New Growth Industry in Human Growth Hormone?

Researchers predict that human growth hormone will soon be used to make short children taller and, possibly, help dieters lose fat and make aging people look young

In the near future, say investigators who study human growth, it is almost certain that many affluent parents of short children will have their children treated with human growth hormone as a matter of course. The children then might grow up to be "appropriately" tall. And there is also a likelihood that obese people will take growth hormone when they diet so that they will lose fat and not muscle tissue. Growth hormone may even be used to retard aging—it may prevent wrinkles and the sort of fat distribution that occurs in old people. Athletes are already taking the drug, obtaining it on the black market, because there is evidence that it may help build muscle. "It is really *Brave New World*," says James Tanner of the Institute of Child Health at the University of London.

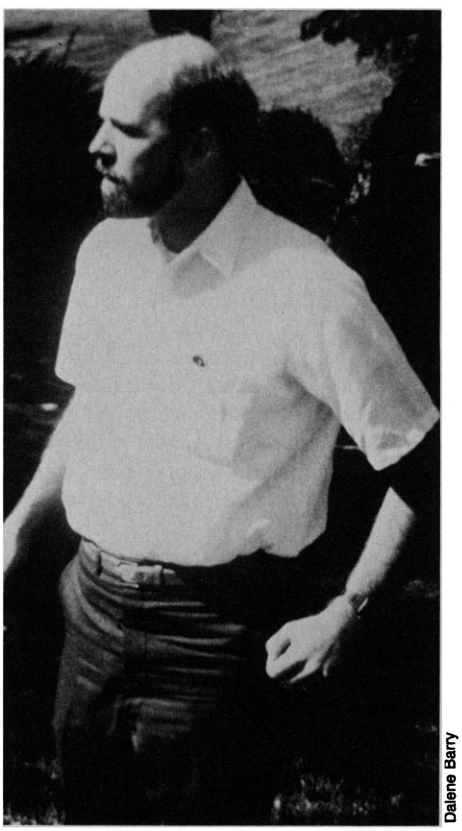
Biotechnology companies and pharmaceutical firms are gearing up to produce large quantities of human growth hormone using recombinant DNA technology. It is a sure bet, said participants at a recent meeting on human growth,* that the companies are not just planning to market the drug for the treatment of pituitary dwarfs, who until now have been the only legitimate recipients of human growth hormone. "Obviously," says Barry Sherman of Genentech, "there aren't that many short kids to treat."

These potential new markets for growth hormone give many researchers pause. They are concerned that the hormone will never be properly tested in clinical trials and they worry about the ethics of what John Parks of Emory University School of Medicine calls "cosmetic endocrinology." Nonetheless, it may be impossible to stanch the flow of growth hormone. "We are now moving from an era in which there were too many patients chasing too little growth hormone to an era in which there will be too much growth hormone chasing too few patients," says Tanner. Genentech, currently the sole supplier of human growth hormone, estimates that the obesity market alone is worth billions of dollars per year.

***"Who's to say there aren't placebo effects? How can you possibly be sure that if you stick a needle in a child's skin three times a week that you won't affect growth?"*—Gordon Cutler**

Growth hormone is produced by the pituitary gland in the brain and it stimulates the liver to produce somatomedins—hormones that are very similar in structure to insulin and that stimulate bones to grow. Children and adolescents produce large quantities of growth hormone, and adults normally produce very little of it. But researchers believe that the hormone's primary purpose may not be to stimulate growth at all.

Children who are malnourished produce excessive amounts of growth hormone, yet they do not grow. Adults, who normally do not make measurable quantities of the hormone, begin producing much more of it when they fast or when they are stressed. Runners, for example, synthesize measurable amounts of growth hormone. Researchers suspect that growth hormone's principal function may be to conserve muscle tissue at the expense of fat tissue during times of stress. "Growth hormone is the hormone of fasting just as insulin is the hormone of feasting," says Robert Blizzard of the University of Virginia Medical Center. "Insulin increases fat storage and growth hormone mobilizes fat from fat cells." This is the reason that biotechnology companies are eyeing it as a drug for dieters.



