If you could dictate the content of your kid's genes, wouldn't you?

IMAGINE THAT

Your grandchildren can pick exactly how their babies will look, think, and act. Your family curse of breast cancer or cystic fibrosis or early heart attack—not to mention dyslexia, fat thighs, shyness, or male-pattern baldness—will be vanquished in a single stroke. Your great-grandchildren will be as lean, literate, loquacious, and long-lived as their parents want them to be. How does that grab you?

If you think that sounds good, you have plenty of company. More than 40 percent of Americans, according to a March of Dimes survey, think it would be okay to use gene therapy to make their children either more attractive or more intelligent than they were otherwise destined to be. A Gallup poll of British parents found many of them also willing to consider such genetic “enhancement,” and for some surprising and rather disconcerting reasons: 18 percent to change a child’s aggression level or remove a predisposition to alcoholism, 10 percent to keep a child from becoming homosexual, and 5 percent to make a child more physically attractive.

At the moment, this genetic equivalent of nip-and-tuck cosmetic surgery exists only in the imagination. After nearly a decade of experimentally transferring genes into human beings with serious disease, the practitioners of gene therapy have yet to cure a single person. Moreover, it is still far from certain that the behavioral traits described above will ever be shown to be genetically “caused.” Still, the controversy surrounding the appearance of a cloned sheep in 1997 highlights how fast the field of genetic engineering can move, and how far we are from a public consensus on how such technology should be used. Gene transfer techniques, once perfected, could treat more than just genetic diseases. They could also offer the ultimate form of preventive medicine—or the ultimate form of intrusive, Brave New World eugenics, depending on your point of view.

Few people question the value of correcting a gene for sickle-cell anemia, cystic fibrosis, or, should the relevant genes be found, Alzheimer’s, heart disease, or cancer. Once the technology is perfected, people will probably also not question making that correction at the earliest embryonic stage, or, more likely, even before conception, to be certain that the healthy gene will find its way into every cell in the body as the baby develops.

But altering genes for the sake of appearance or personality is something else again. Is it fair for parents to make such decisions on behalf of their unborn children? If so, which genes should they be allowed to manipulate? Are the risks of genetic manipulation worth taking just to ensure that a child will have curly hair, blue eyes, tall stature, or a slim physique? What about inserting new genes for high IQ? For heterosexuality? For conformity? For optimism? For skin color? Should gene therapy become the vehicle of choice for creating a whole new class of genetically engineered children, custom-made to carry the “good” versions of genes that are thought to influence the way we look or behave?

And when such manipulations become feasible, what will happen to the quintessential American presumption that all men are created equal?
researchers and ethicists began looking more closely at these questions, and they began imagining the once unimaginable. The National Institutes of Health held its first Gene Therapy Policy Conference, which focused on the pros and cons of altering genes to enhance normal function. Two weeks later the American Association for the Advancement of Science sponsored a colloquium on another aspect of genetic manipulation that so far has been completely off-limits: gene alterations directed not at the somatic, or body, cells (as all such manipulations have been to date) but at the sex, or germ line, cells—meaning eggs, sperm, and very early embryos. Interventions at this stage would change an unborn generation’s genetic endowment in much more profound and permanent ways.

Some conference speakers approached the inevitably paired issues—altering genes for enhancement and altering genes in sex cells—with trepidation. “Before we start doing germ-line gene therapy,” said Cynthia Cohen of the Kennedy Institute of Ethics at Georgetown University in Washington, D.C., “we need to decide whether we want to change what it is to be human. We need to decide whether there is something about human nature that is so valuable that we shouldn’t change it, even if it could be done.”

Are we wise enough, some speakers wondered, to interfere with humanity in all its glorious variety? Perhaps we would remove something important in the very act of removing something objectionable. Or perhaps we would disrupt the delicate balance that evolution has brought us to, in which each genetic trait has an effect on every other. The difference between the DNA of humans and that of great apes, for example, is very slight—just 1 to 3 percent, noted geneticist Huntington Willard, of Case Western Reserve University School of Medicine in Cleveland. “Most of the differences we perceive between these primate species are probably not in the genes themselves but in how they are turned on and off. And that regulation is very poorly understood.” What happens when you “change the recipe” for a human being, asked Malcolm Brenner of the Baylor College of Medicine in Houston. “Is it worth it to have huge muscles, if that means you develop osteoarthritis at age 25 because you haven’t increased the strength of your bone?”

