

## SEVEN

## The Price of Growth

**N**OWHERE HAVE THE GOALS of cure and enhancement become more entwined and calculations of risks and benefits more salient than in the use of growth hormone for children of short stature. The story of growth hormone differs in details from estrogen and testosterone, but what is most remarkable is the many similarities. Shortness has turned into a medical condition, just like aging, and physicians have taken as their duty making children and parents happy. Drug company promotions of growth hormone make their efforts on behalf of estrogen and testosterone seem tame. Indeed, no experience better illustrates how the forces of science, medicine, culture, and commerce have combined, and will combine, to create and popularize enhancement technologies.

Although physiologists in the early 1900s already appreciated that growth hormone (secreted by the anterior portion of the pituitary gland) played a critical role in determining physical size, the state of their knowledge was too rudimentary to design therapeutic or enhancement interventions. Surgeons might occasionally excise a tumor from a patient's pituitary gland so as to prevent gigantism, and some physicians prescribed pituitary extracts, notwithstanding their dubious quality, to try to stimulate growth. But medical interventions were generally unable to affect abnormalities in body height.

The situation remained practically unchanged into the 1950s. Endocrinologists were better able to distinguish among a variety of children with short stature, or "stunted growth," as they called it. They recognized that the great majority were merely experiencing a delay in development; they would catch up to their peers in adolescence. Endocrinologists also recognized that a small percentage of short children were "primordial dwarfs," their short stature one of several physical abnormalities that were probably genetic in origin. But they had a third category that interested them most, "pituitary dwarfs," children who were suffering from a deficiency in the hormone. They had been normal in size and appearance at birth and for months afterward; but then between the ages of one and four, their growth rates lagged. In some instances, a diagnostic workup uncovered a pituitary tumor that was impeding the production of the growth hormone. But most cases were idiopathic, of unknown origin. These children thrived in all other ways. They were not sickly—they just were not growing. Given the crude state of laboratory testing, it was very difficult to learn whether they were truly hormone deficient. The pituitary gland's excretions were irregular (more often discharged at night than during the day) and blood analysis of hormones was indeterminate.<sup>1</sup> Thus, pituitary dwarfism was a judgment call. If the child was several standard deviations below normal height for his or her age group, if the growth curve remained flat, and the levels of pituitary hormone appeared to be low, then the problem might well be hormone deficiency.<sup>2</sup> Yet even after giving the diagnosis, physicians could not do much to ameliorate the condition.

Over the 1950s, investigators explored various possible sources for growth hormone. Researchers from the fields of endocrinology, physiology, and biochemistry did manage to isolate growth hormone (somatotropin) in pure form from the pituitary glands of cattle, but administering the substance to the children brought no changes. Lilly and Merck were actively collecting kidneys from rhesus monkeys in order to cultivate polio viruses for use in the Salk vaccine, and they were willing to retrieve pituitary glands as well. Researchers hoped that growth hormone isolated from monkeys, which was chemically different from growth hormone taken from cattle, might be the answer. But it, too, demonstrated no efficacy in humans.<sup>3</sup> Several pharmaceutical

houses did market "endocrine preparations," but the medical consensus was that they were "without effect in achieving growth in children."<sup>4</sup> Worse, endocrinologists feared that the preparations might have the "adverse effect of actually inhibiting endogenous growth hormone production that the child may have."<sup>5</sup>

The ideal substance for treatment, of course, was human growth hormone. Although it was exceptionally difficult to obtain, the little that was available seemed highly effective. In 1958, M. S. Raben, a professor at Tufts Medical School, reported that he had injected a seventeen-year-old pituitary dwarf with human growth hormone (HGH) over a period of ten months, and the boy grew at a rate of 2.6 inches a year (as compared to a previous growth rate of 0.5 inch).<sup>6</sup> Supply, however, could not approach need. "The scarcity of the raw material," as one review noted, "has sharply limited the use of this preparation in the deserving patient."<sup>7</sup> To obtain human growth hormone, it was necessary first to collect pituitary glands from cadavers. That required contacting families of recently deceased patients and persuading them to give permission for an autopsy—the families were generally not informed that the purpose of the procedure was not to learn the cause of death but to remove the pituitary gland. (If they knew the truth, it was feared, they would say no.) Moreover, interns and residents no longer routinely asked families about autopsies, and even when they did, families generally refused. In the odd case when permission was granted, the extraction process yielded only about 1 to 2 milligrams of growth hormone per gland.<sup>8</sup> Since the treatment regimen for pituitary dwarfs called for 1 to 2 milligrams a day, three days a week for twelve to twenty-four months, human growth hormone was, for all intents and purposes, unavailable to the children it might have helped.<sup>9</sup>

The attempt to substitute other hormones for human growth hormone also proved futile. Some endocrinologists hoped that anabolic steroids, which increased muscle bulk and weight, might increase height, but that proved illusory. There was an expectation that extracts from thyroid glands would exert a positive effect, but that too failed.<sup>10</sup> Facing this desperate situation, in 1963, the National Institutes of Health, through its National Institute of Arthritis and Metabolic Diseases (NIAMD), took the extraordinary step of funding a National

Pituitary Agency (NPA) at Johns Hopkins. Its mission was to expand and improve the system of gland retrieval and to learn as much as possible about the uses and properties of human growth hormone.<sup>11</sup> The NIH also hoped, though it kept this to itself, that the NPA would prevent desperate parents from fueling a black market in growth hormone.<sup>12</sup>

In order to increase donation rates of pituitary glands, the NPA decided to issue a bimonthly newsletter, a far more controversial step than now (when drug company advertisements to consumers and organ donation appeals are commonplace). The formal announcement of the newsletter was remarkably defensive in tone, apologizing for this exercise in "lay publicity." It conceded that calling attention to the efficacy and need for pituitary growth hormone might be misconstrued as exaggerating its potency and encourage quackery. It also appreciated that clinicians were worried that spreading the word about the effectiveness of human growth hormone would cause them to be "overburdened by patients in need of specialized help." "It is morally reprehensible," the NPA itself declared, "to engender hope within a suffering patient when this hope can not be realized." Nevertheless, it proceeded with the campaign. "We are faced with the reality that unless people contribute their pituitaries, not only will we not have the hormone needed for present investigative therapy, but we will not have the hormone necessary to establish its structure so that it may be eventually synthesized and made readily available."<sup>13</sup> In addition, the NPA encouraged magazine articles, television interviews, and films about its work. It even attempted, without success, to insert pituitary dwarfism and the need for cadaveric glands into the plots of such popular television medical shows as *Ben Casey* and *Dr. Kildare*.

The NPA tried to educate hospital interns and residents about the importance of requesting autopsies. Its very eagerness not only led it to ignore principles of informed consent but also to engage in immigrant bashing. The NPA blamed the shortage of autopsies on the "large number of interns and residents from foreign countries now working in American hospitals." Apparently, they had "never been exposed to the fine purpose and established practices of autopsies," and were ignorant of the need for a "final post-mortem investigation of all patients."

Accordingly, the NPA commissioned a thirty-minute color film to imbue this "Anglo-American tradition."

By dint of all these efforts, the NPA at first collected some 50,000 pituitary glands a year, happy to pay a two-dollar fee for each. From July 1, 1964, to January 31, 1965, it sent some 30,000 milligrams of the hormone to investigators, enough to use on some 400 patients for a period of up to three months.<sup>14</sup> By 1970, its totals reached 70,000 milligrams. Even so, supplies were very tight and pituitary hormone went only to selected investigators. "The objective has always been basically research," admitted NPA's advisory board, "even though some of the literature used in the promotion campaign to collect pituitary glands may have permitted other interpretations."<sup>15</sup> The closest the NPA came to supporting clinical practice was to give a team at the University of Buffalo growth hormone for a limited number of patients in order to establish clinical guidelines.

Thus the only way a child could get growth hormone was by enrolling in a research protocol—which lent an element of coercion to subject recruitment even if the practice could be justified by the scarcity of the substance and the many unknowns about its effects. Enrollment criteria were strict: eligible children had to have a growth rate in the lowest 25 percentile of their age group, and measure below 5 on a standard laboratory hormone test. Subjects who completed the research regimen were eligible to continue to receive growth hormone afterward and at no charge, but because of limited supply, the hormone was provided only eight months a year and stopped completely once the child reached 5 feet.<sup>16</sup> Although not so intended, the system of distribution as well as cultural expectations about size and gender gave a distinct advantage to white males. As one survey found, the NPA cohort was 68 percent male, 32 percent female; the average age at which treatment began was 9.6 years, and the average duration of treatment was 2.9 years. Not only girls but also blacks were significantly underrepresented among the research subjects—in fact, the girls and blacks who were enrolled were considerably shorter than the white boys in the protocol.<sup>17</sup>

In 1965, when the annual Ross Conference on Pediatric Research brought investigators together to discuss human growth hormone, the principal conclusion was how much still remained to be learned.

Everyone agreed that only human growth hormone offered pituitary-deficient children "the opportunity to attain a reasonably normal adult stature." Yet, no consensus existed on what constituted the most effective dose. The current regimen was 2 milligrams daily, three times a week. Might twice as much twice as often work better? No one knew. "We have no information on what dose would be optimum."<sup>18</sup>

Over the next twenty years, the NPA increased the retrieval rate of pituitary glands and improved methods for extracting growth hormone from the glands. With a greater amount of the hormone available, former research subjects were able to receive it twelve months a year, and the treatment cap was raised to 5 feet 6 inches for boys, and 5 feet 3 inches for girls. Even so, the hormone remained in very short supply and the NPA still rationed its use.

The frustration in knowing how to cure a condition but lacking the means to do so was unusual in post-World War II American medicine, but not unprecedented. The closest parallel was end-stage kidney disease, where the ability to save lives was limited by the number of dialysis machines available. To cope with dialysis crisis, a number of medical centers established "Who Shall Live?" committees to allocate the scarce resource among would-be recipients. Nothing like that occurred with growth hormone. Since the condition was not life-threatening, NPA researchers were left to their own devices.

Indeed, with medicine unable to satisfy demand for the hormone, psychiatry entered both to evaluate potential candidates and to treat children who were unable to get the hormone. Over the 1960s and 1970s, psychiatric research on the consequences of short stature indicated that parents, teachers, and strangers tended to react more to the physical size of a child than to his or her chronological age, so that short children experienced a "babying" effect. Because of this infantilization, they were prone to developmental deficiencies, immature, and lacking self-confidence.<sup>19</sup> Even health professionals who underwent sensitivity training "continued to find themselves bending down, talking in an unsophisticated manner, and expecting less mature responses from a 9- or 10-year-old child who looked like a kindergarten child."<sup>20</sup> As for the child, "when one's sense of self-worth and personal identity are established mainly on the basis of the reactions of others, major differences in appearance may lead to enduring and profound personality

difficulties." These children often lived "in a secluded inner world of intensified feelings, sentiments, and emotions," their personality traits "mainly a result of experiences associated with dwarfism." They tended to be "less aggressive, less excitable, less dominant" than those of normal height.<sup>21</sup> They suffered from "low self-esteem, social isolation, low level of aggression, and affective withdrawal."<sup>22</sup> They wavered between "feelings of helplessness and hopelessness."<sup>23</sup>

The combination of endocrinology identifying a state of hormone deficiency and psychiatry analyzing the degree of maladjustment suggested that shortness of stature was a disease, and by no means a trivial one. The very short child was a sick child. And yet, at the very same time, physicians were uncomfortable with a definition of an otherwise healthy child as sick. Smallness of size did not easily fit into a disease category. The tension between the two perspectives helps to explain why, well before growth hormone became readily available, physicians were already anticipating a very special dilemma. They wondered if, in the future, parents would be demanding that their children of normal height be made taller. Like the authors of the 1930s high school texts that asked students to think about the ethics of making normal children taller, the physicians, too, wondered whether cure and enhancement would remain separate. Thus, in 1976, Alfred Bongiovanni, a leading pediatric endocrinologist, deeply regretted that growth hormone was not available for pituitary dwarfs. "There is a dire need for ample supplies of HGH and there is an obligation to provide public and private funds to achieve this goal in the near future." But then he added: "It may be predicted that in the wake of such success these pages will carry a commentary, 'The Use and Abuse of HGH,' containing an account of the hazards of large doses and proscriptions against its use in normal somewhat small children." Scarcity bred difficulties, but abundance was likely to bring its own headaches.<sup>24</sup>

relief. In April 1985, the Food and Drug Administration announced that three recipients of human growth hormone had died of Creutzfeldt-Jakob (CJ) disease, now known as prion disease. Early in March 1985, a Stanford University pediatric endocrinologist, Raymond Hintz, had written the FDA that a twenty-year-old man whom he had treated with human growth hormone over a fourteen-year period had died from CJ disease. Hintz wondered whether growth hormone was the source of the infection: "The possibility that this was a factor in his getting Creutzfeldt-Jakob disease should be considered."<sup>25</sup> The disease was not only rare (one case in a million) and usually affected only the very elderly, but also growth hormone seemed a possible vector of transmission. Since the substance was derived from pooled cadaveric pituitary glands (usually about 15,000 of them), the glands might easily have included infectious tissues from one or more patients not suspected of having CJ disease. Although the pituitary extracts were filtered, not much was known about the efficacy of sterilization against this strange agent.<sup>26</sup> In response, the NIH quickly convened a meeting of experts. They recommended a compromise: a halt to all research with human growth hormone, but a continuation of therapeutic use. They reasoned that since the time window for treatment with growth hormone was limited—once the child reached adolescence the substance would no longer have any effect—and there was only one case with no definite link to growth hormone, the risks of transmission appeared less than the benefits of growth.

News of the Stanford case and the experts' recommendation provoked a fierce debate among pediatric endocrinologists. Was the one fatality a coincidence or was it actually due to growth hormone? Was the risk of CJ disease great enough to halt therapies to several thousand children? The controversy ended abruptly a month later when two more cases of CJ disease appeared among growth hormone recipients, one a thirty-two-year-old man in Dallas, the other a twenty-two-year-old man in Buffalo. At this point, the NIH halted all distribution of growth hormone.<sup>27</sup>

And then suddenly the scarcity of human growth hormone and the small number of children who had received it became a source of

~~Exciting questions arise immediately. Is the use of the~~  
~~hormone safe? What are the risks? Are there any other~~  
~~cases like also in England and Europe as well? Were many~~

batches of the substance contaminated or only a few? Were the earliest growth hormone products more dangerous than later ones? And where did responsibility lie for the outbreak? Could it have been averted? What measures might have been taken to better sterilize the product? Finally, physicians had not advised parents about the possibilities of such a side effect. Why had they ignored the risk? Parents might not have chosen to treat for height had they received information about the possibility of the treatment transmitting a fatal disease. (In a very short time, another group of parents, those with children who had hemophilia, would be asking the same questions about fractionated blood plasma, but they at least had the advantage of knowing that the intervention was lifesaving.)

Answers came slowly and with ambiguities. The NIH assembled a team of investigators to survey the 6,284 recipients of growth hormone in its pituitary program. Even as the team went about its work over the period 1985 to 1991, physicians reported two more cases and the team itself turned up an additional two, bringing the total deaths from CJ disease linked to growth hormone in the United States to seven. Although the victims resembled the larger group of growth hormone recipients, they had two distinguishing features: they had begun treatment prior to 1970 and they had remained in treatment longer than average. The team could not pinpoint specific lots of hormone or batches of pituitary glands responsible for the outbreak. Two specific lots were common to the seven infected children, but other children had also received growth hormone from them and had not, at least not yet, contracted CJ disease.