Dalene Barry

Growth hormone also may play a role in aging. Old people make much less of the hormone than younger people. Moreover, says Blizzard, "children who are growth-hormone-deficient age prematurely. A 30-year-old growth-hormone-deficient patient frequently looks 45. They have premature wrinkling and frequently have a fat distribution that is similar to that of old people. It is logical to postulate that some of the changes of aging are related to the fact that growth hormone is not around to the extent that it originally was."

Pituitary dwarfs have been receiving human growth hormone for decades—but only recently has it been possible to produce it cheaply and in large enough quantities to allow the testing of hypotheses about its uses for short children who are not dwarfs and for the obese and the aging.

*The International Workshop on Advances in Research on Human Growth was held on 14 to 16 September and sponsored by the National Institute of Child Health and Human Development.

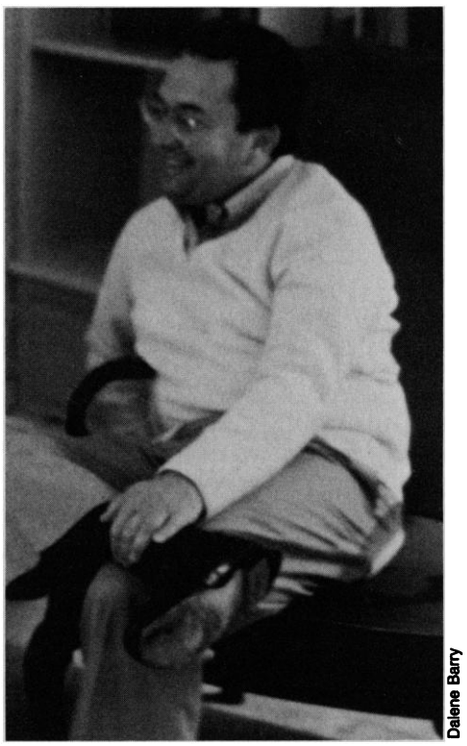
Growth hormone used to be obtained directly from the pituitaries of cadavers, and children who were judged growth-hormone-deficient would receive three injections of it a week to make them grow. The National Hormone and Pituitary Program processed as many as 50,000 pituitaries a year, supplying the growth hormone derived from them to 3500 children and adolescents. Another 2300 patients obtained human growth hormone from Serono Labs and KabiVitrum, pharmaceutical companies that also got the hormone from human pituitaries. Because the hormone was so difficult to obtain, it was always in short supply and, says Michael Thorner of the University of Virginia Medical School, the criteria for deciding whom to treat were quite stringent. The idea, he explains, was to be sure that "every child who received growth hormone was growth-hormone-deficient, not that every child who was growth-hormone-deficient received growth hormone."

About 1½ years ago, a catastrophe occurred and, as a result, the distribution of pituitary-derived human growth hormone was summarily halted (*Science*, 7 June 1985, p. 1176). In March of 1985, federal officials learned that three people who had been treated with the hormone in the 1960's and 1970's died in 1985 of Creutzfeld-Jakob disease, a very rare disease that results in dementia and death and that is caused by mysterious particles, called slow viruses, that live in brain tissue. The most likely reason that these people developed Creutzfeld-Jakob disease is that they received growth hormone extracted from pituitaries of other Creutzfeld-Jakob victims and these pituitaries contained infectious slow virus particles.

But in the fall of 1985, the Food and Drug Administration gave its approval to a genetically engineered version of human growth hormone, produced by Genentech, and the hormone was back in distribution again. Because the Genetech growth hormone is manufactured in bacteria, no human pituitaries are needed, and the Creutzfeld-Jakob threat is gone. The Genentech growth hormone costs about as much as the hormone from pituitaries—$10,000 a year for three injections a week—but health insurance companies pay for it when children are judged to need it.

Now KabiVitrum and Lilly are testing their own genetically engineered human growth hormone. For the first time, it looks like the rigid criteria for receiving it will be abandoned and it seems likely that the price will drop as well. Growth hormone treatment, say Tanner and others, may become as accepted as orthodontia. Among the new questions facing investigators now, says Thorner, is, "How do you tell if a child is growth-hormone-deficient or not?"

