Widely touted as a panacea against aging, growth hormone does provide some benefits. The molecule helps the elderly build muscle and burn fat, according to some clinical studies, yet no one knows whether long-term therapy is safe—or if it improves a person’s life. Furthermore, laboratory work suggests that less growth hormone is the secret to exceptional longevity. Researchers are sorting through the data and devising new approaches to understand the two sides of this molecule.

Elite athletes aren’t the only ones who strive for optimal performance. As people age, they hope to maintain vigor, whether that means continuing to run in weekend 10K races or retaining enough strength to get out of a chair. According to its promoters, growth hormone (GH) therapy is a boon for all these folks—it builds muscle and burns fat, they say, and it smooths wrinkles, boosts libido, and fights depression. GH treatment might confer at least some benefits, according to clinical studies. Yet laboratory work indicates that quashing the activity of GH and related molecules extends life span in a number of species, suggesting that gains from GH treatment might come at a dire cost: early death.

“The lay public hears that growth hormone is the fountain of youth. Yet if you take away growth hormone action, animals live longer,” says molecular biologist John Kopchick of Ohio University College of Osteopathic Medicine in Athens. GH therapy “is very, very controversial.” As researchers weigh the pros and cons of boosting hormone doses, they hope to devise the best way to compete in the ultimate human race—the one in which finishing last is the goal.

Bulk Up, Shed Fat—At a Price

As its name suggests, GH prods tissues and organisms to enlarge. Multiple times during the day, the pituitary gland, a small body at the base of the brain, squirts out pulses of the hormone. It enters the bloodstream and urges cells in various tissues to manufacture another hormone called insulin-like growth factor-1 (IGF-1). This hormone prompts cells to grow and divide, helping bolster muscle and strengthen bone. GH production begins to ramp up after birth and peaks during puberty. Then GH release gradually slows; by age 70, most people’s GH production is half what it was in their 20s.

The decline in GH might underlie the body’s deterioration over time, posit some researchers. Although the idea isn’t proven, studies of GH abnormalities support the possibility. For instance, adults with inefficient pituitaries—usually resulting from tumors in the gland—gain fat, lose muscle, and have thin bones, symptoms of aging. In addition, such patients die young and have an increased risk of cardiovascular disease and diabetes. With GH treatment, these individuals lose fat, bulk up, and live longer. GH also improves metabolism by helping cells respond to the sugar-regulating hormone insulin.

Although this therapy might be counteracting an illness rather than reversing accelerated aging, its success in people with GH deficiencies fostered the idea that dosing healthy elderly people might ameliorate some of the scourges of aging. Fanaticism about the “antiaging” effects of GH erupted in 1990, after a clinical trial revealed that GH prompted older men to shed fat and accrue muscle. In that work, endocrinologist Daniel Rudman of the Medical College of Wisconsin in Milwaukee and colleagues studied 21 men between the ages of 61 and 81 who carried unusually small amounts of blood IGF-1. (Because GH amounts fluctuate over the course of a day, researchers commonly use IGF-1 concentration, which is nearly constant, as a gauge of GH production.) After 6 months, the 12 men who received GH showed a 9% increase in muscle mass, a 14% decrease in fat mass, and a 7% increase in skin...
thickness—a sign of rejuvenation, as skin tends to thin and weaken with age—the team reported in the New England Journal of Medicine. The nine individuals in the control group, who did not receive GH, showed no significant changes in these characteristics. The study seized the public’s interest, especially because the researchers reported that the changes in body makeup reversed those incurred during 10 to 20 years of aging. “Everybody’s looking for something that counteracts aging,” says endocrinologist Michael Thornor of the University of Virginia in Charlottesville. “There’s no doubt it was provocative.”