What risk did children who had received growth hormone face?<sup>28</sup> There were no certain answers. CJ disease has exceptionally long latency periods (ten to twenty years), and many recipients were still well short of that benchmark figure. The optimistic view was that the seven fatalities had the bad luck of consuming "contaminated hormone preparations [with] a small number of infectious units scattered randomly among individual vials of hormone." But it was entirely possible that the number of cases would mount over time. In England, for example, with about the same number of fatal cases identified, investigators were warning that "all patients treated [with growth hormone] in the

UK must, at this stage, be considered as at risk."<sup>29</sup> By 1994, almost ten years after the initial outbreak, the number of deaths had climbed, but not to catastrophic levels: 51 cases of CJ disease worldwide attributable to growth hormone; 10 of them were in the United States, 10 in Britain, and 25 in France. By 2000, the United States had a total of 21 confirmed cases; France, 62 cases; England, 32 cases. But even now, no one can be absolutely certain that the outbreak is over.<sup>30</sup>

The answers to the questions of responsibility for the outbreak were also equivocal. With the benefit of hindsight, prudent investigators might have anticipated the risks of growth hormone extracts before 1985. However, knowledge about CJ disease had never seemed particularly relevant to their work. The infectious character of CJ disease was established in 1967–1968, mostly through the research of D. Carleton Gajdusek. Working closely with anthropologists, he identified kuru, as it appeared in the Fore tribe in New Guinea, as a form of CJ disease and attributed its spread to a mourning ritual in which women and children of the tribe ate the brains of the dead soul. In 1969, Gajdusek and a colleague reported in *Science* that chimpanzees inoculated with tissue from patients diagnosed with CJ disease themselves contracted it, thereby confirming its infectious character.<sup>31</sup> But kuru seemed an exotic disease, irrelevant to developed countries. Surely no one there would come into such intimate contact with the tissue of a person who died of kuru or of CJ disease.

This seemingly reasonable expectation was soon proved wrong. In 1974, the first known case of CJ disease transmitted person to person in the developed world appeared in a report of a corneal transplant. The donor, it turned out, had died of CJ disease and the recipient then contracted it. In 1977, another case of surgical transmission came to light, this one through the instruments that had been used on a CJ patient and then sterilized in a solution of alcohol and formaldehyde. The standard solution did not kill the agent. These instances notwithstanding, other specialists, including pediatric endocrinologists, failed to see a relevance to their own practices.

There was an exception. In late 1976, an English veterinary scientist wrote to the British Medical Research Council (MRC) to warn of the possibility that sheep scrapie-like agents, akin to the CJ agent, might

be transmitted through growth hormone. It took the MRC more than a year to begin to investigate his warning. (Indeed, it took a lawsuit by parents of children infected by CJ disease to get this material on record.) One MRC consultant had taken the threat of contagion seriously: "We are in the uncomfortable position of suspecting the worst but not knowing how bad the worst is. Any clinician who uses growth hormone must be made aware of the gruesome possibilities."<sup>32</sup> But no steps were taken to make them aware. The risk inherent in using cadaver-derived human growth hormone was never communicated to clinicians in England, or in the United States. What knowledge there was, was scattered among neurologists, anthropologists, and veterinarians, but not shared among pediatricians, endocrinologists, or growth specialists. If they thought of CJ at all, it was as an elderly person's degenerative disease.

When all the facts became known, the children who received growth hormone had to live with the fears of succumbing to a deadly disease, and their parents had to live with the guilt of putting them at mortal risk because of something as minor (compared to premature death) as short stature. The rest of us have to confront the stubborn question of how to calculate the risk of a procedure when almost all the experts see no risk. Right up to the outbreak, the medical literature confidently asserted that "growth hormone has been shown to be safe in patients deficient in the hormone."<sup>33</sup> The confidence was misplaced in this case—might it be misplaced in another? Absent acute disease but present unhappiness or the prospect of enhancing performance and capacity, just how much risk is one prepared to take?

### III

In 1985, Genentech, a California biotech company whose synthetic version of growth hormone had been undergoing clinical trials for several years, scored an extraordinary coup when CJ disease was linked to cadaveric sources. As one NIH investigator concluded, when "the hormone was officially executed . . . only Genentech was not in mourning."<sup>34</sup> Even had the company been forced to compete with the natural

product, it would have profited handsomely. But by the stroke of (mis-)fortune, it had the territory almost entirely to itself.

Just how Genentech managed to produce a synthetic version of growth hormone was the subject of a long-running lawsuit between the University of California at San Francisco (UCSF) and Genentech. The company itself was founded in 1978 by Robert Swanson, a brilliant venture capitalist, and Herbert Boyer, a world-class genetics researcher at UCSF. Both recognized that the new tools of DNA research—which allowed for the isolation and replication of particular genes—had the potential to revolutionize the creation of pharmaceutical agents. Just as the new company was getting organized, investigators at UCSF, including Peter Seeburg, managed to isolate the gene responsible for producing growth hormone. Genentech then recruited Seeburg to continue his research under its auspices; UCSF, for its part, had Seeburg sign an agreement that gave it all property rights to the work he had already performed in the university laboratory.

What happened next is the subject of bitter dispute. According to Seeburg, he and his Genentech colleagues, including David Goeddel, were unable to replicate their earlier work and isolate the growth hormone gene for Genentech; after several frustrating failures, Seeburg raided his old UCSF lab, stole the gene, and he and Goeddel swore never to reveal the theft. Goeddel claims that the story is pure fabrication, that he was able to isolate the gene and, in fact, published the results in *Science*. But Genentech did not back up Goeddel's story, and his research notebooks lacked the specific data entries that would have confirmed it. The question of theft is unlikely ever to be resolved because the lawsuit between Genentech and UCSF was settled in November 1999, when Genentech agreed to pay UCSF \$200 million. At the university's suggestion, \$50 million of the \$200 million was to be used to construct a science building at its new research campus, and Genentech would have the right to name it. The project was completed in 2003, and the building opened as Genentech Hall.<sup>35</sup>

By whatever route the gene arrived, Genentech figured out how to insert it into *E. coli* organisms and produce large quantities of growth hormone. In October 1985, the FDA, in record time, only four months after Genentech's application, approved the bioengineered growth hor-

more Protropin. Everyone who had been receiving pituitary-derived growth hormone now had an effective, albeit expensive, substitute available. (Genentech set the price high—\$18,000 for a year's supply.) Even so, the Genentech feat meant that the need to ration the substance was over. An intervention that had once been managed by a federally funded not-for-profit organization was under the control of a for-profit and exceptionally hard-driving drug company. Care and treatment would no longer be controlled by a small team of endocrine experts. For better or for worse, clinical investigators, endocrinologists, physicians, parents, children, and bioethicists, along with drug companies, a U.S. attorney, and a federal judge would shape the growth hormone story.

Looking back on the pre-1985 period, one endocrinologist who had closely followed the uses and abuses of Genentech's growth hormone pined for the not-so-good old days. Yes, the drug had been in short supply, but at least no hard choices had been required. The little growth hormone that was available was reserved for children who were demonstrably growth hormone deficient. But once supply was assured, a host of questions surfaced. First and foremost, who should receive the hormone and under what regimen? Clearly, children who were growth hormone deficient, which was the use for which the FDA had approved the drug. But what about short children who were not clearly hormone deficient by the old and rigorous measurement standards? Was the traditional scoring scale for hormone deficiency too restrictive? Moreover, it was still unclear at what age treatment should be started and at what age it should be stopped. When the hormone had to be rationed, it made sense to begin as late as possible and end as quickly as possible. But was that right? Finally, with the shortage over, it was necessary to revisit the question of optimal doses and frequency.

The lack of clinical data made each of these questions difficult to answer. Yes, growth hormone should go to children with growth hormone deficiencies, but methods for measuring its levels were still unreliable. Since the pituitary gland released growth hormone episodically, no single blood draw provided an accurate reading. But to take blood every fifteen minutes over a twelve-hour period at night was difficult to arrange, expensive, and burdensome to the child. A more preferred method was to inject the child with a substance known to stimulate the

output of growth hormone (such as insulin) and then immediately measure the amount of hormone in the blood. But the assays for identifying growth hormone in the blood were not very accurate—different laboratories used different assays of varying quality—and the margins of error were considerable. In light of these problems, some endocrinologists recommended that the better part of wisdom now was to forgo hormone measurements altogether and rely instead on diagnosis by trial (as had been suggested for testosterone). Administer growth hormone to very short children and see what happens.<sup>36</sup> If the intervention produced results, keep using it. If not, discontinue.

To the extent that reliance on hormone measurement persisted (which had more to do with insurance company rules governing reimbursement than medical judgment), the criteria for determining hormone deficiency relaxed and the gap between a normal and abnormal reading narrowed.<sup>37</sup> Thus, the definition of growth hormone deficiency varied not by medical criteria but by supply.<sup>38</sup> "Category creep" was under way.

Some data drawn from the NPA research suggested that growth hormone administration should begin at a young age, should be given six or seven days a week, and the dosage should increase as the child approached puberty. But the findings were soft; the number of clinical trials was low, as was the sample size, and there were considerable differences among the research subjects in terms of age and level of hormone deficiency. Nor was there agreement on when to stop treatment. Some pediatric endocrinologists relied on X rays of bone formation to indicate when growth was ending, but others thought the method was imprecise. Some stopped treatment when the child completed sexual development but others believed that this was too early. Still others stopped growth hormone when the child was one or two standard deviations below normal height, or had reached the average height of the two parents combined, but critics found these end points too arbitrary. As a result, variation became the rule, and endocrinologists were free to follow their own instincts.

The most glaring gap in the data was a lack of solid evidence on outcomes. The most obvious question was still unanswered: What return in inches will come to a hormone deficient child who takes growth hor-

money? Or as some parents might ask it: How many inches will my child grow if I make the \$18,000 investment in growth hormone? The very diversity of regimens, the small number of trials, the absence of randomization, the lack of agreement on stopping points, and the number of children "lost to follow-up" because they stopped seeing their pediatricians precluded conclusive findings.<sup>39</sup> One major review of findings (in 1991) looked at the leading six studies but could not come up with useful guidelines. None of the trials had used the gold standard of a placebo control group, so there was no way to know how much growth would have occurred anyway. The range of age at which treatment began varied from eleven to fourteen; the duration of treatment varied from four to six years. Only three of the studies included information on the subjects' height before and after treatment. With all these limitations in mind, it seemed that three of the studies showed an average increase in height (from 121 to 157 centimeters). All reported an improvement in subjects' standard deviation from normal height; they were on average  $-4$  when starting treatment but  $-2$  when concluding treatment. But no group receiving the hormone achieved average height.<sup>40</sup> So, in principle, growth hormone benefited very short children. But just how well it worked, precisely for whom, and under what conditions was not known.<sup>41</sup>

#### IV

All these uncertainties about treatment would not have been so consequential had the only recipients of growth hormone been dwarflike children. Their handicap was so severe as to justify diagnosis by treatment or an intervention that had a good but not exceptional prospect of success. But from the moment that researchers began to appreciate the role of hormones in stimulating growth, everyone, physicians and the public alike, had anticipated the likelihood of "diagnostic creep," that some number of short but not hormone deficient children would seek treatment. In the period of scarcity before 1985, this possibility was theoretical. But with the hormone readily available, the issue became real, and the debate acrimonious.

Some pediatricians and endocrinologists were uncompromising in opposing growth hormone for short but not hormone deficient children.<sup>42</sup> In part, it reflected their acute skepticism about its efficacy. Data on whether growth hormone actually made non-hormone deficient children grow taller was, at best, equivocal. They were also skeptical of the extent of the burden that short children carried. "Neither we nor others," contended one group of researchers, "have been able to document markers of adverse psychological effects in normal short children."<sup>43</sup> Indeed, the negative psychological and social effects of a daily routine of injections might be even more damaging.<sup>44</sup> They were concerned, as well, in the aftermath of CJ disease, about new and unanticipated risks. The recombinant growth hormone product was free of infectious agents, but it might render children carbohydrate intolerant, stimulate an overgrowth of tissue and bone, cause carpal tunnel syndrome, or increase the risk of tumor formation and tumor growth. None of these effects were as yet well documented, but that did not mean that the intervention was risk-free.

Other objections addressed matters of equity. Critics worried that if growth hormone for normal short children became standard treatment, an undue amount of health care resources, particularly federal benefits, would be devoted to it. Growth hormone was so expensive that far more urgent public health needs would be neglected. The numbers were easy to do. An estimated 90,000 children were in the lowest percentiles of height; were they all given growth hormone at federal expense, the national bill would amount to over \$8 billion. The alternative to a government subsidy was equally unacceptable. To allow wealthier families to pay for it themselves and leave the poor to their own devices would only entrench inequities in health care. We might reach a point wherein only poor children were short children.<sup>45</sup> And even were growth hormone effective and made widely available, all that would follow would be a shift in the distribution curve. Children who had been one step above the lowest percentiles in height would now drop to the bottom; they would then seek treatment, and the reshuffling process would begin all over again.

Opponents were also adamant in insisting that medicine should resist crossing the line from cure to enhancement. Shortness was not a disease.



Some considered it a "natural human variation." Others thought of it more in terms of stigma, regretting the prejudice but not finding it catastrophic.<sup>46</sup> As a group of University of Chicago endocrinologists put it: the intervention would constitute "a form of cosmetic therapy, rather than a treatment for a disease." Not that all cosmetic therapy should be ruled out. This one team would allow cosmetic surgery for a cleft lip because the condition was "so disforming." But treating shortness, like altering an unshapely nose, it found "unacceptable," representing an "unwarranted tampering with nature." It never did explain what made one condition disforming and another merely annoying, or when medicine should tamper with nature and when it should not. But the team worried that if endocrinologists ignored their advice, the specialty would confront the nightmare of giving growth hormone to a "child of normal height to make him or her a better basketball player."<sup>47</sup>

Equally credentialed and every bit as aggressive, proponents defended giving growth hormone to what they labeled children with idiopathic short stature. (In medicine, as in other disciplines, labels count for a lot.) These were not short normal children but patients who evidenced the clear symptoms of a yet unidentified pathology. They objected strenuously to basing decisions on laboratory-derived growth hormonal levels. The measurements were far too unreliable. Why enshrine as the gold standard a diagnostic procedure that was, at best, brass?<sup>48</sup> Indeed, many American endocrinologists had already given up testing hormone levels, and in countries such as Australia, physicians did not use the tests at all. Simpler was better. Make clinical decisions on the basis of growth-rate charts. If the line was not gradually sloping upward, give the child a trial of the hormone.