***"Obviously, there aren't that many short kids to treat."*—Barry Sherman, director of clinical research, Genentech**



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There is, says Thorner, no sharp cutoff between growth hormone deficiency and growth hormone sufficiency. Moreover, there is some evidence that taller children make more growth hormone than children who are at the short end of normal. So the decision that a child is growth-hormone-deficient depends, at least in part, on how tall you want that child to grow.

The sociology literature is full of data on the advantages of being tall. Executives and bank presidents are taller than average. Bishops tend to be taller than priests. In fact, says Tanner, each inch of height is worth several thousand dollars a year in income.

Well aware of the social and economic advantages of height, parents of short children are starting to pressure researchers to make their children taller. And some of the children are not even particularly short. S. Douglas Frasier of the University of California in Los Angeles tells of a father who brought his boy in to be tested for possible growth hormone deficiency. Frasier's colleague told the father that there was no cause for concern—the boy's predicted adult height was five feet seven inches. At that point the father roared, "That's absolutely unacceptable!"

Maria New of New York Hospital-Cornell Medical Center says that even girls are not satisfied unless they are tall. "For the first time in my life, I am seeing girls who want to be taller. The social acceptance of tallness in women used to be negative. Now it is positive."

Of course, when researchers make analogies between growth hormone therapy and orthodontia, they are assuming that the treatment works, that any child who receives growth hormone will grow up taller. And many at the meeting are convinced it does work. They argue that given enough growth hormone, any child will grow. The only question is the dose. As evidence, they point to pituitary giants, whose pituitaries pour out enormous quantities of growth hormone and who frequently end up more than 7 feet tall. So, in testing growth hormone therapy for children who are short, but not pituitary dwarfs, these investigators believe it unnecessary, even possibly unethical, to have a placebo-treated control group.

The clinical trials that are now under way in the United States, England, Switzerland, and Japan are designed so that the children serve as their own controls. In a typical study, one group of short children will receive growth hormone for 6 months, then be untreated for 6 months. Another group will be untreated for 6 months, then receive growth hormone for 6 months. The treatment will be considered effective if the children start to grow more rapidly and their predicted adult heights increase when they take the hormone.

But Gordon Cutler of the National Institute of Child Health and Human Development takes strong exception to this method of assessing growth hormone's effectiveness, and a few others agree. "Cutler is absolutely right," says Ron Rosenfeld of Stanford University Medical Center.

First of all, Cutler says, it is not so clear that any child will grow, given enough growth hormone. We need a placebo-controlled clinical trial to find out and the only way to do that is to give one group of children injections of growth hormone and the other injections of placebo and then wait to see which children, on the average, grow taller.

Among the reasons why you cannot argue from the example of pituitary giants that growth hormone will work, according to

Cutler, is that giants are exposed to growth hormones for much longer times and at times that may be crucial for it to be effective. Most giants are born making too much growth hormone, whereas most doctors do not diagnose a child as destined to be short until age 2 at the earliest, and some children are not diagnosed until they are 9 or 10. Yet, says Cutler, that first couple of years of life with huge amounts of growth hormone may be absolutely essential for the hormone to work.

There are some hints that children treated with growth hormone may actually reach puberty earlier than untreated children and so stop growing earlier. It is possible that growth hormone–treated short children will end up even shorter than they would otherwise have been. Giants do not go through puberty, says Cutler, which is one reason why they grow so tall.

A placebo-treated group, rather than simply an untreated control group, is necessary in a clinical trial because it may well be that the extra attention a child gets when he is injected three times a week influences growth. Or it may be that the implication that something is wrong with the child will affect his growth. The fact is, says Cutler, that "the brain controls growth." Virtually every known neurotransmitter has some effect on controlling the release of growth hormone. Emotions affect growth—abused children, for example, may not grow. "Who's to say there aren't placebo effects?" Cutler asks. "How can you possibly be sure that if you stick a needle in a child's skin three times a week that you won't affect growth?" The data from the current studies, says Cutler, "will never convince me."