Ever since the paper’s publication, hucksters have cited it as proof that GH turns back aging. The editors of the New England Journal of Medicine were so alarmed by this practice that in 2003, they published an editorial warning that such references overstate the conclusions of the study. Although the work showed a benefit to body composition, it didn’t establish that GH was safe or beneficial, says endocrinologist S. Mitchell Harman of the Kronos Longevity Research Institute in Phoenix, Arizona. The study followed a small number of patients for a short period of time and didn’t assess whether the physiological changes imparted by GH treatment improved the subjects’ mobility or health.

More recent work supports the idea that GH therapy thins and strengthens bodies (see “Lean, Yes—but Mean?”*), but “we still haven’t shown that GH treatment improves a person’s ability to perform activities of daily living,” says Harman. Moreover, researchers haven’t assessed the risks of GH therapy over the long haul, and side effects could be severe. For instance, short-term studies have revealed that people undergoing treatment frequently suffer from carpal tunnel syndrome and diabetes. The regimen might also increase cancer risk. “It’s not ready for prime time in terms of clinical application,” says endocrinologist Mark Blackman, director of the National Center for Complementary and Alternative Medicine in Bethesda, Maryland. “We haven’t learned enough about the long-term effectiveness and safety.”

Long Life Lowdown

And laboratory studies suggest that even greater dangers might be lurking. Mice live exceptionally long and resist oxidative stress when they have mutations that result in too little GH and IGF-1 (see Bartke Viewpoint† and “One for All”‡). Disparate organisms seem to share this life-prolonging mechanism: Glioblast in the fly and nematode versions of the IGF-1 pathway also delay those creatures’ demise. In addition, calorie restriction, which extends life span in many species, reduces concentrations of IGF-1 (see Masoro Review§). “You can become very old and very healthy with essentially no growth hormone at all,” says gerontologist Richard Miller of the University of Michigan, Ann Arbor. Those observations suggest that GH could shorten human lives, even if it streamlines bodies. “If you look at the fundamental mechanisms that regulate the onset of aging and life expectancy, [you see that] the hormones that promote growth and development and sexual maturation are probably not good for longevity,” says physiologist Andrzej Bartke of the Southern Illinois University School of Medicine in Springfield.

Researchers don’t yet know whether people with low GH production live long, but clues are coming from rare individuals with the same pituitary defects that long-lived dwarf mice have (see “Power to the People”¶). Mortality data are sparse. Nevertheless, some individuals live to old ages, suggesting that these people don’t suffer from shortened life span—and that findings on aging in rodents and other lab denizens might transfer to people.

Clinical researchers and lab scientists warn against giving GH to otherwise healthy elderly people and denounce marketing of GH-boosting treatments. Yet some experts say that GH therapy might be useful in certain circumstances. For instance, elderly people prone to frailty—a weakened condition characterized by low muscle mass and fragile bones, among other problems—might benefit from the added strength conferred by GH, says Blackman (see Lipsitz Perspective¶ and Walston Perspective§). “GH may well find its place,” agrees Bartke. “For somebody who is 80, life expectancy is not the issue; the issue is function. If GH detracts from life expectancy [but improves quality of life], so be it.” That distinction might explain the apparent discrepancy between the much-touted antiaging power of GH and the conclusion from lab animals that less is better. “When experimental gerontologists talk about antiaging, we’re talking about prolonging life,” but when GH advocates talk about antiaging, they’re talking about feeling and looking younger, says Bartke.

Researchers say that in the future, they hope to tease apart the ups and downs of GH. “Growth hormone has both good and bad effects,” says endocrinologist William Sonntag of Wake Forest University School of Medicine in Winston-Salem, North Carolina. “The question is, when during the life span do they occur?” Previously, researchers have studied animals that are GH deficient their entire lives, and their exceptional longevity might result from a scarcity of hormone early in development. “It’s quite clear from the animal work that low growth hormone in early life leads to excellent longevity,” says Miller. “That doesn’t say anything one way or the other about whether [having] high levels or low levels in late life is a good thing or a bad
thing. It’s possible for both things to be true. Those are separate questions that need to be addressed independently.” Next, scientists need to manipulate GH amounts at different stages of an animal’s life, says Sonntag. In addition, they need to analyze animals with reduced hormone activity rather than none. Such studies should allow scientists to appraise the impact of GH activity on longevity and health.