The pro-treatment camp was impatient with what it considered overly rigid definitions of disease. Shortness, they were convinced, was a grave disability and its victims suffered deep psychological scars. Very short children were teased relentlessly on the playground (their lunch taken and hung just out of reach) and humiliated in the classroom (always marching first in a line organized according to height). In adulthood, they faced curtailed life chances. Short men earned less than tall men; one study concluded that people who were 5 feet 6 to 7 inches tall made \$2,500 a year less than those who were 6 feet to 6 feet 1 inch

tall.<sup>49</sup> Short men also had fewer options in marriage because social conventions did not allow them to date taller women. Language itself discriminated against them, as in "getting the short end of the stick" or "coming up short." And a surprising number of medical journal articles cited as a relevant fact that since 1900, the taller of the two presidential candidates had won all but two of the elections.<sup>50</sup>

Did growth hormone actually increase height in normal short children? Although the answer to this question should have been determinative—who would advocate for a futile treatment?—it was not. There was good evidence that the hormone produced a spurt in growth among short children, at least during the first year of treatment. But whether the spurt resulted in a positive gain in final adult height remained uncertain. An occasional journal article reported growth hormone provided several additional inches, but typically, the number of subjects in the studies was small. Besides, other articles reported no change in final height at all following treatment.<sup>51</sup> The equivocal findings spurred conflicting interpretations. To one camp, the lack of demonstrable final adult height was another powerful reason not to intervene. To the other, a growth spurt in and of itself brought psychological benefits, even were final height unchanged. And some found the treatment itself and the promise of benefit (whatever the data) sufficient justification. As two University of North Carolina pediatricians insisted: "The question that should be asked is not whether GH therapy will produce a taller adult, but whether it will produce a better [adjusted] adult."<sup>52</sup>

Given all the unknowns, advocates for growth hormone wanted to give short children a six-month trial of the hormone and, if they had a spurt in growth, to continue with it for several years. They also raised the possibility that should subsequent research confirm the efficacy of growth hormone, then physicians who had withheld it had missed, forever, the chance to treat. Once a child entered late adolescence, the growing stage was over.<sup>53</sup> When it was now or never for treatment, it was prudent to treat.

The closer one examines the split, the more significant is the cure-enhance divide. The endocrinologists most concerned about the overuse of growth hormone shared a classical, really old-fashioned, definition of disease, taking laboratory data as the only reliable marker of illness.

When a physiological test revealed an abnormal score, then disease was present and cure should be sought. "Health," as one pediatrician insisted, "is not social or cultural, and is not defined in relation to others. It is a property of biologic entities."<sup>54</sup> Many bioethicists readily agreed. "Abandoning the treatment/enhancement distinction," observed one of them, "does not just open the door to GH therapy for short normal children. . . . It begins a cascade of changes in the scope of medicine that would forever change its face and might threaten the social consensus that gives medicine the strong moral grip it has on us."<sup>55</sup> Loosening the reins around disease categories would subvert society's collective ability to differentiate the normal from the abnormal, the genuine needs of patients against the frivolous desires of consumers. And the more the lines were blurred, the more impossible it was to realize a just health care delivery system and to enact national health insurance. "To expand the entitlement pie at a time when we hardly know how to divide the present pie, and at a time when many children do not get pieces of even that pie, would seem foolish."<sup>56</sup>

Endocrinologists prepared to dispense growth hormone focused less on societal issues and more on the well-being of the individual patient. If shortness brought penalties, the physicians should try to increase the height of the child, not alter social attitudes or worry about national health insurance. They riveted their attention on the specific child, not the larger system. They also invoked several decades of research in the social sciences and the history of medicine that fully demonstrated the ambiguous character of such concepts as disease and cure. Disease was always a socially constructed category, subject to fluctuating definitions by place and over time, with cases in point ranging from alcoholism to homosexuality (at one moment a crime, at another an illness, at still another a legitimate choice). Bringing this orientation into pediatric endocrinology meant that laboratory tests should not be allowed to dictate treatment decisions. "The point is," as one interventionist pediatrician concluded, "that short children of equal height have the same handicap regardless of cause."<sup>57</sup> To justify one intervention as a "cure" and denigrate the other as "enhancement" made no sense.

From this perspective, the problem was not whether gym-door fathers should be allowed to make their children into professional

basketball players but how best to respond to the indignities of everyday life that very short children suffered. The stories these pediatric endocrinologists tell is of the thirteen-year-old girl who at 4 feet 6 inches has to shop in the kiddie section of the clothing store while her friends go to the teenage or adult section. Or the twelve-year-old boy who at 4 feet 9 inches is the mascot of his class or the butt of jokes. Or the twenty-one-year-old who is too short to fulfill her ambition to join the military. These physicians will offer such patients growth hormone, hoping to make them taller or, at least, happier.

## V

Perhaps the most dramatic example of how tenuous the divide was between cure and enhancement appeared in 1990, when the National Institutes of Health organized a clinical trial to test the efficacy of growth hormone for short, non-hormone deficient children. Its purpose was to determine, once and for all, whether the intervention worked. The design was rigorous: Half the children would receive three injections weekly with the hormone; the other half would receive three injections with a placebo (saline solution). The children would then be followed for eight to ten years (with both groups getting between 600 and 1,100 injections), and the results would finally settle the question of efficacy.

In 1993, two advocacy groups, the Physicians Committee for Responsible Medicine and the Foundation on Economic Trends, led by Jeremy Rifkin (best known for his efforts to stop several human and plant genetic experiments), urged the NIH to abort the research. That effort failing, they sued in federal court to halt the protocol. Their arguments echoed the positions of the anti-treatment school, emphasizing that shortness was not a disease and that the hormone might not be safe. Although the court rejected their plea, the questions were troubling enough to have the NIH take the unusual step of convening a special outside panel to review the ethics of the research.

The panel, composed of endocrinologists, biostatisticians, lawyers, and bioethicists, opened their report with an estimate that some 15,000

children were receiving growth hormone, approximately half of whom were not hormone deficient. Because of the intrinsic difficulty of determining hormone levels, the panel believed that the number who were not hormone deficient was certain to increase in the coming years. Clearly, then, "determining the efficacy of hGH therapy is an important issue in pediatric endocrinology." But was it important enough to justify the protocol? Was it appropriate to give the control group hundreds of injections of a placebo over many years? The subjects, after all, were children, and federal regulations governing human experimentation considered children a "vulnerable" group, in need of special protection. Section 46.406 of the regulations contained the relevant standards. The section title was long but directly on point: "Research involving greater than minimal risk and with no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition." It allowed such types of research to be conducted only if three criteria were satisfied: (1) the additional risks over the "minimal" had to be minor; (2) the intervention had to be "reasonably commensurate" with the subjects' medical or social situations; (3) "the expected knowledge is of vital importance for the understanding or amelioration of the subject's disorder or condition."

All but one of the panel members believed that the research met the first criterion—the risks were not great. The dissenter found the placebo injections too discomforting and inconvenient. The majority admitted that no one really knew what the experience of regular injections over years would mean to the children but, rather than prohibit the research, they recommended administering a survey. As for the second criterion, the research being reasonably commensurate with the children's experience, the committee found that the standard itself was highly ambiguous but that since the children would be getting comprehensive and rigorous medical evaluations, the protocol was acceptable.

The most difficult issues involved the third point, that the research had to be of "vital importance" for understanding or ameliorating a "disorder or condition." It was here that cure and enhancement faced off. The panel first argued that the standard of "vital importance" was satisfied because growth hormone was being used widely, and therefore warranted investigation in the name of public health. But what about

the clause that the research had to address a "disorder"? To approve the research, the panel would have to make short stature into a disease, which it then did. It emphasized "functional impairment and psychosocial stigmatization." "Children and adults with extreme short stature may experience difficulty with physical aspects of the culture designed for individuals taller than themselves (e.g., driving a car). They may also be harmed by deeply ingrained prejudices resulting in stigmatization and impaired self-esteem." Did these disadvantages make shortness into a disease? Apparently yes, for the panel approved the protocol.<sup>58</sup>

The fundamental lesson to be drawn from the NIH experience was that if a condition causes unhappiness, psychological pain, and social disadvantage, then it represents a disease, and interventions to remedy it should be considered cures. Indeed, the NIH attitude affected the FDA. An advisory panel on the use of growth hormone for short, non-hormone deficient children met in June 2003 and recommended that very step. Some of the panel's members were unhappy with the decision, complaining about the medicalization of shortness and the absence of data about long-term treatment effects. But the majority supported the intervention on the grounds that some children did experience a spurt in growth and that the stigma of shortness and the psychosocial pains associated with it were severe.

Thus, any and all attempts through endocrinology now, or genetics in the future, to try to reduce unhappiness, pain, and disadvantage, whether the result of physical appearance, memory capacity, sleep patterns, muscular strength, or advanced age, have legitimacy. Truly, cure and enhancement are becoming one.<sup>59</sup> In July 2003, the FDA accepted the recommendation, approving HGH for normal but unusually short children.

## VI

No one had a greater stake in eliminating the distinction between cure and enhancement than the pharmaceutical companies producing growth hormone. A market composed exclusively of children with laboratory-defined hormonal deficiencies would amount to no more than 7,500 children a year, a small enough number to qualify the drug for "orphan"

status, so little prescribed as to warrant special federal incentives for its continued production. But were the market to include short children, then the numbers could swell to 100,000, perhaps 200,000—and given potential profits, companies would happily forgo the orphan drug designation. It became the mission of Genentech to have its drug, Protropin, reach that larger market well before the FDA decision.

To this end, Genentech's strategy, as pieced together in congressional hearings and a federal criminal trial in Minnesota, relied on all the standard promotional approaches, including medical journal advertising, free samples to doctors, and visits from detail men, and now, detail women. But it also invented new strategies and embellished old ones, in the process demonstrating the exceptional difficulty of regulating the conduct of pharmaceutical companies and their physician allies.

One of Genentech's first forays was to help underwrite the costs of a foundation whose mission was to alert parents and school staffs to growth disorders. The Human Growth Foundation (HGF) was founded in 1965 by a small group of concerned parents, assisted by Robert Blizzard, the first head of the National Pituitary Foundation. It attracted some one thousand families as members and had forty-two chapters across the nation. The HGF served as a support group for parents, as an advocacy group, as an educational resource, and as a grant maker to encourage young researchers to enter the field. After 1985, Genentech became its single biggest funder, accounting for one-quarter of its budget, and several of the company's executives sat on the foundation's board.<sup>60</sup>

One of HGF's major activities, paid for by Genentech, was to fund elementary and secondary school screening programs. It provided materials and personnel to train school staff on how to measure student growth and maintain growth charts. Parents of children who fell below the 5th percentile for their age group received a letter advising them of this fact and recommending that they see their doctor. The letter contained no manufacturer's name and did not recommend specific physicians or treatments.

When the foundation and Genentech officials were asked by a congressional committee about the propriety of this joint venture, their response was quick and confident. This was a health program, alerting

parents to potential problems that might be hormonal in origin, or nutritional or physiological (including the possibility of pituitary tumors). "Growth screening is one component of essential medical preventive care," the foundation noted. To screen, educate, and facilitate referrals were unrelated to any "alleged marketing efforts of any pharmaceutical company."<sup>61</sup> Genentech added that seven states had mandated such screening programs on their own, thereby demonstrating their value. "If the focus of the program is public health and if it supplants largely unavailable public funds, it is a public good."<sup>62</sup>

Others, however, found the program entirely too self-serving. Because Genentech had a financial stake in increasing the number of short normal children who used growth hormone, the screening effort seemed obviously designed to expand its customer base. In one sense, the charge was a stretch. No one had ever accused school dental, eye-sight, or hearing screening programs of being fronts for physicians or dentists, or charged that a school lice inspection program was a get-rich scheme for dermatologists and shampoo manufacturers. But height screening seemed different, perhaps because Genentech had a well-earned reputation for aggressive marketing or because shortness was not the equivalent of cavities or lice. In any event, criticism mounted to the point that Genentech ended its financial support.

The HGF and Genentech experience made two points eminently clear. First, from a marketing perspective, the tactic made sense and worked well. Once a disease category was created, particularly in a shadowy and new area, then the more cases diagnosed the greater the company sales. Second, from a regulatory perspective, it was nearly impossible to distinguish the fair from the foul. Health education and disease prevention were legitimate activities—and no one could delin-  
eate where health prevention left off and crass self-interest began.

However advantageous it was to work with parents, schools, and the communities, Genentech devoted greater time, energy, and money to physicians. Here, too, the propriety of its actions evoked criticism and, in one case, a substantial fine. But again, it had ample reason to insist that it was only doing what everyone else did. The major company activity involved post-marketing surveillance of growth hormone treatment. Since the FDA had moved quickly to approve its drug and the

clinical data available from the pituitary hormone period was, of necessity, limited, it seemed appropriate to continue to collect information on the efficacy of the drug as it was used in doctors' practices. Genentech was eager to underwrite the costs of the effort, not so much because of the information itself—since the drug was already approved, new data might hurt as well as help its marketing—but because of the ties it could forge with the prescribing physicians.

The arrangement designed by Genentech gave it a seemingly legitimate way to persuade doctors to prescribe its product and then reward them financially for doing so. Some would label it a kickback; the company insisted it was a research grant. And often, albeit not always, it was impossible to say who had the stronger case.

In order to carry out post-marketing surveillance of growth hormone, physicians had to maintain careful records of the patients they treated, the dose level, the duration, the side effects, and the outcome. Each child had to have his or her own chart, scrupulously maintained and updated; the entries were to be reported to a central office. It was a time-consuming procedure, although not substantially more than any meticulous pediatrician might do. Genentech's contribution, in neutral language, was to reimburse physicians for keeping the records and then cover the costs of their travel to meetings to share their findings with colleagues. As with its support of the Human Growth Foundation, the company's activities could seem to be not only legitimate but very valuable: imagine what could be learned from the data and taught to physicians. But in more skeptical terms, post-marketing studies gave Genentech the opportunity to pay doctors to prescribe growth hormone. The company's payments to physicians varied, but several thousand dollars per child treated was not uncommon. Needless to say, Genentech chose the best hotels and resorts for their meetings—always warm and sunny—with spouses invited and paid for. Genentech's detail men often filled out the forms and did the paperwork for the doctors, facilitating contact with them. In short, post-marketing surveillance was an ideal umbrella under which to distribute company largesse and promote its product.

In at least one instance, the bounds of legality were overstepped. In 1994, the U.S. attorney general's office indicted Genentech's top sales

executive and officials at Caremark, a home health care provider with exclusive rights to distribute Genentech's drug outside of hospitals, for paying kickbacks to a Minnesota physician, David Brown. Over an eight-year-period, he reputedly received \$1.1 million in return for prescribing Protropin. Caremark settled its part of the case with an admission of guilt and a payment of a \$110 million fine. Brown was also indicted, pleaded innocent, and came to trial in federal court in August 1995. The outcome was more uncertain than might be anticipated in light of Caremark's admission of guilt because the judge ruled at the outset that Caremark's settlement was inadmissible as evidence. To let the jury learn of it would be too prejudicial to the defendant.<sup>63</sup>

Over the course of the trial, no one denied that Genentech had paid \$1.1 million to Brown. Indeed, Brown had recorded every dollar he received. The open question was whether the money represented bribes and payoffs for the prescriptions he had written or reimbursement for legitimate research and consulting activities. Brown's defense was simple. Part of the money went to cover the costs of his research. After all, Genentech, like other pharmaceutical companies, dispensed research grants and he, like thousands of other investigators, had accepted one. He had conducted the investigations, as evidenced by the research abstracts he had presented at annual pediatric endocrinology meetings. No matter that he had never published an article in a peer-reviewed journal or, for that matter, in any journal.

