. He wore his height deficit like a winter overcoat that grew heavier each year as the gap between his height and "normal" stature widened. Shown a photograph of a group of children with baseball caps and asked to describe the scene, C said: "The boys are playing baseball. One boy wants to join while they are planning what to do. They don't know if they want the boy to join. It makes him feel sad. They can't decide if they want him to play."

A year and a half later, after thrice weekly intramuscular injections of growth hormone, the boy's growth rate increased slightly — by about 1.5 cm a year. But in school, his grades dropped and C's mother watched her child become apathetic and listless at home. Shown, after treatment, the same photograph of children at play, he said, "The boys are telling secrets. Maybe they want to beat him up. They beat him up in the end and this makes him feel very bad." Most children in Rotnem's study grew more than C did, but the disappointment of some was just as profound. Though injections of growth hormone had shifted them from extremely short to the low side of average, many still felt short. In the eyes of the child who longed to be tall, the treatment had been a failure.

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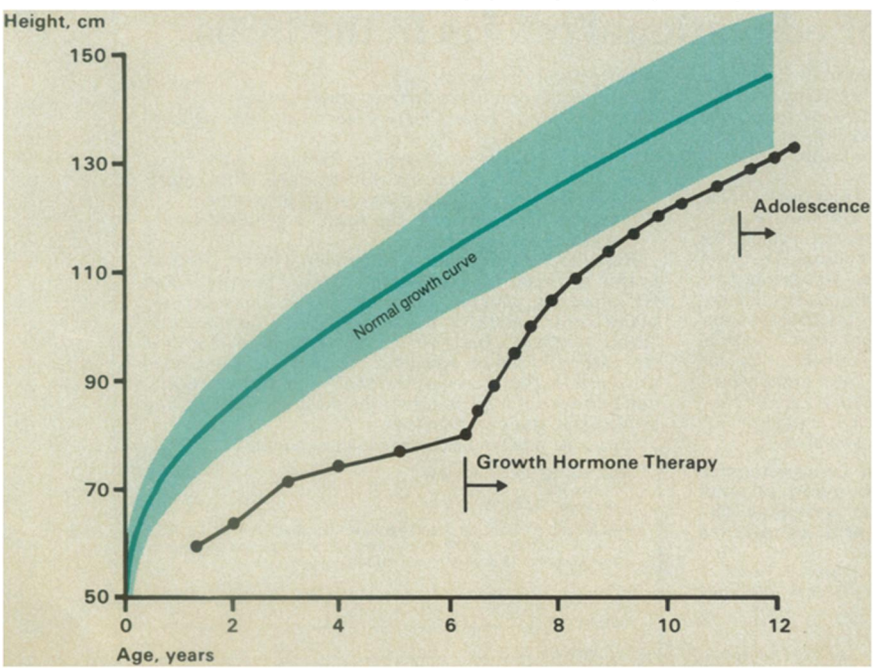

The dotted curve charts the initial growth spurt that later tapers in a child with insufficient growth hormone of his own who is responding well to treatment.

"The benefits of hGH therapy should not just be an increase in stature, but an improvement of psychosocial adjustment," says Albert Jonsen, a bioethicist at the University of California at San Francisco. "A short child is a short child in relationship to the world he lives in.... What about the child who doesn't show any stress [from being short] at all? Should he be treated? These are hard areas and we need more information."

The findings that psychosocial support is as important to successful hormone therapy as the injections becomes even more important as the advent of synthetic hormone makes it possible to prescribe treatment from any corner clinic, Jonsen says. While most of the experimental programs have included a psychological component to treatment, there is no guarantee that prescribing physicians will recognize psychological issues once synthetic hormone is deregulated.

"We're not talking about expensive psychotherapy," says Stabler. "Often just holding family conferences, alerting a school counselor or minister — someone close to the family [about the treatment limitations and changes to expect] — will be enough to help the child through the transition."

Robert M. Blizzard, a pediatric endocrinologist who has been testing the Genentech product at the University of Virginia in Charlottesville, applauded the call for more research into the environmental influences that affect short children undergoing treatment. "As physicians treating with growth hormone, we need to understand; are we treating the patient, are we treating the parent, or are we treating both?" he says.

Stabler reports preliminary evidence on the families of 14 hypopituitary children who received the synthetic hormone. Nearly 45 percent of the patients and their parents overestimated the child's height in relation to peers, and nearly 80 percent had unrealistic expectations of how much hGH therapy would help the child to grow. In particular, fathers, who are often neglected in studies of parent/child relationships, may play a strong role in shaping their child's expectations of and adaptation to growth treatment, Stabler says. Anecdotal evidence gathered after the splash of publicity surrounding synthetic hormone in the last few months indicates that the "normal short" children and their parents who are now inquiring about therapy with the new hormone may be particularly hard-driving, aggressive and intelligent "Type A" families who may present a new list of psychological responses to the therapy, Stabler says.

"Once the drug is licensed, it can be used by anyone who has a license to prescribe — that's the law," says Jonsen. "There's one potential problem with people's expectations being disappointed, and another with some parents trying to make basketball players out of their children. That's the kind of thing I think we really need to worry about. There are going to be physicians who will cave-in to parents' demands about trying to make their [normal] kids taller, and... there's no legal way of controlling it."

Genentech began clinical testing of the drug in 1982. Expectations that the hormone would soon be approved for general use were strong enough to prompt a recent National Institutes of Health conference on its use, though both the FDA and Genentech have been tightlipped about predicting deregulation.

"If the consuming public decides that it wants to get this drug, they will use or abuse it at will, no matter what regulations are set up," Stabler says. Aside from educating clinicians and the public about the drug, the only way researchers of the hormone can influence its use is by quickly establishing "appropriate standards of care" that can serve as guidelines in health insurance reimbursements and malpractice suits, Jonsen says. To that end, Genentech is planning a study of the synthetic hormone's effects on more than 300 nonhypopituitary children at 10 U.S. medical centers as part of an international effort to standardize studies that will permit a better understanding of both the physical and psychological components of "shortness" and its treatment.

"As we go around the elephant," says Stabler, "even though we may be blind, let's at least make sure we all have on the same thickness of gloves."

Despite their concern that the increased hormone supply not be abused, endocrinologists are enthusiastic about the new hope for previously untreated children. "This is what we've been working for since growth hormone was first tested in 1958," Blizzard says, "It's a very, very significant event." □