Some speakers, however, considered that if genetic enhancement could be safely performed on adult body cells, the practice, in principle, would be no different from manipulations such as bodybuilding, liposuction, and hair transplants. Other speakers noted that specific enhancements might be permissible if they could pass the following test: Would the treatment still have value if given to everyone? Improved memory or immune function, for example, would confer an intrinsic benefit on everyone. Altered height, skin color, or musculature, on the other hand, would confer only competitive social advantages—if everyone had them, no one would end up better off. But still other speakers thought that giving a child any advantage through genetic engineering meant crossing an important moral divide. They worried about the “biological reinforcement” of class distinctions that could result, since genetic enhancement would almost certainly be available only to the very well-to-do.

Thomas Murray, director of the Center for Biomedical Ethics at Case Western, noted that many people feel apprehensive about allowing parents to create more “perfect” kids. Even if well meant, such strategies might have the deeply troubling effect of reducing tolerance for people who are different. As genetic screening tests increase in accuracy, there will be many more opportunities to intervene in childbearing. These options could create pressure to tailor one's reproductive decisions to the prevailing norms of what is considered “desirable” in children. Cohen echoed that concern. “This is involuntary intrusion into future generations,” she said. “The whole thing is very chancy. There are so many ways in which we can go wrong. Who knows what the effects of our actions today will be in 2200?”

COHEN MAY BE JUMPING THE GUN. NO ONE CAN ENVISION EFFECTIVE GERM-LINE GENE THERAPY, for any reason, say geneticists, until most of the kinks that still plague somatic-cell gene therapy are ironed out. “Talking about germ-line gene transfer today,” said Brenner, “is a bit like the Mars spacecraft designers agonizing over whether their craft is fit for interstellar travel.” Transferring a new gene into a cell—whether a sex cell or an ordinary body cell—involves several steps. First you must identify and isolate the gene of interest. Then you have to find a way to get it into an appropriate host cell. After getting it there, you must direct it to approximately the right spot along the host cell’s DNA. Finally you must get the gene to produce the protein it encodes at a biologically appropriate level. While experimentation has proved that these steps can be accomplished, at least in animals, there have often been accompanying difficulties.

One of the first problems arose in the “vectors”—the experimental vehicles designed to carry new genes into cells. Most experiments now use stripped-down viruses, but even with their infectious genes removed, these viruses can still stimulate potentially harmful immune responses. Scientists are now looking at nonviral vectors to chaperone new genes into the cell. Someday genes might be carried into a cell on an artificial human chromosome, a streamlined version of the natural model that will reproduce and make proteins with every cell division. Still another possibility is injecting into

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transfer are, in a manner of speaking, already underway. In one experimental reproductive technique known as cytoplasmic transfer, all of the cytoplasm—the material that makes up the inside of a cell, not counting the nucleus—is sucked out of an older egg and replaced with cytoplasm from a younger, healthier egg. Although most of the genes are inside the nucleus, the cytoplasm contains a few short-lived genes of its own, within the mitochondria. “Does that mean that fertility clinics doing cytoplasmic transfer have already done a crude sort of germ-line gene transfer?” asked Thomas Murray of Case Western. “They have, after all, removed and replaced the mitochondrial genes in these eggs.”

Fertility clinics are the wild card in genetic engineering. They are among the most advanced, and least regulated, biotech research centers in the country. Because they are for-profit enterprises that accept no federal funding, they are not subject to federal regulations that currently prohibit experiments involving the transfer of human genes into human sex cells. Human gene transfer experiments funded by federal money must be approved by the local institutional review board, by the RAC, and by the Food and Drug Administration—a three-layer process that ensures no scientist is inserting genes into people without excellent evidence that the risks are outweighed by the expected benefits. But private fertility clinics haven’t had such constraints. When germ-line gene transfer begins in earnest, it will most likely happen there.

“People talk about the technological imperative, which loosely translated means, ‘What can be done, will be done,’” said Murray. “With the technology ripening—though it hasn’t quite matured yet—these more questionable uses of gene transfer technology are things we need to talk about. I’m quite sure there will be advocates for them.”