Brown insisted that Genentech's other payments to him, which included a percentage of his nurse's salary, were to facilitate his participation in its post-marketing survey. Data on his 200 to 300 patients were incorporated in the major Genentech study of growth hormone results and in every one of its smaller subgroup studies. Even the fact that his total payments were far greater than those received by other physicians could be rebutted. The company did not set a fixed or flat fee for services rendered. As a Genentech official testified on his behalf: "I mean for any study, for any doctor, there is a negotiation, if you will, because costs differ in different places. You can't develop one budget and try to implement that throughout the United States because things cost more in New York than they do in Iowa." To be sure, Genentech conceded that it never audited Brown, or for that matter any other physician. "We

don't audit, you know, individual people for the time they spend on the work." The company trusted the doctors.

The prosecution, for its part, derided the quality of the research that Dr. Brown performed, stressing that it was never published. More telling, the funds paid to him came not from Genentech's research division but from its marketing and sales division. The prosecution also read from documents showing that Brown negotiated a fee that gave him 5 percent of all proceeds from his prescriptions of growth hormone and that Brown was the highest dispenser of Genentech's Protropin in the Minnesota area. To clinch its case, the prosecution brought in Dr. Robert Ulstrom as an expert witness to testify that Dr. Brown inappropriately prescribed growth hormone to his patients, seemingly practicing bad medicine in return for good money. Ulstrom, a retired endocrinologist from the University of Minnesota, had done substantial research over the period 1954 to 1964, but had published only two papers on growth hormone. Why did the prosecution select a physician who was retired and not particularly expert in growth hormone? Because all the other experts that the government wanted to use had ties, loose or otherwise, to Genentech or to other companies producing growth hormone.

The prosecution led Dr. Ulstrom through seven of Dr. Brown's patient records, trying to establish a pattern of overuse of growth hormone. The first case was Mark Miller, a thirteen-year-old who, when he first saw Dr. Brown, was only as tall as the average ten-and-a-half-year-old. His father was short, so was his sister, but his mother was 5 feet 8 inches. Reviewing the case, Dr. Ulstrom opined that Miller was not hormone deficient as measured by challenge tests and overnight blood tests but, nevertheless, Dr. Brown had prescribed growth hormone. Miller did enjoy a spurt in growth, which Dr. Ulstrom explained was because the boy was entering puberty and the drug had a short-term but not long-term effect. And so it went with the other six cases—children who were not growth hormone deficient but to whom Dr. Brown had given the drug anyway.

The defense had an easy time demolishing Ulstrom's testimony, not only because his credentials were weak but because it had no difficulty finding professional support for Dr. Brown's decisions. First, it stressed

how arbitrary the definition of growth hormone deficiency was. "One of the things that kind of plagues this area," testified a Genentech official, "is that there is no single object measure that gives a clear answer as to a specific child who should or shouldn't be treated with growth hormone. . . . And so this is an area where particularly physicians' judgment is important."<sup>64</sup> Second, physicians were right to base treatment decisions on more than laboratory findings. Other considerations "weigh heavily on their mind—as to how psychologically affected the child is, how many problems they are having in school, how many problems they are having with their peer group."<sup>65</sup>

As for the specific cases, the defense obtained a letter from one of Ulstrom's Minnesota colleagues justifying Brown's prescriptions. "Although we do not usually treat children with adequate responses to growth hormone stimulation studies . . . there is suggestive evidence that such treatment may be indicated in 'normal' short children." It also introduced data from a recent survey indicating that 82 percent of pediatric endocrinologists had on occasion given growth hormone to children who were not by standard laboratory definitions hormone deficient. The defense also brought in a more up-to-date endocrinologist, Ron Rosenfeld of the University of Chicago, who testified that Brown's treatment decisions were well within the professional standards in the field. In fact, on cross-examination, Ulstrom himself conceded that laboratory tests had a number of "limitations," and findings of hormone deficiency were more in a "gray zone" than definitive.

Because Mark Miller had grown taller, a courtroom dialogue ensued that revealed how different judicial standards of evidence and proof were from scientific evidence and proof. To Dr. Ulstrom, the fact that Miller had come within two inches of his predicted adult height was irrelevant. As a physician and researcher, the null hypothesis ruled—that is, Miller might well have achieved that height anyway. The burden of proof was on Dr. Brown to establish that his treatment had been the determining factor. But the courtroom adhered to a different standard. The presiding judge interrupted Ulstrom to explain that a criminal charge had been levied, and the burden of proof in a criminal case rested with the prosecution, not the defense. It was not Dr. Brown who had to demonstrate efficacy of treatment but Dr. Ulstrom who had to

refute it. Unless the prosecution could prove beyond a reasonable doubt that growth hormone was not responsible for the growth, Dr. Brown was innocent of the charges.

The end of the case brought several surprises. Despite the able defense, the jury convicted Brown of taking kickbacks. But the judge then set aside the verdict because of juror misconduct; one of them had learned about Caremark's admission of guilt and shared the information with his fellow jurors, who then discussed it in the course of their deliberations. The judge ordered a new trial, but the federal prosecutors decided not to proceed. This prompted several parents whose children had been treated by Dr. Brown to file their own civil suit against him for failure to disclose the kickback scheme; they could not pursue a malpractice claim because the statute of limitations had run out. The court, however, refused to hear their case, on the grounds that it was a malpractice suit in disguise, not a real case of consumer fraud.

When all was said and done, Dr. Brown walked away with no criminal penalty and no fines, in the process providing an object lesson.<sup>66</sup> Criminal prosecution is rarely an effective means for regulating medical practice. And it certainly has no chance of succeeding when the prosecution must rest its case on a distinction between cure as good medicine and enhancement as bad.

## VII

The growth hormone story does not end with short children—it has a second life with healthy older men. The logic for giving them the drug has a familiar ring. The fact that growth hormone levels in the elderly are lower than in the young suggests the possibility that a hormone deficiency is the cause for their frailty. Since HGH improved the physical condition of children, it should improve the physical condition of the elderly. Grandparent as well as grandchild might both reach for their growth hormone vials.

The first step was giving growth hormone to patients whose pituitary glands had been removed or radiated to prevent the spread of tumors.

In 1962, writing in the *NEJM*, M. S. Raben reported that he treated a thirty-five-year-old schoolteacher suffering from pituitary gland insufficiency with growth hormone three times a week; after two months, the patient experienced exceptional physical and psychological benefits, including "increased vigor, ambition, and a sense of well-being."<sup>67</sup> The case did not immediately spur further research or change clinical practice because of the acute pre-1985 shortage of growth hormone. But once Genentech synthesized the hormone, physicians began to administer it to adults with impaired pituitary functioning. One British team reported that growth hormone given to twenty-four adults with severe growth hormone deficiencies reduced body fat and cholesterol and increased muscle mass. Although some patients experienced fluid accumulation and joint pains, the benefits outweighed the risks.<sup>68</sup>

The findings were well received because they were consistent with the effects of growth hormone in children. Since the drug increased muscle strength and reduced body fat among hormone deficient youngsters, it should exert the same effects in hormone deficient adults. Moreover, the fifteen-year experience with giving synthetic growth hormone to children had not produced serious side effects, which made it seem all the more reasonable to administer it to pituitary-damaged adults.

In no time at all, the distinction between pituitary-damaged adults and normal adults evaporated. If growth hormone improved body composition in one cohort, why not try it for another? Skeptics noted that an age-related increase in fat might be the cause, not the result, of a decrease in growth hormone production, so interventions should emphasize weight reduction, not the administration of a drug. They were also dubious about generalizing from children to adults, and from older patients with pituitary disease to older patients who were healthy—perhaps only those with severe deficits benefited. Nor were they convinced that older men and women were actually growth hormone deficient. Why set the normal level by the teenager and consider all sixty-five-year-olds deficient? Why not age-adjust the measure, taking the average sixty-five-year-old reading as normal? In effect, the debate about levels was a debate about the wisdom of nature. Were the lower levels of growth hormone protective or injurious? Did we tamper with nature at our peril or to our benefit?

Despite these larger questions, research on HGH in adults continued. In 1990, Daniel Rudman at the University of Wisconsin reported the first results of administering growth hormone to a group of healthy men between the ages of sixty-one and eighty-one. He gave twelve of them injections of growth hormone three times a week, and gave a control group of nine men a placebo. At the end of six months, the growth hormone recipients demonstrated an average increase in body muscle of 9 percent, a decrease in fat tissue of 14 percent, and an increase in skin thickness of 7 percent—findings that Rudman presented as a “reversal of the effects of 10 to 20 years of aging.” (This phrase, as we shall see, had a very special appeal to the media and drug companies.) The control group showed no significant changes at all. Side effects appeared very minor; none of the recipients had edema or increases in sugar levels or blood pressure. Rudman’s conclusion was that reduced levels of growth hormone in otherwise healthy men were responsible, at least in part, for the loss of muscle, gain in fat, and thinning of the skin, and these changes could be reversed by administering growth hormone.<sup>69</sup>

These claims, as would be expected, spurred further research. As might also be expected, there was no consistency in the design of the studies. Teams used different dosages of growth hormone, different measurements of growth hormone levels, different populations, different lengths of administration, and different body measurements. There was also no consistency to the findings. One Stanford group reported much less favorable outcomes and a dropout rate of 11 of the 19 subjects because of the severity of side effects, including carpal tunnel syndrome and severe joint pain. Other teams found that growth hormone strengthened the lumbar spine but not the hips. Still others detected no effects whatsoever on adult bones: “It is difficult to justify optimism that any tolerable dose of GH will provide a major skeletal anabolic effect in elderly men and women.”<sup>70</sup> One team gave growth hormone to healthy sixty-four- to seventy-six-year-olds every evening for six weeks and learned that muscle strength increased significantly as measured by the use of a rowing machine, increased only slightly as measured by a shoulder press or leg curl, and increased not at all by other strength tests. Body weight, body fat, body muscle, and cholesterol levels were

all unchanged.<sup>71</sup> Another team reported “no evidence of an association between GH secretion and muscle mass,” or between short-term hormone administration and bone mineral density at the forearm, spine, or thigh.<sup>72</sup>

The negative evidence continued to mount over the 1990s. One particularly thorough study by Maxine Papadakis at the San Francisco Veterans Administration Center, published in the *Annals of Internal Medicine*, involved the effects of growth hormone in fifty-two healthy adults of an average age of seventy-five. Half the group received the hormone for a six-month period, the other half received a placebo. Those receiving the hormone did have increased body muscle and decreased fat, but the changes had no impact on functional ability. Both groups performed the same on tests of muscle strength and endurance. Those with the hormone did better on some cognitive tests and worse on others. There were no differences in mood or in measures of depression. However, there were major differences in side effects. Recipients commonly reported edema and joint pain. In all, physical exercise (which cost nothing) led to better performance levels than growth hormone (at \$18,000 a year), and with no side effects. Papadakis’s conclusion: “Growth hormone should not be used to preserve or improve function ability in healthy, functionally intact older men.”<sup>73</sup>

In light of these negative findings, several teams took another look at the use of growth hormone in patients with pituitary tumors and discovered many more serious side effects than originally reported. It turned out that adults with growth hormone deficiencies responded differently than children; they were far more likely to suffer major adverse events, including edema, numbness, and joint pain. The worst side effects were experienced by those who had been considered most likely to benefit from the hormone, the overweight patients.<sup>74</sup> So too, the benefits turned out to be minimal. Although some patients reported genuine gains, the great majority did not. “A definite improvement in well-being when replacement GH is given to large groups of patients have [*sic*] yet to be established.”<sup>75</sup>

Thus, by the end of the decade, the consensus among investigators was that growth hormone served no purpose in otherwise healthy, older men. It altered body composition but offered no “significant improve-



ment in muscle strength or exercise tolerance."<sup>76</sup> At a minimum, as one reviewer commented in 1999, the case for it was "certainly 'not proven.'"<sup>77</sup> That same year, the National Institute on Aging of the NIH issued a guideline against giving growth hormone to healthy adult men because "too little was known about it." It went on to state that neither growth hormone nor anything else should be given "as an anti-aging remedy, because no supplement has been proven to serve this purpose."<sup>78</sup> Nevertheless, a vocal minority did not want to abandon growth hormone.<sup>79</sup> As the members of a prestigious growth hormone research society insisted: "It is likely that GH replacement will in the near future become as routine . . . as sex hormone replacement."<sup>80</sup>

The irony of this prediction aside, growth hormone use soon became even more problematic. A few small studies had found that growth hormone helped patients with severe illness to recover more quickly, particularly patients in intensive care units who had undergone cardiac or abdominal surgery. The findings were of such potential therapeutic importance that they stimulated a multi-center research project by a consortium of Finnish and Western European investigators. The teams gave 250 patients in intensive care units high doses of growth hormone and gave another 250 a placebo. The results, published in 1999 in the *NEJM*, were as unambiguous as they were unsettling. The group receiving growth hormone was far more likely to die in the hospital than the group on the placebo (roughly 40 percent compared to 20 percent). Even among survivors, those treated with growth hormone had worse exercise tolerance than those on the placebo. Why the outcomes should have been so negative was unclear; the speculation was that growth hormone impaired the body's immune defenses. But whatever the reason, as the editorial that accompanied the publication of the finding declared: For now "growth hormone should not be given to patients with critical illness."<sup>81</sup>

Another shadow fell on growth hormone a few months later when researchers examining physical growth and life span in a special breed of mice—who had a gene knocked out so as to decrease their levels of growth hormone—reported a surprising finding: the mice who were growth hormone deficient lived considerably longer than mice with normal levels of growth hormone. "The results," they wrote, "impli-

cate GH deficiency as the major factor in increased longevity and suggest the use of a cautionary approach to the therapeutic administration of GH, especially as an anti-aging agent, until more studies can be completed." It was possible that growth hormone was not the culprit; the gene that had been knocked out may have performed other vital biological functions, so that its absence produced a general debility. But here was another piece of evidence that higher levels of growth hormone might be life-shortening. The verdict of "not proven" was changing to "dangerous to your health."<sup>82</sup>

In retrospect, healthy older consumers would have been wise to avoid the risks of taking growth hormone. But how were they to know that caution was appropriate? Not from reading the initial press accounts. Although some reports of Rudman's 1990 University of Wisconsin paper were circumspect,<sup>83</sup> the Associated Press release had as its opening line: "Hormone injections can reverse some of the damage of aging and give people back the firmer flesh of their younger years." It went on to explain that growth hormone, now available in greater supply, would "help elderly people build up sagging muscles, take off flab and grow more youthful looking skin—turning back the clock as much as 20 years in just six months." Moreover: "The volunteers who got the shots said treatment made them look better and feel stronger, and their wives agreed."<sup>84</sup> The AP was not selling growth hormone, it was selling stories, and the hook lay in the effectiveness of growth hormone, not the preliminary nature of the findings. Its account had to be positive—and so the promise that growth hormone would reduce flab and make you feel stronger, and heighten sexual performance. Although in interviews Rudman himself sounded notes of caution, he often repeated the "twenty years younger" line, which in its very specificity gave credence to the intervention and aroused still more interest.