**Growth Industry**

Clinical researchers are also devising more sophisticated ways to exploit the benefits of bolstering GH while ameliorating the downsides. Future work should track more patients over longer periods of time to better assess the pros and cons of GH supplementation, says Blackman. Furthermore, those endeavors should monitor a patient’s mobility and quality of life in addition to measures such as muscle mass and body fat.

Lower doses might minimize risks yet remain effective. Until now, researchers have based doses on those used in children with GH deficiency. Because GH quantities wane over time, that amount might be too much for an older person, but little solid data on that issue exist. “Practitioners of GH replacement therapy to ward off symptoms of aging] claim that they give lower doses and don’t see side effects,” says Harman. “That’s all well and good, but where’s the evidence that [lower doses are] beneficial?”

Ongoing work promises to address that question. For instance, endocrinologist Fred Sattler of the University of Southern California in Los Angeles and colleagues have embarked on a clinical trial in which elderly patients receive as little as one-third the amount of GH typically administered. That study will conclude in 2006.

Researchers are also examining other ways of maximizing GH’s benefits. For instance, the pituitary emits GH in multiple daily surges, but an injection produces a single burst that decays slowly. Compounds that prod the pituitary to generate youthful patterns of GH might prove more effective than one shot. Pill peddlers already claim to have products that accomplish this feat—typically amino acid supplements that include arginine. But these supplements likely do nothing, says Thorner. The approach is based on studies showing that an infusion of arginine into the blood of patients with GH deficiency raises the peaks of hormone waves. However, other work has indicated that taking the agent orally doesn’t work, he says: “People have cherry-picked the literature for data that support their product.”

But legitimate compounds that do perform might be in the offing. For instance, in the 1990s researchers at Merck identified molecules that tickle a protein called ghrelin. Ghrelin spurs the discharge of GH-releasing hormone from the brain’s hypothalamus, which in turns prods the pituitary to disgorge pulses of GH. Merck scientists originally hoped that the compounds would hasten patients’ recovery from hip fractures, but the drugs failed. Now, researchers are revisiting the strategy. For instance, Thorner is currently testing a Merck compound that amplitude and health.

**Ebb tide.** The pituitary discharges growth hormone in multiple daily pulses that peak during deep sleep; these undulations dampen with age, and new treatment strategies aim to strengthen them. The graph shows the predicted GH secretion pattern in young and old adults. Note the lower and more gradual surges in the older group.

plifies GH waves in elderly patients. His team is collecting data on fat, muscle mass, and general well-being, as well as assessing the ability to walk and climb stairs. Thorner doesn’t yet know whether this treatment will show fewer side effects than GH injections, but he notes that only two patients out of 60 have dropped out of the 2-year study, and he suspects that maintaining the pulsing pattern of GH release will harm people less. Popping this pill is cheaper and less painful than injecting GH preparations, which can run $15,000 per year or more.

Other approaches might also stimulate natural patterns of GH release. Pituitary output peaks at night, during deep sleep, which the elderly don’t get as much of as younger people do. Encouraging this type of rest might help bolster GH. For instance, researchers showed in 1997 that young men who receive a compound called gamma hydroxybutyrate, a deep-sleep inducer, pump out more GH. Exercise also sparks GH production, although working out doesn’t spur as large a surge in older people as in the young. Following up on these approaches might help researchers hone in on a safe treatment that harnessed the rejuvenating power of GH. As lab researchers and clinicians further define how GH—or its absence—influences the longevity and health of animals and people, they’ll get a better handle on whether the hormone can live up to its antiaging hype.

R. John Davenport is an associate editor of SAGE KE. He prefers injections of humor.

**References**