Just as germ-line gene therapy might slip into practice without official sanction, so might genetic enhancement. Already gene therapists report fielding calls from people hoping to apply their findings in some outlandish ways. According to speakers at the NIH conference in September, a sports physician recently phoned a scientist studying gene transfer for rheumatoid arthritis to see if the gene for muscle strength could be transferred into his athletes. In another case, a researcher received an e-mail asking if it would be possible to change a person’s skin color. Cosmetics companies have also approached investigators studying albinism about the possibility of creating products to alter skin or hair color.

These requests might sound fanciful, but they point to a common theme in medical history whereby a treatment that begins as therapeutic often ends up in the much more lucrative arena of cosmetic enhancement. This can happen because of a quirk of the current drug approval process, which allows any FDA-approved treatment to be used for any purpose, even for an “off-label,” untested use, once it reaches the marketplace.

**Plastic Surgery**

For example, was developed to correct the gross facial deformities of war injuries, but was soon used to straighten “ethnic” noses and tighten older, sagging skin. Breast implants were developed to reconstruct breasts in women who lost theirs to mastectomy, but were soon inserted into healthy women who just wanted to change their B cups to D cups. Growth hormone therapy was developed to add a few inches to hormone-deficient children who would always be abnormally short, but was soon sought after by parents who wanted to make their shortish kids less short or, in at least one instance, to make their tall daughter taller in hopes of snagging a college basketball scholarship.

Gene therapists foresee a time when something similar will happen with their technology too. Consider a gene therapy now under investigation to treat atherosclerosis by delivering the gene for VEGF (vascular endothelial growth factor), a protein produced by cells to grow new blood vessels. In a small study at St. Elizabeth’s Medical Center in Boston, researchers delivered “naked” DNA for the gene via a catheter into the legs of patients with leg arteries so narrowed by atherosclerosis that some faced amputation. The treatment improved the condition of nearly all the patients. And researchers at New York Hospital-Cornell Medical Center have come up with a similar procedure—called the biobypass—that may work for treating patients with blocked coronary arteries. By delivering VEGF genes through a catheter directly to the heart, they hope to prompt new blood vessels to form around the clogged ones—an achievement most of us would celebrate without qualification.

But what happens when healthy people want to grow new blood vessels for reasons that have less to do with saving life? Perhaps they are runners or soccer players hoping to get more oxygen to their legs; maybe they are convinced that better blood flow to the brain will boost their own or their child’s intelligence. Should these enhancement uses of the bio-bypass technology be allowed?

According to bioethicist Eric Juengst of Case Western, gene transfer for just about any enhancement purpose could begin as gene therapy for a medical condition. “You won’t see a protocol come to the RAC or the FDA labeled ‘genetic enhancement protocol,’” he said at the AAAS meeting. “It will of course be aimed first at a pathological problem.” But it’s a short step, he said, from developing gene therapy to treat the baldness that results from cancer chemotherapy to offering that same genetic alteration to a far greater market: normal middle-aged men with run-of-the-mill male-pattern baldness. Although Juengst, despite his own receding hairline, considers baldness “a frivolous reason to do gene therapy,” he said that nothing in our current regulatory climate could stop the off-label use of products ostensibly developed for respectable therapeutic purposes. Such a product is already envisioned by researchers at Columbia University College of Physicians and Surgeons, who in late January reported identifying the first human gene linked with hair loss. Eventually, they noted, it may be possible to create a topical treatment for baldness containing the gene.

The question becomes one of where to draw the line. Bioethicists like to talk about the “slippery slope,” the path that links the acceptable to the unacceptable, though such ethical issues are argued. The first step along a slippery slope is dangerous, because all successive steps seem inevitably to follow. Ethicists often invoke the slippery slope to keep people from taking that fateful first step.

But in the case of gene transfer for nontherapeutic purposes, any kind of slope may be too gradual an image to be of much use. “There is no slippery slope to genetic enhancement,” said Juengst. “There’s no slipping at all. As soon as we approve the bio-bypass, or the chemotherapy adjunct for follicle stimulation”—the baldness remedy—we’re already at the bottom.”
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cells unembellished, or “naked,” DNA for a desired protein. Ultimately the vehicle used will probably vary depending on the condition being treated.