Endocrinologists soon were telling reporters that they were deluged with requests for growth hormone, which only served to increase interest. "They've called me at home—people wanting growth hormone for their parents," commented one expert, Mary Lee Vance. Some physicians worried about a black market in the hormone, and rumors were circulating about offshore clinics dispensing growth hormone. But the "avalanche of demands for immediate access to the hormone" delighted

Rudman. Whatever else, the frail elderly would no longer be "written off as hopelessly debilitated."<sup>85</sup>

Or so it seemed until the mid-1990s, when the doubts intruded. The press occasionally reported on the expanding list of side effects and some physicians' skepticism—the elderly on growth hormone "don't suddenly want to go cartwheeling down the corridor." Then came the Papadakis article, and although the *Annals* is not a journal as thoroughly covered as the *NEJM*, it is visible enough for a story on negative findings to create a stir. In this instance, the press did not bury the retraction. *USA Today* ran a front-page headline: "Elderly See Few Benefits from Growth Hormone." To be sure, the *New York Times*, which had put Rudman on page 1, put Papadakis on page 13, but its account did open with Papadakis's remark that "We cannot recommend it. . . . It's not the fountain of youth." And in a corny but not inaccurate rendition of the findings, the banner at *New York Newsday* ran: "Fountain-of-Youth Springs a Leak."<sup>86</sup>

Thereafter, a far more skeptical tone dominated media accounts of growth hormone. Individual endorsements ("I feel like I have restored my body to what it was like in college") were counterbalanced by physicians' warnings ("I tell everyone who calls, 'Don't take it!' "). When the scary report on growth hormone and mortality among ICU patients appeared and was soon followed by the finding of increased life span among growth hormone deficient mice, the press reported both stories as reinforcing already existing doubts on growth hormone efficacy.<sup>87</sup>

One might have imagined that all this would bring closure to the growth hormone story—a roller-coaster ride, to be sure, but everyone getting off safely, explosion followed by implosion, and final verdicts reached in relatively efficient fashion. But that is not the final word. Growth hormone use is ongoing, providing an object lesson in the challenges that Americans confront and will continue to confront in evaluating and regulating would-be enhancements. First, HGH promotion goes out through the modern version of traveling snake oil salesmen, reinvented as Web "health" sites. Second and even more distressing, a number of physicians, clinics, and societies unabashedly promote it, along with other purported enhancing techniques. These market-

ing ploys have escaped both regulatory authority and professional discipline.

The snake oil first: At least a dozen Web sites advertise and sell substances purported to be growth hormone. Thus, hgh-pro.com offers "the 'proven' most effective Human Growth Hormone product available without a prescription." It is dispensed by a nurse, "a medical professional actually involved with the clients, rather than a salesperson with no medical training." Buy two bottles at regular price and get a third free. Results are guaranteed: improved energy, muscle mass, hair growth, immune system, mood, sexual performance, and a sense of well-being. Exactly what the product is is never made clear. It cannot be growth hormone itself, since that requires a prescription. Rather, these are supposedly natural substances, whatever that may mean, with the promise that they are the market's best.

Go to the World Health Network to have a choice of purveyors of growth hormone-like substances. There is A Physician's Blend HGH or Regensis Plus (an "elite growth hormone product" in an oral spray). Regensis is also available at young4ever.com. In the first month, it will bring more vivid dreams and better sleep along with heightened energy; in the second month, it delivers weight loss and enhanced sexual function. By the sixth month, it will lower blood pressure and improve cholesterol levels. AgeForce sells it too, urging consumers to buy the product from them since they are a pharmaceutical manufacturer, not a marketing company. AgeForce also provides a bibliography on growth hormone, with selective quotations from the literature, including Rudman's statement on reversing twenty years of aging. Needless to say, Papadakis is not on the reading list and no mention is made of the recent ICU findings or the results with mice. Lifespanlongevity.com promises to effect "a dramatic slowing and even reversal of the aging promise" and backs up its claim by noting that the *NEJM* has reported that human growth hormone can reverse "the aging process . . . from TEN to TWENTY years." Of course, the column on "What researchers have to say about hGH" leads off with Rudman. All the Web sites close with the same tag line: "The information provided has not been evaluated by the FDA and is for educational purposes only. It is not intended as a diagnosis, treatment, for prescription for any disease. Consult your physician."

Seeing a doctor, however, does not provide as much consumer protection as might be hoped. A growing number of physicians present themselves as "anti-aging" specialists and their calling card is access to hormones, often growth hormone. In the early 1990s, a dozen physicians created the American Academy of Anti-Aging Medicine (A4M), which now claims 8,000 members. It administers an examination that gives physicians "board certification" in anti-aging medicine. It sounds impressive—after all, board certification is the gold standard for specialties—but it is entirely fictive, not recognized by the Council on Graduate Medical Education, which governs specialty certification. The unwary or unsophisticated consumer, not likely to know this, might believe that A4M is a genuine specialty board, akin to those in internal medicine or surgery.<sup>88</sup>

Members of the A4M are as aggressive as they are unembarrassed by the problematical nature of their practice. They boast, in the tradition of Brown-Séguard, of being their own best customers, perfect advertisements for the wonder of growth hormones. Dr. Ronald Klatz, president of A4M and author of *Grow Young with HGH*, claims that since taking the hormone, his waist lost two inches and his chest expanded two inches; he is chronologically forty-four years old, but only thirty-four biologically.<sup>89</sup> Dr. Alan Mintz, head of the Cenegenics Anti-Aging Center, declares: "I've been taking hGH for 3 years, and I've never felt better or stronger."<sup>90</sup> Dr. Adrienne Denese, who practices anti-aging medicine on Manhattan's wealthy East Side, injects herself as well as her patients with growth hormone. "It takes a few days to feel it mentally, and the physical effects—like extra muscles—you can see in a month."<sup>91</sup> In the tradition of Gertrude Atherton, physician testimonials go hand in hand with celebrity testimonials, including those of Oliver Stone and Nick Nolte.

Estimates of how many Americans take growth hormone for enhancing physical capacity range from 5,000 to 30,000 to 250,000. The annual report of Pharmacia, which sells Genotropin, now the best-selling growth hormone product in the United States, says its sales are up 25 percent to a total of over \$475 million. But how many of the purchasers are children, adults with pituitary disease, athletes, or otherwise healthy adults remains unknown. One Web site, [humangrowthhormonesales.com](http://humangrowthhormonesales.com),

sells Lilly's growth hormone product. (Purchasers must have a doctor's prescription, which the company will honor for one year.) Between February 24, 2001, and June 14, 2001 (when we logged in), the site had 7,686 visitors. But log-in does not mean purchase, as witness our own visits.

At least 100 clinics advertise themselves as anti-aging medicine centers. Most of them, as might be guessed, are located in California and Florida, with ample numbers in New York, Nevada, Arizona, and Texas. The patient base is not enormous—most report 50 to 150 clients—but Las Vegas-based Cenegenics claims 1,200. (Note the self-promoting name, *cene* to suggest centenarians, *genics* to suggest, incorrectly, that genetics is involved.)<sup>92</sup> The fees are hefty and for the most part not reimbursed by insurance companies; they range from \$1,750 for a workup at Cenegenics to almost \$5,000 at Lifespan, with follow-up packages of hormones, vitamins, and enzymes adding another \$1,700.<sup>93</sup> Adopting the model of personal trainers, some clinics, like the Anti Aging Medical Associates of Manhattan, set an annual fee, with patients entitled to unlimited visits. Only rarely will a clinic advertise "cost effective" services with "discounts available."

Some clinics are run by plastic surgeons or dermatologists who, as we have seen, are eager to add anti-aging to their practices. But most clinics are free-standing and devoted exclusively to anti-aging. What that means, first, is a vast and truly bewildering array of diagnostic tests. One such clinic runs patients through a roster of laboratory tests that takes 22 pages to describe, so as "to assess more than 150 relevant biomarkers of aging," as though anyone knew what the markers were. The workup includes standard blood tests and examinations (like an EKG), but also (with a disclaimer "for investigational purposes only") blood or urine levels of beta carotene, hydroperoxides, tocopherol, melatonin, and trace metals (tin, zinc, mercury, nickel), oxidative stress measures, and, of course, hormone levels. Once the tests are completed, it moves to therapeutics. Through the administration of growth hormone, it promises to restore "youthful levels," which will produce more muscle, reduce fat, improve bone density, improve short-term memory, and enhance "clarity of thought." Another competitor, the Institute of Anti-Aging Medicine, located fifteen minutes from Houston's airport,

claims that "through the use of state-of-the art technologies such as comprehensive hormone replacement therapies, including growth hormone, the aging process is dramatically retarded, even reversed." The California Anti-Aging Institute in San Diego, headed by Dr. Ron Rothenberg, who is board-certified in (of all things) emergency medicine, provides "hormone replacement programs for men and women including human growth hormone." The promised results: "the reversal of the aging process and peak human performance."<sup>94</sup>

Although anti-aging physicians will sometimes acknowledge that their interventions do carry risks of side effects, they are hardly concerned about them. Some keep the dose levels low, probably too low to do much good were these interventions effective, but low enough also to prevent the most harmful consequences. They are quick to discount the specter of cancer. As Ronald Klatz commented to one reporter: "If there was a risk of cancer, where are the bodies?"<sup>95</sup>

The clinics have not been curbed and the practitioners not reined in. The FDA is helpless to do anything about the off-label use of drugs already on the market for therapeutic purposes. As Murray Susser, who practices anti-aging medicine in Los Angeles, notes: "It's legal, and people have a choice. It's only misuse if I lie to them. I say to people who are taking it, 'It's experimental, it may help, but I don't know for sure.'" Nor can the FDA now do anything about so-called natural substances, which congressional action has removed from its purview. Professional medical societies are notably silent. The organization representing clinical endocrinologists, for example, has declared that no evidence exists for the efficacy of any of these interventions. But it does nothing more than issue such statements, perhaps taking comfort in the fact that most anti-aging practitioners are not board-certified endocrinologists. Anti-aging physicians could be sued for malpractice and it would not be difficult to demonstrate that their practice patterns deviate seriously from professional standards. But patients have not been inclined to take them to court, either because they do not want to admit publicly to seeking anti-aging medicine or, more likely, because they have found the physician sympathetic to their problems and ready to give them ample time. Or perhaps these patients are the quintessential risk-takers, determined to be the first in line, ready to suffer disappoint-

ments but come back again for the next regimen. As one frequenter of these clinics boasted: "I wasn't worried because I'd read a lot about it. But as with anything new, people are afraid."<sup>96</sup> All of which helps explain why enhancement technologies, whatever their putative benefits or demonstrated risks, will have significant space in our future.

## EIGHT

## Peak Performance

OVER THE PAST DECADE, an explosion of knowledge about the human genome has dramatically increased the prospects for refashioning the self. Although specific interventions to enhance performance are in drawing board stage, the possibilities inherent in the new technologies have sparked extraordinary public and professional interest. A spate of popular and academic books explores some of the promises of modifying genes so as to enable ordinary men and women to perform exceptional physical and mental feats. They then go on to ask what it will mean when genetic engineering is able to make us stronger, smarter, less in need of sleep, more able to run, lift, and swim. What if gene manipulation could make us more assertive or considerate or cautious or venturesome? What if genetic knowledge could double the average life span, enabling people to live far longer productive and active lives?

As the historical record we have traced makes apparent, these issues have both a personal and social dimension. As individuals, each of us now stands in roughly the same relationship to medical knowledge and practice as our predecessors did in the 1920s and 1930s. Then we were our hormones; now we are our genes. Although the quality of scientific research may have advanced, so has its sense of adventure. It is far from clear whether investigators' impressive credentials or physicians' enthusiasm will serve as adequate guides to the emerging technologies. There are already numerous examples of interventions that promised to enhance physical strength and longevity but, in fact, reduced

them. Nevertheless, the benefits of being Forever Young or Forever Awake are likely to be presented with such exuberance as to obfuscate the profound risks of harm.

The advances in genetics are reordering our conceptions of the respective roles of environment and genetics. For most of the twentieth century, genetics was understood as a fixed and limiting factor for any single individual. In the popular imagination and in most scientific circles as well, inheritance was a lottery that produced winners and losers, determining physical features (eye color, skin color, height) and mental and behavioral traits (from the degree of memory to the type of personality). By contrast, the liberating factors emerged from the social environment. Through the right influence of family, school, and community, through the impact of good housing, diet, and health care, individuals would be able to shape their own futures.

As we know all too well, a few societies have tried to apply a program of positive and negative eugenics to improve the nation's stock. No country more brutally pursued these tactics than Nazi Germany. It encouraged some sectors of the population to reproduce (Aryans), and discouraged or prevented others from doing so (including Jews, the mentally ill or retarded, tuberculosis patients, homosexuals, and Gypsies), either through forced sterilization or murder. In less horrendous but still coercive fashion, the United States in the 1910s and 1920s incarcerated and sterilized so-called mental defectives to try to change the composition of the population. As late as the 1980s, China was using compulsory sterilization to these same ends.

However inhumane and cruel these efforts, they were futile. Because of a basic ignorance of the rules of inheritance (Down's syndrome, for example, is not inherited), or because the imposition of such controls was beyond the capacity of the state (in the United States, courts prevented some of the worst abuses), eugenic efforts came to naught. And even at their most grotesque, the programs did not, and could not, seek to alter the inherited characteristics of a given individual. The hope was

that in some distant future the nation would become all white or blond or Aryan, but in the here and now people still had to play the genetic codes they had been dealt.

By contrast, liberal and reform-minded social activists designed and implemented public programs for the explicit purpose of countering and overcoming genetic influences. Governmental interventions to ameliorate the social environment were intended to expand individual life choices and in this way benefit the larger community. The Progressive agenda in the opening decades of the twentieth century epitomized the movement. Improve housing, and a constitutional proclivity to a disease like tuberculosis would be offset. Establish schools, and mental capacities would increase. Build playgrounds and organize settlement houses so that children would grow up to be cooperative and lawful. The work of the anthropologist Franz Boas typified the approach. Boas was committed to the principle that seemingly inherited traits reflected environmental conditions, and his case in point was height. The prevailing belief was that immigrant children, because of their inferior stock, were shorter than native-born children—and size was an indicator of general physical and mental capacity. Boas demonstrated that immigrant children raised in healthy environments grew as tall as native-born children. Social conditions mattered most, not hereditary traits.

Now, in a genome era, the older divide between a liberal-social environment camp on the one hand and a conservative-genetics camp on the other has weakened, almost disappeared. Take the dictum “You are your genes.” Rather than encourage passivity and resignation before fate, the postulate is turning into a call for intervention. Genes can be manipulated. The organism is fluid. As soon as the biological mechanisms of heredity are understood, the genetic sentence can be altered, whether it involves cure (as in the case of an inherited propensity to breast cancer) or enhancement (as in an inherited propensity to forgetfulness). In effect, the idea of genetics as a limit is giving way to genetics as a tool for redesigning the individual.

The importance of this shift cannot be exaggerated. It means, first, that the goals of genetics are far more focused on altering individual characteristics rather than group characteristics. We are not back in the Nazi era with a dream of collective change, but on the brink of an era that promises individual change. Second, genetic engineering in the

future is not likely to be imposed by the state from above, but pursued by individuals, embraced from below. The goal is to improve each one of us, not all of us through collective means. Third, the social environment is being defined as more restrictive than liberating. The quicker and easier route to change may be through genetics because manipulating a gene may be far simpler than altering societal institutions. For all these reasons, opponents of genetic engineering will not be able to invoke the experience of eugenics. The many forces driving enhancement that we have been tracing, from science to medicine to culture and commerce, will not be derailed by an appeal to historical precedents. Technologies that we once feared as coercive are being viewed as liberating.