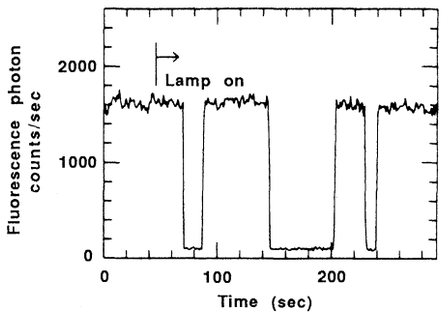
In answer to those who say a placebo-controlled trial would never get past an institutional review board and, even if it did, you would never get volunteers, Cutler responds that his group had permission from the National Institutes of Health ethics review board for just such a study and had enrolled 30 families, all of which understood that they could get growth hormone outside the study and all of which decided to participate, largely for altruistic reasons. But the study was never begun because, just when it was about to start, the Creutzfeld-Jakob cases were discovered and growth hormone was pulled from distribution. Cutler would very much like to start his study again.

Other studies, such as obesity and aging studies, are even less advanced. And, chances are, growth hormone, like so much else in medicine, will be used without a truly scientific evaluation. Yet, says Tanner, "all of us, in our hearts, believe it will work. But, in many ways, I rather think it would be better if it did not." ■ GINA KOLATA

Quantum Jumps Seen In a Single Ion

Researchers can monitor an infrequently occurring quantum transition in a single ion as it happens by measuring the fluorescence due to a frequently occurring transition

ALTHOUGH the optical properties of matter are well described in terms of transitions between the quantum states of atoms, molecules, and solids, observation of individual quantum jumps have only recently been reported. The sightings, which were made by groups at the University of Washington and at the National Bureau of Standards (NBS), Boulder, Colorado, on single ions confined in an electromagnetic trap, resolve the theoretical question of whether quantum jumps can actually be seen. Moreover, they open the way to a new kind of high-resolution optical spectroscopy and allow tests of the quantum statistical behavior of atoms and the like.



Quantum jumps. *A typical trace of the bright fluorescence showing the quantum jumps after the lamp excites the weak transition.*

Interest in the possibility of observing quantum jumps grew after a publication in March 1985 by Richard Cook of the Air Force Institute of Technology, Dayton, Ohio, and H. Jeffrey Kimble of the University of Texas at Austin. Cook and Kimble presented a simple theory outlining the statistics of quantum jumps in a model atomic system comprising a ground state and two excited states that differ in energy and by many orders of magnitude in lifetime.

The transition between the ground and one excited state is a so-called strong transition. "Strong" means that the probability for absorption of a photon when light of the appropriate wavelength irradiates the atom is high and that the atom quickly relaxes back to the low-energy state by radiating a photon. The fluorescence from even a single atom is easily visible because of the large number of transitions per second. The transition between the ground and the second excited state is weak or forbidden, so that a photon of the appropriate wavelength is infrequently absorbed and that, once excited to this quantum state, the atom waits a long time before relaxing to the ground state. The question is, what happens when light sources with the proper wavelengths for exciting both transitions are present?

In sum, most of the time the strong transition is excited, and a continuous bright fluorescence signal is observed. On those rare occasions when the weak transition is excited, the fluorescence disappears until the atom returns to the low-energy quantum state. Consequently, the disappearance and subsequent reappearance of the bright fluorescence signal transitions to and from the long-lived excited state; that is, the fluorescence monitors quantum jumps as they occur.

Actually, the notion of using the bright fluorescence from a strong transition to monitor a weak transition predates Cook and Kimble's analysis by 10 years. Hans Dehmelt of the University of Washington earlier proposed the idea as a means of obtaining spectroscopic information on weak optical transitions in single atoms. Such transitions are of interest because their spectral lines are intrinsically very narrow, which makes them candidates for optical frequency standards and possibly for atomic clocks. In principle, one could study the fluorescence that is emitted when the long-lived quantum state relaxes. But the long lifetime, which is responsible for the narrowness of the spectral line, makes this approach impractical.

Consider an excited state with a lifetime of 1 second and neglect background radiation. Photons are emitted throughout the full 4π solid angle around the atom, whereas photodetectors intercept only a small fraction of it. Moreover, photodetectors are inefficient and do not record every photon that comes their way. Between these two effects, if only one photon is registered for every 1000 emitted, a photon would be counted on the average only once every 17 minutes.

Even with these detector inefficiencies, however, the disappearance of the bright