Once the new gene is in the appropriate cell—say, a lung cell, to treat cystic fibrosis—there's the tricky matter of ferrying it where it needs to go. So far, the location of the new gene has been almost entirely unpredictable. This is not a problem for many forms of gene therapy, in which the goal is simply to get a high enough proportion of cells (even if it's no more than 5 to 10 percent) to make enough protein to do some good. But it could present a major risk if the new gene gets in the way of another gene—especially if that other gene is responsible for regulating cell growth and its disruption leads to cancer.

To eliminate such surprises, gene therapists’ ultimate goal is to direct a gene to a specific target on a particular chromosome—ideally, to replace a damaged gene by inserting a healthy version in exactly the same spot. Such a one-for-one swap can be achieved by a process called homologous recombination. But it’s not easy.

Molecular geneticist Oliver Smithies of the University of North Carolina at Chapel Hill is one of the pioneers in the field. When he started his research in 1985, he was able to achieve homologous recombination in only one cell in a million. He has since gotten perfect homology at a rate closer to one in 100,000—a significant improvement, but still, as he put it, “a frequency far too low to be useful for gene therapy.”

The real danger of nonhomologous recombination arises not so much in gene therapy for body cells, which can tolerate some degree of genetic error, but in germ-line gene transfer. For germ cells, nothing less than perfect homologous recombination will do. Since the gene-manipulated cells will develop into every single cell in the body, any mistake will become grossly magnified, probably with devastating results.

“We know from our experience with a wide range of species that germ-line gene transfer can have some very unexpected consequences,” said Huntington Willard. Among these are gross physical abnormalities and birth defects—malformed limbs, for instance—and the eventual development of cancer, even in animals that at first seemed to be successfully gene-corrected. “You might call those consequences ‘interesting’ when you see them in flies or in mice,” Willard said. “But the same surprises can be nothing short of disastrous when they occur in humans.”

**Despite All**

these difficulties, gene therapy still holds promise for revolutionizing medical care. But its first successes may not occur, as was once supposed, in the correction of “classic” genetic diseases—cystic fibrosis, hemophilia, sickle-cell anemia, muscular dystrophy—that involve a single defective gene. Rather, gene therapy will probably make its mark as an ancillary technique for treating infectious or degenerative diseases like cancer, AIDS, and, to a lesser extent, heart disease, Alzheimer’s, arthritis, and diabetes.

The Recombinant DNA Advisory Committee (RAC) of the National Institutes of Health, which ensures that all gene therapy experimentation in any institution receiving federal funds conforms to NIH guidelines, has registered 222 experimental procedures, 190 of them for testing therapeutic approaches (the others are designed to answer basic research questions). Of the therapeutic experiments, 132 (69 percent) involve gene therapy for cancer—something not considered to be a traditional genetic disease at all.

Gene therapy for cancer is so aggressively pursued partly because it offers a relatively easy target. Only a small proportion of cells need to be gene-corrected, and only a low degree of homology is necessary, to boost a person’s immune system response to cancer. But gene therapy for cancer is also being pursued for another, possibly more important, reason: money.

“There’s not much money to be made in treating single-gene defects,” said W. French Anderson, director of the gene therapy laboratories at the University of Southern California in Los Angeles. The major pharmaceutical companies, he said, which now bankroll the lion’s share of gene therapy experiments, are interested in supporting clinical trials only on treatment approaches for which they can expect a sizable return on their half-billion-dollar investments. And cancer patients far outnumber patients with diseases from a single-gene defect.

An experimental treatment for myelogenous leukemia, scheduled to begin this summer, is typical of this new direction in gene therapy. Researchers at the University of Minnesota hope to treat a patient’s bone marrow cells with a double dose of new genes: an anticancer gene attached to a gene for resistance to the chemotherapy drug methotrexate. After receiving massive radiation (the standard treatment for leukemia), the patient will receive these treated cells, along with a course of methotrexate. The only bone marrow cells that will survive are those that carry the methotrexate-resistance gene—which are also those that have successfully received the anticancer gene. The idea is that ultimately these cancer-free cells will repopulate the patient’s bone marrow, in effect offering a leukemia cure.

All the same, the gene transfer applications that inflame the imagination of the public, the media, the policy makers, even the scientists themselves are the more far-fetched, futuristic ones. When they become feasible, they will represent humankind’s ultimate victory over inherited diseases—and in so doing, overturn our conventional notions of human biological inheritance.

In fertility clinics, procedures that look very much like germ-line gene