In more specific terms, genetic research is exploring the operation of the brain, including the mechanisms of memory as well as the causes of Alzheimer's disease and schizophrenia. It is also examining the biological sources of behavior, ranging from alcoholism to temperament (introverted or extroverted, conservative or risk-taking). So too, investigators are exploring the genetic basis of longevity, looking well beyond the possibility of extending the life span by 20 percent (which occurred over the course of the twentieth century) to 50 percent, so that an average life span would be in the range of 140 to 160 years. There are formidable barriers to realizing all these agendas, but the field may be on the brink of revolutionary changes.

There is no holding back the enterprise. Not only are the goals highly attractive to many people, but even more important, the research itself begins typically with an attempt to cure a disease and then at a subsequent stage explores the possibilities of enhancement. Thus, investigations that initially seek to repair shattered memories may eventually provide clues to expanding normal memory. Research that seeks to cure mental illness may uncover mechanisms to promote optimal behavior.

Because the possibility of such accomplishments takes the breath away, the need to understand the methods of the research and their likely outcomes is essential. As this history of enhancement has demonstrated time and again, routine methods of oversight will not be adequate, nor will the advice of individual physicians or professional medical societies or government regulators. What is required is an intimate understanding of the nature of the research and the reliability of

the results. Only with this information at hand will consumers be able to calculate potential risks and benefits to know whether to join the line outside the doctor's office, or demur.

## II

The prospect of enhanced memory would be welcomed by almost everyone and would not require extraordinary individual or societal readjustments. (An expanded memory, for example, would not necessarily weaken psychological mechanisms like repression.) In attempting to fathom the "underlying biology of memory formation," various teams are trying to identify the relevant genetic components in both animals and humans.<sup>1</sup> One team, which is experimenting with different types of flies, has discovered that "long-term memory formation can be greatly augmented if selected single genes are activated prior to training." Moreover, it notes, "recent studies in the *Drosophila*, *Aplysia*, and *Mus* have been particularly suggestive of a common mechanism for long-term memory among arthropods, molluscs, and mammals."<sup>2</sup> Since learning itself makes a specific and physical imprint on brain circuitry, genes are likely important to the process and specific genes may release substances that aid neurons in establishing and maintaining circuitry in the regions of the brain that store information as memory. As soon as the genes and their substances are identified, methods for maintaining or improving synaptic plasticity and strengthening the activity between neurons could emerge. Hence, the team without any hesitation concludes that its finding "encourages the speculation that gene therapy, applied in humans to regions of the brain that are crucial for memory function may provide . . . interventions for repair or enhancement of memory function."<sup>3</sup>

No less important, if too easily overlooked, is the fact that research into memory in flies highlights the complex trade-offs that may characterize the risks and benefits of an intervention. One team tested for memory in *drosophila* by measuring the length of an association of a specific odor with an electric shock. The flies with better memory would sniff the odor and then avoid going into the chamber where they had earlier received the shock; those with weaker memory went right

back into the chamber. The design enabled researchers to distinguish between short-term (one-day) and long-term (seven-day) memory and to begin to identify their underlying genetic components. It turns out that interventions that help extend long-term memory undercut short-term memory. More, the genes involved for memory affect other, non-memory-related, functions, including reproduction. So even at the level of the fly, there are gains and losses, with improved memory coming at the cost of reduced fertility. How this might work out in humans is unknown, but imagine the dilemma that would face an ambitious thirty-year-old stock analyst or academic.<sup>4</sup>

Investigators have also learned to use embryonic stem cell gene-targeting technology to produce a strain of mice with a disruption, or knockout, of a particular gene. The animal without the gene is given a series of tests to understand the functions of the now missing gene.<sup>5</sup> Although the technology is novel, the method is old; pioneering endocrinologists, as we have seen, castrated animals to investigate the functions of the testes. Between 1992 and 1997, some fifty articles explored the phenomenon of memory by using knockout gene technology, but almost all of them came up against a methodological problem. Since each gene has more than one function, investigators could not be certain whether a finding of reduced memory was linked to the missing gene or whether it reflected a general disability in the organism that manifested as weakened memory.<sup>6</sup> To be sure, research tools are becoming more refined, now able, for example, to knock out a gene later in the embryonic development and to target specific cells, not all cells, thereby reducing the possibility of general disabilities. But the field has a distance to go, including complaints from investigators that a major "shortcoming of current gene knock-out technology is not-so-infrequent cases of premature death of the mutant mice."<sup>7</sup>

Moving from rodents to people and from the laboratory to the clinic, memory experiments often involve patients with Alzheimer's disease (AD). For obvious reasons, memory research with humans has focused its attention here, and a future ability to enhance human memory might well result from these efforts. AD represents the progressive loss of memory and cognitive function, particularly in an older population. Although precise estimates of the total number of cases are hard to reach, it may affect some 4 million Americans. Dementia itself, which is

most commonly caused by Alzheimer's, affects some 10 percent of all people aged sixty-five and almost 50 percent of all people aged eighty-five. (The percentage climbs because older cases survive and newer cases are added.) In AD, the brain undergoes several pathological changes, including the formation of amyloid, that is, dense plaques that clog intercellular space, the appearance of flame-shaped neurofibrillary tangles, and a sharp decline of neuronal activity. There is evidence, too, of cellular inflammation and a marked drop in the amount of acetylcholine in the brain, the substance that facilitates the transmission of signals across synapses.

Given the devastating consequences of AD both to the affected individual and the family, many pharmaceutical agents have been used to ameliorate the disease, but with marginal success. Prescribing cholinergic substances to offset the deficit and restore neurotransmission has not been successful. Preparations that have some efficacy in animal models have failed in humans or proved too toxic at the necessary dose levels. Velnacrine, which apparently improved memory functioning in rats, had only "modest" impact on Alzheimer's patients.<sup>8</sup> The FDA has approved a drug for Alzheimer's, tacrine, but since it has significant side effects (liver toxicity) and only very limited benefits, not many physicians prescribe it.<sup>9</sup> The list of other failures is lengthy. Drugs with antioxidant properties have no impact. Nor does extract of ginkgo, derived from the leaf of a subtropical tree and sold in health food stores as an antioxidant.<sup>10</sup> The record with vitamin E is no better.

Failures to identify an effective agent have intensified the search for a genetic component in AD. Although it is by no means an exclusively inherited disease, genetic influences do appear to play a role in its etiology. People who have first-degree relatives with AD are 40 times more likely than others to contract it themselves; children with affected parents have a 50 percent likelihood of getting it.<sup>11</sup> Although several specific genes have been implicated, the leading candidate is the (epsilon) 4 variant of apolipoprotein E (apo-E), a protein encoded by a gene on chromosome 19.<sup>12</sup> People who have two copies of this allele, or variant gene (2 percent of the population), are far more likely to contract the disease; by age seventy, 50 percent of this group will have it.<sup>13</sup> To be sure, 50 percent with the two copies will not contract it, and other considerations, such as smoking or high cholesterol, may be affecting the

outcome.<sup>14</sup> Nevertheless, the apo-E 4 linkage persuades many investigators that future research should follow "molecular approaches that modify the effects of mutations in critical genes."<sup>15</sup>

Although genetic therapies have yet to emerge, an energetic research effort is under way to learn whether the apo-E 4 variant influences general cognitive performance in the normal population. Researchers have explored whether age-associated cognitive decline, which is usually considered a normal part of growing old, is actually a less severe form of Alzheimer's. If so, elderly people with the apo-E variant might be more predisposed to cognitive deficits, and were that the case, a genetic intervention might protect not only against AD but also what has heretofore been considered "normal" declines. Which brings us right to anti-aging and enhancement.

The first research results seemed to confirm the link between the gene variant and lower cognitive functioning. A study of elderly nondemented women found that subjects with the apo-E allele performed less well on memory and learning tests than women without it. Another study analyzed the genetic composition of Finnish centenarians and found that, as a group, they had few apo-E variants. However, initial findings have not held up. Subsequent research demonstrated that in non-AD persons, the presence of the apo-E variant did not bring reduced attention span, impaired language skills, or any other cognitive deficit. The allele may mark a high percentage of AD cases, but has no relevance for other conditions.<sup>16</sup>

In the end, the dynamic of the research, although not the immediate results, suggests just how nimbly investigations of a disease move over to enhancement. Eventually, a genetic factor may be identified that both prevents deterioration of memory and improves memory, producing an intervention capable of curing Alzheimer's and improving cognitive functioning in normal people. Then we will face the predicament of how much risk to assume for how much added memory.

### III

Over the past decade, the field of behavioral genetics has gained attention for its ambitious efforts to understand and modify the genetic con-



tribution to human behavior. Although even the most enthusiastic investigators agree that environmental contributions are important, they are confident that genetics plays a crucial role. They concede that linking complex personal interactions to genes is not easy; behavior is so rooted in family and societal contexts that forging the connections may become heavy-handed and reductionist, as though we were truly nothing other than our genes. Still, there is something commonsensical about exploring genetic influences. Aphorisms such as "like father, like son" or "the apple does not fall far from the tree" embody the idea. So does the common experience of having one's children evince behavior patterns that mirror those of grandparents they never met. Behavioral geneticists pick up on this attitude, eager to tell the story of how identical twins separated soon after birth were reunited many years later and discovered to their amazement that they both held the same kind of job, were divorced, had remarried women with the same first name, and smoked the same brand of cigarettes.

To go beyond anecdote, researchers must first devise uniform and comparable classifications of behavior, which is no simple exercise. Centuries ago, people were classified by theories of humors into one of several temperaments: they could be fiery and aggressive (the blood tipped to bile), or phlegmatic (with an excess of blood). But such groupings had fallen out of favor, at least until behavioral geneticists resurrected them. They identify five major behavioral types: people characterized by extroversion; agreeableness; conscientiousness; emotional stability; and intellectual openness.<sup>17</sup> Through elaborate questionnaires, they assign respondents to one or another of these categories, and then begin the search for the underlying genetic contributions.

Their strategies have been ingenious although never powerful enough to satisfy skeptics. Investigators have honed in on identical twins (monozygotic) who have been reared apart, on the supposition that similarities between them that are greater than the similarities among siblings in general indicate a genetic influence. Their next favorite group to study is identical twins reared together, whose behaviors are then compared to fraternal twins reared together. To the extent that identical twins demonstrate greater similarities than fraternal twins, the trait has a genetic component. If a trait in one identical twin appears 60 percent

of the time in the other identical twin, but the same trait in one fraternal twin appears only 20 percent of the time in the sibling, then 40 percent of the trait is genetic. So if the brother of an identical homosexual twin is far more likely himself to be homosexual than the brother of a fraternal twin, then homosexuality has a genetic component.

Researchers also study adopted children to learn whether their personality traits resemble more their adoptive parents (which speaks to the environment) or their biological parents (which speaks to genetic inheritance). Perhaps most controversially, researchers are analyzing children and adults with special behavioral features, some desired (musical aptitude), some undesired (mental illness, criminal behavior), to see whether they run in families. Were children of schizophrenic parents or incarcerated parents more likely to suffer the illness or be convicted than others, genetics might be a factor in the etiology of the condition.

The ultimate task of the research is by far the most difficult: to locate the gene or, more likely, the several or many genes responsible for the behavior. Investigators must find the allele that is common to schizophrenics or to extroverts. Then they have to figure out what this genetic variation does biologically and how it might be manipulated to do more or to do less or to do otherwise. The whole enterprise may seem fantastic, but imagine if an allele could be tweaked to embolden shy people or tame aggressive people.

What has been accomplished so far? Researchers believe that they have identified a number of personality characteristics with genetic bases. One investigator finds that "extroversion," for example, correlates to .68 for monozygotic twins reared apart, .55 for such twins reared together, and .20 for biological siblings, thereby indicating that "individuals who share genes are alike in personality regardless of how they are reared."<sup>18</sup> To be sure, the environment, and the "non-shared environment," that is, the social settings that one sibling experiences but not the other, exert a powerful influence on an individual. But if the trait did not have a genetic base, why is it more common to monozygotic twins reared apart than to biological siblings?

Other researchers have searched for the genetic basis for "novelty seeking." Although they report correlations with a gene known as D4DR, which helps regulate dopamine (the powerful neurotransmit-

ter whose absence causes Parkinson's disease), their own calculations suggest that the genetic influence affects only a small proportion of people with the trait.<sup>19</sup> "D4DR," concludes one researcher, "accounts for roughly 10 percent of the genetic variance, as might be expected if there are 10 or so genes for this complex, normally distributed trait."<sup>20</sup> No wonder that to date "modest" is the descriptor usually attached to even positive finding of behavioral genetics.

Although the infant science may grow to maturity, fundamental problems complicate its research—and before succumbing to its allure or interventions, it is important to understand them. First, the personality categories lack internal consistency. The "extroversion" type includes people who are gregarious, social, dominant, and adventurous. But these traits are at odds with one another—gregarious may conflict with dominance, social with adventurous—giving the category a grab-bag quality. This is even more true for "novelty seeking," which lumps together such behaviors as exploratory, fickle, impulsive, extravagant, and quick-tempered; those inclined to be exploratory might not be, or wish to be, extravagant and quick-tempered, traits that would certainly impede effective explorations.<sup>21</sup>

Second, twin studies that rely on the fact of being "reared apart" may be misleading. Although the twins may not be residing with the same family, they may be in very similar families—social welfare agencies typically place children with adoptive families that closely resemble their biological families in color, religion, social class, and general interests. Moreover, twins who have a stake in being twins—getting psychological payoffs for the status—may exaggerate the qualities that they share, or even the extent to which they have been reared apart.<sup>22</sup>

Third, little progress has been made to date in linking personality traits to specific genes or alleles. The likelihood is that when biologic bases for behavior are identified, there will be multiple genes interacting in different ways with one another and with the environment to produce the results. To carry out what is called a "bruté force scan" of the entire genome, casting a very large net to find a putative gene, is difficult and expensive. The alternative, to use families known to have the trait in order to identify it, which works well in a one-to-one, gene-disease model, is less effective with behavioral traits. It is far more difficult,

really almost impossible, to identify and locate an extroverted family or a novelty-seeking family than it is to identify such an individual. Yet, searching for genetic similarities among single individuals who scored high on a screening test is too broad-gauged an approach to genetic screening. To make research matters worse, when the trait under investigation is a negative or stigmatized one, as may well be the case for novelty-seeking and surely is for criminal behavior, research faces extraordinary barriers. Informants may lie about their behavior, or communities, fearful of stigma, may protest vigorously against the project. In sum, the promise of behavioral genetics to enhance performance is still very much in the future, and when potential interventions do emerge, they will be particularly chancy and problematic.

#### IV

These many complications notwithstanding, the quest to understand the genetic bases for behavior is certain to continue, driven by the desire to cure illness, especially mental illness. The best example is schizophrenia.<sup>23</sup> This devastating disease disproportionately strikes young people as they enter adulthood. Given the special symptoms that mark it, including hallucinations, delusions, speech defects, and flattened affect, many investigators are persuaded that it is physiological, not psychological, in origin, reflecting deficiencies in "neural connectivity." Schizophrenia becomes a disease of the brain that manifests itself as a disease of the mind, and an excellent candidate for genetic study.

Researchers have long recognized a pattern of family inheritance in the occurrence of the disease. Only 1 percent of the population but 13 percent of the children of a schizophrenic parent are at risk; when both parents are schizophrenic, the risk climbs to 46 percent. So, too, 48 percent of identical twins with a sibling who is schizophrenic will themselves contract the disease.<sup>24</sup> Epidemiological research using the exceptionally complete Danish medical and population records was able to identify 2,669 cases of schizophrenia in a country of some 1.75 million people; the odds that any given person would contract schizophrenia were far greater if mother, father, or sibling had it than for others. To be

sure, most schizophrenics did not have an affected parent and even among identical twins fully half did not contract the illness after their sibling did. The Danish data also pointed to the effects of the environment. People born in cities were more likely than their rural counterparts to suffer the disease. Children whose mothers had a viral infection during pregnancy were more likely to become schizophrenic.<sup>25</sup> In all, schizophrenia is by no means an exclusively genetic disease, but it probably has significant genetic components.

Despite considerable effort, researchers have not been able to identify the gene(s) that contribute to the etiology of the illness. They have searched for alleles on more than half of 23 chromosomes, but still do not know which play a crucial role. What confounds the search? For one, defining the characteristics of schizophrenia (the phenotype to be studied) turns out to be very complicated. The psychiatric diagnostic manuals (*DSM III* and *DSM IV*) are useful starting points but are not sufficient to the task. The symptoms of the disease are so wide-ranging that *DSM III* and *IV* have to set out four different categories, running the gamut from a narrow to a very broad definition. Manic-depressive behavior fits the narrow category; alcoholism and anxiety join in the broadest category.<sup>26</sup> Moreover, the manuals recognize that some schizophrenics will manifest the disease with reduced emotional affect and apathy, while others will be delusional and hallucinating.

The breadth of symptoms does not trouble a practicing psychiatrist who writes a prescription for a particular patient. Most of the drugs are broad-acting, covering a wide range of symptoms. But genetic researchers are in a more difficult position. It is entirely possible, even likely, that each behavioral pattern has its own special or only partly overlapping genetic roots. Schizophrenia may not be, genetically speaking, one, but several diseases. So, if one research team works on a study population that is mostly in one category (say, manic) and another team uses a study population from another category (say, alcoholic or delusional), the likelihood that the teams will confirm each other's genetic findings is reduced. Moreover, the difficulties in identifying the right genes are exacerbated since schizophrenia is almost certainly not a single gene defect, like Huntington's disease; small variations among many genes may add up to a predisposition to the disease, which may or may

not then occur, depending on the particular environment. To circumvent some of these problems, investigators are attempting to identify physical traits that accompany all variants of schizophrenia, such as abnormalities in gait and unusual eye movements. But the effort is highly preliminary and may further complicate investigators' tasks. Now they will have to identify what may turn out to be separate although associated genetic determinants of both a physical and a mental disease.

In the meanwhile, genetic research findings regularly contradict one another. One group announces that it has located a promising lead on a section of chromosome 13, which some investigators then confirm and others disconfirm. Another team identifies a relevant region on chromosomes 5 and 10, but others disagree. There have been several positive findings for regions on chromosomes 6, 8, and 22, but since a region, or "locus," on a chromosome involves hundreds of genes, it is not easy to narrow the finding even "on these potentially promising regions."<sup>27</sup> For the moment, "no specific gene in any of the regions has been identified, let alone one identified with a specific neurochemical defect."<sup>28</sup> No interventions are in sight, either for cures or for enhancements. But optimists believe that breakthroughs on both fronts are sure to occur, so the question of which team and which findings to trust will sooner or later be upon us.

## V

Research into the genetics of alcoholism presents even more intriguing enhancement possibilities. Many twin and adoption studies point to a hereditary component in alcoholism. If one identical twin is an alcoholic, then the likelihood that the other will be is greatly increased in comparison both to fraternal twins (when one is an alcoholic) and to the general population. The finding holds as well when the identical twins are reared apart.<sup>29</sup> So too, children (particularly male) of an alcoholic father are 2 to 10 times more likely than others to become alcoholics. But almost all of the problems endemic to schizophrenia research reappear here as well. To identify the relevant genes, researchers must delineate

specific behavioral characteristics within the general trait of alcoholism, identify subsets of the population that manifest them, review the genetic characteristics of these subsets to find the alleles that might be common to them and associated with alcoholism, and finally, understand the biological mechanisms at work and learn to modify them.

Each step poses a myriad of problems. Alcoholism is a far more elusive category even than schizophrenia, representing, as one investigator notes, "one of the most complex [syndromes] known."<sup>30</sup> Described as a psychiatric illness in *DSM IV*, alcoholism manifests itself in so many different ways that researchers are hard-pressed to delineate discrete populations for study. It varies by age of onset (from adolescence to adulthood), by amount of drinking (hard drinkers to very hard drinkers), and by the severity of hangovers (moderate to heavy). There are differences by sex and by group (Japanese versus Americans, African-Americans versus Caucasians). Sometimes, but not always, alcoholism correlates with smoking, illicit drug use, and violence. So a vicious drunk may not be the same as a happy drunk. A drug-abusing drunk may not be the same as one who only drinks. To the extent that such differences matter, the relevant gene(s) become more elusive.

Researchers looking for uniform patterns above this behavioral diversity have uncovered unique brain wave patterns among alcoholics, along with particular visual and spatial defects and low blood platelet activity.<sup>31</sup> They also find metabolic deficiencies (the liver is unable to process the alcohol) and neurological deficiencies (lowered serotonin or endorphin levels). But the question remains whether these changes are the causes or the effects of alcoholism. Does a lowered serotonin level follow on hard drinking or encourage hard drinking? To answer the questions would require identifying potential alcoholics in advance, measuring their physiological functioning, and then returning to study them after they have, or have not, become hard drinkers. It is not an impossible design, but it is certainly not a simple or efficient one.

All these considerations affect how researchers conduct their genetic studies. When selecting a cohort of alcoholics to investigate, they must decide whether to rely on a personality questionnaire, a psychiatric interview, behavioral criteria, or a neurological, hematological, or gastroenterological examination. They have to choose between early-onset alcoholics and late-onset alcoholics and alcoholics with or without his-

tories of other types of substance abuse. Given the range of choices, different teams invariably make different selections, which helps explain why genes identified by one study do not turn up in another. The situation is tailor-made for divergent findings.

One genetic marker for alcoholism that has attracted some support among researchers is the allele *ALDH2-2* on chromosome 4. Those who carry this variant metabolize alcohol much more slowly than normal and, therefore, manifest such alcohol-related symptoms as a flushed face and a racing heart. Because it generates these unpleasant side effects, the allele is probably protective against alcoholism and is found disproportionately among Asian and Jewish populations, both groups with low levels of alcoholism.<sup>32</sup>

Findings about another allele, *DRD2 A1*, located near the dopamine receptors in the brain, have spurred much more controversy. Ernest Noble, a psychiatrist at UCLA, and Kenneth Blum, a pharmacologist at the University of Texas Health Center at San Antonio, reported in *JAMA* in 1990, that after examining DNA from thirty-five deceased alcoholics, they found the *DRD2* allele in 69 percent of the sample, compared to 20 percent in a normal control group. What made this finding so interesting is that people with this very same allele have abnormally low levels of dopamine. Accordingly, Noble and Blum contended that since alcohol is known to increase dopamine levels in the brain, alcoholism may well be a gene-based response to a shortage of dopamine. The alcoholic is drinking because his body is trying to raise its dopamine levels. Extending this argument further, they suggest that *DRD2 A1* is actually not itself an allele that causes alcoholism but rather is a "reward gene" that plays a crucial role in many types of addictive behavior. Because the allele reduces dopamine levels, it triggers a variety of responses, all seeking to raise the levels, and the responses can take the form of food abuse and drug abuse, as well as alcohol abuse. Thus, we may have at hand "a new paradigm in our understanding of the genetic basis of addictive-compulsive behaviors."<sup>33</sup>

As would be expected, other investigators immediately attempted to replicate these findings but, with a single exception, could not. One team considered the argument a "castle in the air," another was highly doubtful that the allele was actually a "trait marker for susceptibility to alcoholism."<sup>34</sup> But Noble did not back off. He insisted that other inves-

tigators had not used the appropriate cohort of alcoholics and control groups. For example, they had wrongly excluded severe alcoholics and had not tested the controls for other addictions that might account for the presence of the same allele. Moreover, he cited findings that treating alcoholics with bromocriptine, a substance that raises the body's level of dopamine, was proving an effective antidote to alcoholism; among those with the allele, the group receiving bromocriptine showed "the greatest and most significant decreases in craving and anxiety."<sup>35</sup> Noble was also encouraged by the findings of an NIH research team that, using a new scanning device, reported that obese people had fewer dopamine receptors than others and concluded that overeaters were trying to increase their dopamine levels and produce "feelings of satisfaction and pleasure." In light of all this, Noble suggested that "subjects with this [DRD<sub>2</sub>] allele may compensate for the deficiency of their dopaminergic system by the use of alcohol and other substances, agents known to increase brain dopamine levels. Stimulation by dopamine of A<sub>1</sub> allelic subjects' fewer D<sub>2</sub> dopamine receptors could provide enhanced feelings of reward and pleasure."<sup>36</sup>

If Noble is right, the prospects for genetic enhancement have escalated. Suppose investigators identify a gene or genes that could be manipulated to stimulate dopamine receptors and dopamine levels and thereby increase feelings of pleasure and reward. Such an intervention would likely win FDA approval as a means to treat alcoholism, obesity, and substance use. In short order, however, it would be prescribed off-label to elevate feelings of pleasure in a normal cohort. Investigators' curiosity, physicians' readiness to make their patients happy or happier, company marketing strategies, and people's readiness to experiment with new agents will ensure that even before the data are clear or potential side effects recognized, the technology will be used.

## VI

Of all the enhancement possibilities, none has greater potential for transforming individual lives and social relationships than a dramatic extension of life expectancy. Some geneticists confidently predict that

new knowledge and techniques will be able to double the life span, not by conquering the leading causes of death, but by understanding the cellular basis of aging.

The prospect of realizing this agenda has dismayed not only a variety of social commentators but also prominent cell researchers. They fear that the changes would be unnatural, burdening the environment, sparking an intergenerational warfare for power and resources, and stifling innovation. Overpopulation might well lead to state-coerced birth control. The hundred-plus-year group would have such an iron grip on resources that innovation in political, economic, and cultural life would be drastically reduced. Even from the individual's perspective, longevity might be a curse. One critic quotes a 1922 play, *The Makropoulos Secret*, written by Karel Capek, (famous for his *R.U.R.* robot story), in which the heroine, Emilia, having swallowed the now lost recipe of longevity concocted by her father in the sixteenth century, declares in her 337th year that her problem is "Boredom. No, it isn't even boredom. . . . You people have no name for it. . . . One cannot stand it. For 100 years, one can go on. But then . . . one's soul dies. . . . No one can love for 300 years—it cannot last."<sup>37</sup> Another opponent, Leonard Hayflick, whose original findings on cellular division lay the foundation for the cutting-edge work in the genetics of aging, wants nothing to do with promoting longevity. "I do not believe that our goal should be to tamper with the fundamental processes of aging, even if that were possible," he recently remarked. "The problems that would be created far outweigh any potential benefits. Indeed, I cannot imagine any scenario where tampering with the aging process would be beneficial. . . . To arrest or stop the aging process will not accrue to our benefit or that of society."<sup>38</sup>

Other investigators, however, are impatient with these objections. After all, to a thirty-year-old in 1800, the prospect of people living into their eighties and nineties would have seemed no less perverse. And by what standard is it wrong to extend the life of those already on the planet even if it meant creating fewer children? The 140-year-olds would bring their added wisdom and experience to the service of mankind. The likelihood is also strong that the technologies and knowledge that doubled longevity would ensure that the elderly would be

healthy enough to remain employed, not idle in a nursing home. Personal and social readjustments will be necessary, but it is not beyond our ability to learn how to function as great-great-grandparents.

Longevity, as in the other fields we have explored, probably has a genetic component. Epidemiological data suggest that just as children of alcoholics are more likely to become alcoholics, siblings of centenarians are far more likely to live longer than the general population; indeed they are 17 times more likely than others to become centenarians themselves. Animal studies also indicate a genetic contribution. In one simple and convincing experiment, researchers selected the longest-lived mice from a cohort and then mated them with other long-lived mice and eventually created a breed that had twice the longevity of ordinary mice.<sup>39</sup> In another experiment, investigators working with both the nematode worm (selected for a particular genetic mutation) and the fruit fly (selected for later fertility) were able to breed strains that had twice the normal species life span. In the case of the fruit fly, longevity was accompanied by other "functional enhancements," including resistance to stress and "increased locomotor capacity at later ages."<sup>40</sup> Not deterred by the biological distance from flies and worms to humans, these investigators confidently concluded that "we can now legitimately address the question of the postponement of human aging in a practical manner."<sup>41</sup>

In fact, mice have provided the most dramatic example of an intervention that actually increases longevity. Adult mice placed on caloric restriction (CR), following diets 25 percent to 50 percent lower than normal, outlive and outperform control groups. Why CR exerts this effect is not understood; it may improve DNA repair capacity or alter gene expression or reduce oxidative stress or lower metabolism. And even though hundreds of genes may be involved in the changes, the findings have been called "among the most important ever obtained in gerontology. . . . They constitute some of the best evidence available concerning the postponement of aging in mammals."<sup>42</sup>

Other longevity research takes as its starting point genetic diseases that cause premature aging and death. Werner syndrome affects the one person in 25 million people who has two copies of a defective gene, WRN. Because of this mutation, they show signs of aging in their early twenties, including balding and loss of skin elasticity; in their thirties,

they suffer diabetes and osteoporosis. They die on average in their late forties, usually from cancer or atherosclerosis. Another premature aging disease is Hutchinson-Gilford progeria, in which very young children suffer skeletal damage and cardiac disease, giving them an average life span of fifteen years. By studying these two diseases, geneticists hope to identify the particular gene(s) at fault for premature aging and for atherosclerosis; when they understand the mechanisms, they will be better able to grasp the role of the many other genes that affect aging. One team has already identified a genetic variation that might explain why patients with progeria have a greater incidence of myocardial infarctions, and the finding might have relevance to heart disease in the general population.

Although researching the genetics of early-aging diseases seems a sensible strategy, not everyone agrees with it. Rare diseases may involve completely idiosyncratic genetic defects and not serve as useful models. In the case of myocardial infarctions among progeria patients, for example, other teams have not replicated the identification of a particular genetic variation. Nevertheless, the study of these rare diseases provides a telling example of how research with a therapeutic goal can easily have profound enhancement consequences. As investigators learn to prevent premature aging through a genetic fix, they may also learn to prevent "normal" aging through a genetic fix—at which point we may enter a period of dramatically increased longevity.

But only "may enter" because genes may not be all-powerful. For one, environmental influences cannot be ignored. Longevity rates differ by socioeconomic class and by race; the wealthy live longer than the poor, whites longer than blacks. For another, genetic advantages in promoting longevity might not pass from generation to generation; life span *after* reaching the age of reproduction falls outside the dynamic of natural selection. As Darwin explained, the process favors only those genetic advantages that enhance reproductive capacity, not duration of survival afterward. There might even be a conflict between reproductive capacity and longevity. According to the concept of antagonistic pleiotropy, the attributes that contribute to effective early survival and reproductive capacity up to age thirty, including heightened immune responses and high levels of such hormones as testosterone and estrogen, may, twenty or thirty years later, turn out to be disadvantageous to

good health; a heightened anti-immune response might cause autoimmune disease, and a high level of estrogen, cancer. By the same token, natural selection might not encourage the development of highly efficient and continuous cellular repair mechanisms were these mechanisms to inhibit cellular growth in the first thirty years of life and, thereby, reduce reproductive potential.

Another daunting and, as we have seen, familiar challenge facing researchers is to move from hypothesizing genetic contributions to longevity to understanding the processes by which genes affect longevity. The most promising approaches follow on the findings of Leonard Hayflick. Hayflick discovered that the number of times a cell will divide has an upper limit; after fifty divisions, the cell falls into disrepair and soon dies. This limit is not a response to a biological clock—elapsed time is not the determining feature—but to a biological counter. After fifty divisions, in what has become known as the “Hayflick limit,” cells became mortal. There are a few exceptions. Cancer cells keep dividing and dividing, and in that sense are immortal, and so are stem cells. But all others are not.<sup>43</sup>

What sets the counter? How do cells know when they have reached fifty divisions? The answer was found in the end of the chromosome, the telomere, as it is called, whose purpose is to keep the twisted ends of the double helix of the chromosome from attaching to each other and blocking DNA division and replication. Each division of the cell causes a progressive shortening of the telomere, and the shortening eventually disrupts normal DNA replication. After fifty divisions the telomere becomes so short that the cell can no longer divide effectively; some of its genes are then turned off, others turned on, including some oncogenes (which may turn a normal cell into a tumor cell), and still others disarranged so that they send out disruptive messages. In Werner syndrome, for example, telomeres allow cells to divide at only half the rate of normal cells, which may help explain premature aging.

Once the function of telomeres became clear, the next question was whether some methods might be discovered to take cellular divisions beyond fifty. Researchers plunged in. The question was never whether to do it—concerns about the social impact of longevity did not cause a ripple—but how to do it. How could cellular division be increased and cellular aging prevented without turning the newly invigorated cells

into cancer cells? One answer came in 1998 from a team made up of investigators from the Geron Corporation and Texas Southwestern Medical Center. They inserted a newly cloned enzyme, hTERT, or telomerase, into human cells and these cells then went on to divide past the Hayflick limit by no fewer than thirty-six added doublings. Apparently, decreasing amounts of telomerase enzyme restricted cellular division; if the amount of the enzyme was increased, the cell would continue to divide. The team reported finding no gross changes in the proliferating cells and no signs of cancerous cells. They were not surprised—stem cells proliferated indefinitely without becoming cancer cells.

The team addressed the significance of the finding by moving immediately from cell to organism, and, curiously, from the active voice to the passive voice, as though the conclusion was too startling to consider. “Cellular senescence is believed to contribute to multiple conditions in the elderly that could in principle be remedied by life-span expansion.” These remedies could correct for loss of skin elasticity, age-related deterioration of optical cells, and atherosclerosis. The report ended with an obvious understatement that echoed the famous line that closed the Watson-Crick paper on DNA: The findings had “important implications for biological research, the pharmaceutical industry, and medicine.”<sup>44</sup>

As would be expected, the report attracted substantial attention. Writing in *JAMA*, Michael Fossel, editor of the *Journal of Anti-Aging* (and, as his disclosure form noted, a stockholder in Geron), first explained the “startling” research that took cells beyond the Hayflick limit.<sup>45</sup> Then, he, too, jumped from cell to organism, extending the diseases that the new method might cure to arthritis, immune deficiencies, and Alzheimer’s disease, and minimizing the risks that might accompany such an intervention. There was “no evidence yet that telomerase expression per se causes malignant transformation.”<sup>46</sup> (The “yet” was Fossel’s hedge against future findings.) And he, too, closed his review awkwardly but portentously: Medicine was advancing in its “potential to treat human disease, to alleviate patient suffering, and—raising the possibility ‘in proportion to its dignity’—that we may alter ‘the thread of life itself.’”<sup>47</sup>

Although other teams soon confirmed the enzyme’s ability to extend cellular division, fundamental disagreements erupted over the question

of risk, specifically whether the addition of telomerase reduced the cell's ability to protect itself from becoming a runaway cancer cell. In January 1999, the Texas team confirmed its earlier finding that using telomerase to double cell life span "does not lead to alternated patterns of growth typical of cancer cells."<sup>48</sup> The process "does not bypass cell-cycle induced checkpoint controls and does not lead to genomic instability."<sup>49</sup> But then, in June 2000, another team found otherwise. Although it readily acknowledged the promise of "cell-based therapies by allowing indefinite expansion of normal human cells without damaging their genomes," its own studies of cells that surpassed the Hayflick limit uncovered an increased presence of a particular oncogene, one whose activation "occurs in a wide variety of tumour types."<sup>50</sup> In fact, adding telomerase to the cell "has little, if any, immortalizing potential until the . . . tumour suppressing gene has been inactivated." In other words, the very effectiveness of the enzyme depended on its undermining the cell's protection against cancer growth. The team's conclusions, therefore, were far more guarded: "Expansion of normal human cells for therapeutic purposes must be approached with caution."<sup>51</sup>

Telomerase research actually reversed the traditional line of influence that takes a cure on to enhancement—in this case, enhancement research fed back into cure. Even as investigators were exploring the role of telomerase in extending longevity, others were examining telomerase as a potential cancer therapy. Since almost all cancer cells reactivated telomerase, the enzyme might be fueling malignant growth. If it were possible to inhibit the production of telomerase, the growth of tumor cells might be arrested. It was a promising but very risky strategy: restrict cell growth and so increase the prospect of cell death in order to curtail cancer cell immortality. Whatever the eventual outcome of these approaches, telomerase, like so much else in the enhancement arsenal, is a double-edged sword.

As novel as these cellular findings are, their implications follow the analytic path that we have marked out before. First, no matter how vocal critics may be about the deleterious consequences of increased longevity, the scientific work is far too fascinating and consequential for investigators to abandon it. Second, even were there a systematic effort to rein in laboratories, it would be impossible to distinguish anti-aging

research from anti-disease research. Since telomerase and telomeres may hold a key to the cure of cancer, research is certain to move ahead.

Third, the new telomere technology is also likely to present an exquisite risk-benefit calculus. Since aging occurs gradually over time, it may be too late to intervene at age sixty or seventy. By then, the cellular damage may have occurred. The right time to act may be at age thirty or forty, when the subject is healthy, in the prime of life, with the immune system at its peak, the DNA repair system working well, and the body still free of accumulated cellular defects. But consider the risks of experimenting with very young and healthy subjects. An intervention that might extend longevity might also cause disability or premature death. How should one balance the possibility of immediate risks with benefits that might (or might not) appear decades later? It might prove feasible to test the new technologies on the very elderly, willing to volunteer because they think they have less to lose. It might even be possible to devise surrogate markers for mortality so that the effectiveness of the intervention could be known more quickly. But there is no certainty that such solutions will be feasible.

These problems might give even daring investigators, ambitious biotech companies, and adventurous consumers pause. But if the past is a guide, there is certain to be someone ready to do the research, someone to fund it, and someone ready to serve as the first subject. Yes, there will be risks—but just imagine enjoying the benefits of an extra seventy years.

## VII

We close where we began, with a recognition of the ongoing, in fact, intensifying, interest in the promise and perils of medical enhancement. Even without any stunning breakthroughs in knowledge or technology, the first six months of 2003 witnessed a remarkable outpouring of books, both fiction and non-fiction; articles; and newspaper stories on the subject. The stance of some authors is predictable. Scientists, for example, have difficulty understanding what all the fuss is about. James Watson took the occasion of the Fiftieth Anniversary of his and Francis



Crick's publication of the double helix structure of DNA to argue in favor of the pursuit of enhancement. Elevating genes over environment, he insists that rather than invest in extra tutorials for slow learners, we should be exploring how to manipulate their genetic inheritance to bring them up to speed. Like so many of his fellow investigators past and present, he is thoroughly impatient with the idea that nature knows best. Watson speculates that were it not for the Nazi experience, we would have few doubts about the wisdom of genetic enhancement. Indeed, that very experience prompts him to observe: "Do we dare restrain our own research community, especially in light of the fact that other research communities, less trustworthy than ours, might be making progress?" His answer is absolutely not.<sup>52</sup>

Fictional accounts, like those by Margaret Atwood, take a very different posture, fearful that enhancement technologies will profoundly upset the balance of nature. Atwood's latest novel, *Oryx and Crake*, follows in the spirit of her earlier *The Handmaid's Tale*, and in the still earlier tradition of Mary Shelley. Her protagonist's father helped to "engineer the Methuselah Mouse as part of Operation Immortality," worked on the "pigeon project," to grow multiple organs for human transplantation, and to "create a genuine start-over skin that would be wrinkle- and blemish-free."<sup>53</sup> (His wife objected to the projects: "You're interfering with the building blocks of life. It's immoral. It's . . . sacrilegious.")<sup>54</sup> But worse was yet to come. The son, Jimmy/Snowman, who is among the last of human kind, lives in a wasteland. The devastation was the result of a viral epidemic that was spread by the anti-hero Crake, who promoted pills that promised users protection against all sexually transmitted diseases, an unlimited supply of libido and sexual prowess, and prolonged youth. It delivered, on a worldwide scale, death. Along the way Atwood lampoons institutes devoted to "Anoo-Yoo" and "Rejoov," as well as "pills that make you fatter, thinner, hairier, balder, whiter, browner, blacker, yellower, sexier, and happier."<sup>55</sup> We pursue enhancement at our collective peril.

Bioethicists such as Carl Elliott, in *Better Than Well*, share a visceral unease about enhancement. It "rubs me the wrong way," Elliott declares; it is "too close to fakery."<sup>56</sup> He finds a paradoxical quality in consumers' responses to the technology. Although they describe it in

terms of fulfilling a personal sense of identity, they are actually allowing the opinion of others to determine their sense of self. A "social mirror," not their own judgments, holds sway. Although you may explain your preference for plastic surgery in terms of satisfying your own desires, "you feel different because of the way other people perceive you."<sup>57</sup> Ultimately Elliott cannot make his peace with "the fragility of selves that depend so intimately on the good opinion of others for their survival."<sup>58</sup> So if Atwood is worried about the threat of enhancement to the well-being of all of us, Elliott is concerned with its threat to the authenticity of each of us.

All the while, the media cover enhancement closely. They highlight purported innovations in laboratories and clinical practice. The news section along with the style and personal sections devote considerable time and space to the latest developments in mouse memory and longevity, as well as to cosmetic surgery and liposuction techniques. At the same time, the media also issue cautions based on new research findings. It is difficult to know what readers take away from these mixed messages, but there is, unavoidably, a spasmodic quality to the coverage. Yes today, no tomorrow—with little consistency of perspective within, let alone among, the presentations.

Perhaps most disappointing, medicine itself has provided very little leadership. It is not surprising that drug companies will be less interested in educating consumers to be skeptical about new products than in persuading them to have their physicians prescribe the latest pill. But surely medicine has an obligation to be more proactive and diligent. There are self-correcting mechanisms in research; eventually, investigators learn whether a particular intervention does more harm than good. But *eventually*, as with estrogen, can mean decades of conflicting findings about risks and benefits. To be sure, some specialty societies issue practice guidelines. Even then, however, as the use of testosterone and growth hormone as anti-aging compounds reveals, medical organizations make almost no effort to discipline physicians who violate these guidelines, some prescribing these compounds through the Internet without so much as examining the patient. Nor will they curb physicians who present themselves as anti-aging specialists when practically every expert agrees that there are no effective anti-aging medicines. Should a

state legislature attempt to regulate medical practice, for example, mandating greater oversight in office-based surgery, physicians together with medical societies will strenuously protest. But rarely does the medical community step in to fill the vacuum.

From our perspective, the real dangers of enhancement do not lie in our souls (as with Elliott) or in our ambitions (as per Atwood) or in our history (as per Watson) but in our enthusiasms and credulity. We do not believe that enhancement will necessarily violate nature, subvert our humanity and dignity, or undermine social order. What the technologies do represent is a test of the outer limits of allowing science to set its own agenda, of allowing happiness to drive clinical care, of allowing profit motives almost unbounded license, and allowing individuals to exercise autonomy and choice. Setting boundaries is an exceptionally difficult task. Let moralistic minorities abridge science? Restrict doctors from responding to emotional pain? Substitute state collectivism for the profit motive? Enshrine paternalism over choice? None of these are attractive, or even feasible, alternatives. What remains is the possibility, no more than that, of consumers making decisions wisely, taking account of both self-interest and societal interest. They will need to be at once wary and restrained to minimize personal and collective risks, and open and generous to democratize benefits. If we have encouraged and contributed to such an enterprise, we will have accomplished our task.

## Notes

### Introduction

1. H. J. Muller, *Out of the Night: A Biologist's View of the Future* (New York: Vanguard Press, 1935), 125.
2. Joshua Lederberg, "Viruses and Humankind," in *Emerging Viruses*, ed. Stephen S. Morse (New York: Oxford University Press, 1993), 3-9.
3. National Institutes of Health Gene Therapy Policy Conference, "Human Gene Transfer: Beyond Life-Threatening Disease," Bethesda, Maryland, September 11, 1997. See also Eric T. Juengst, "Concepts of Disease After the Human Genome Project," in *Ethical Issues in Health Care on the Frontiers of the Twenty-First Century*, ed. Stephen Wear, James J. Bono et al., 125-52 (Dordrecht; Boston: Kluwer Academic Publishers, 2000); David B. Resnick, "The Moral Significance of the Therapy-Enhancement Distinction in Human Genetics," *Cambridge Quarterly of Healthcare Ethics* 9 (2000): 365-77.
4. Leon Kass, "The Wisdom of Repugnance," *New Republic* 298 (June 2, 1997): 18.
5. Francis Fukuyama, *Our Posthuman Future* (New York: Farrar, Straus and Giroux, 2002). On the other hand, William Haseltine, head of a new biotechnology company, comments: "We are redefining what it is to be a human—taking a new measure of man. We add to the classical and neo-classical view of the human body as a collection of organs, tissues and cells, the notion that [the] human body can also be described as a collection of genes and the protein each gene specifies," in Howard Gardner, Mihaly Csikszentmihalyi et al., *Good Work: When Excellence and Ethics Meet* (New York: Basic Books, 2001), 81-82.
6. William Kristol and Eric Cohen, "Should Human Cloning Be Allowed?," *Wall Street Journal*, December 5, 2001.
7. Lee Silver, *Remaking Eden* (New York: Avon Books, 1997), 4-7. See also Maxwell Melhman, "How Will We Regulate Genetic Enhancement," *Wake Forest Law Review* 67 (1999): 671-714.
8. In the extensive literature on enhancement, we found most useful: LeRoy Walters and Julie Gage Palmer, *The Ethics of Human Gene Therapy* (New York: