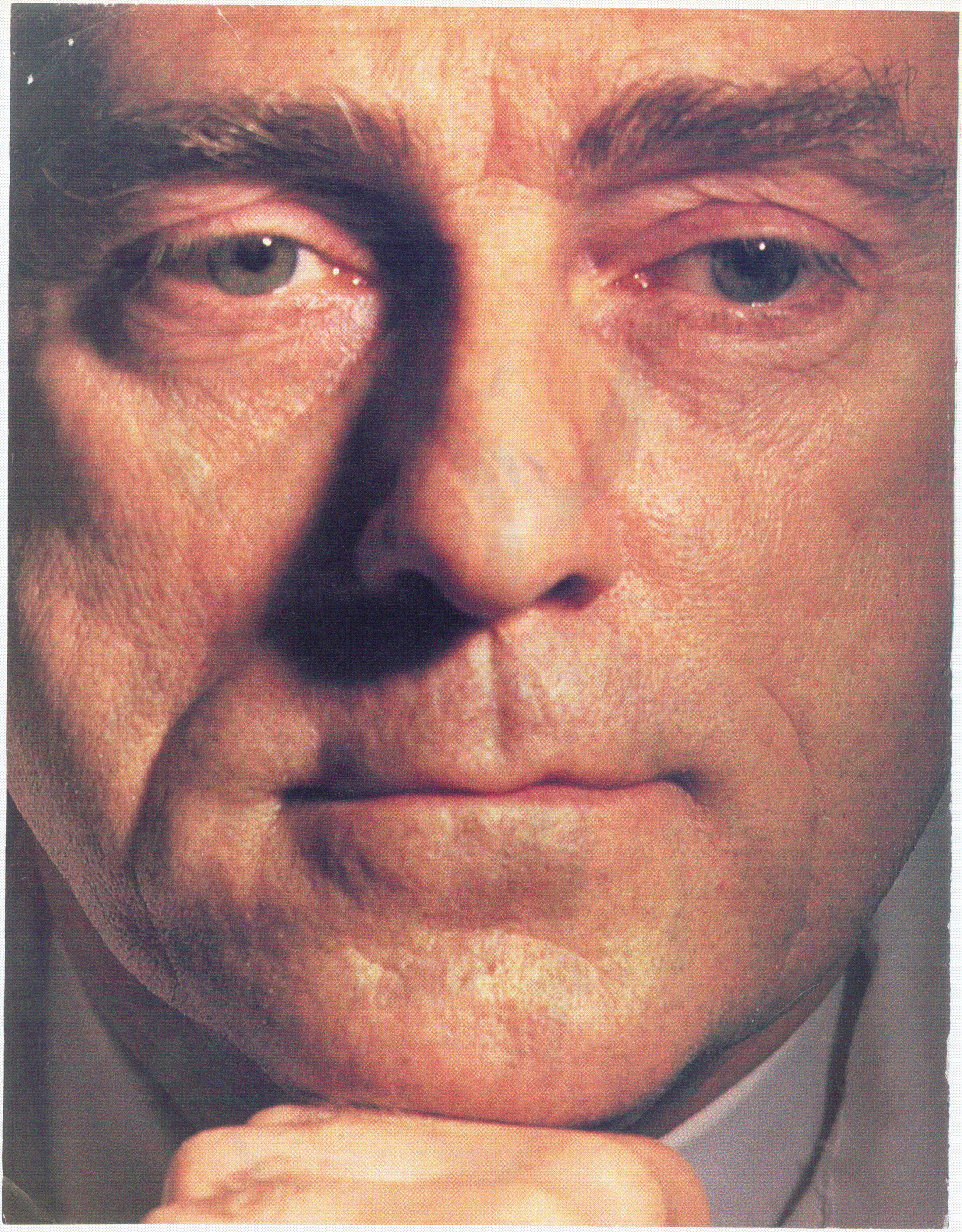
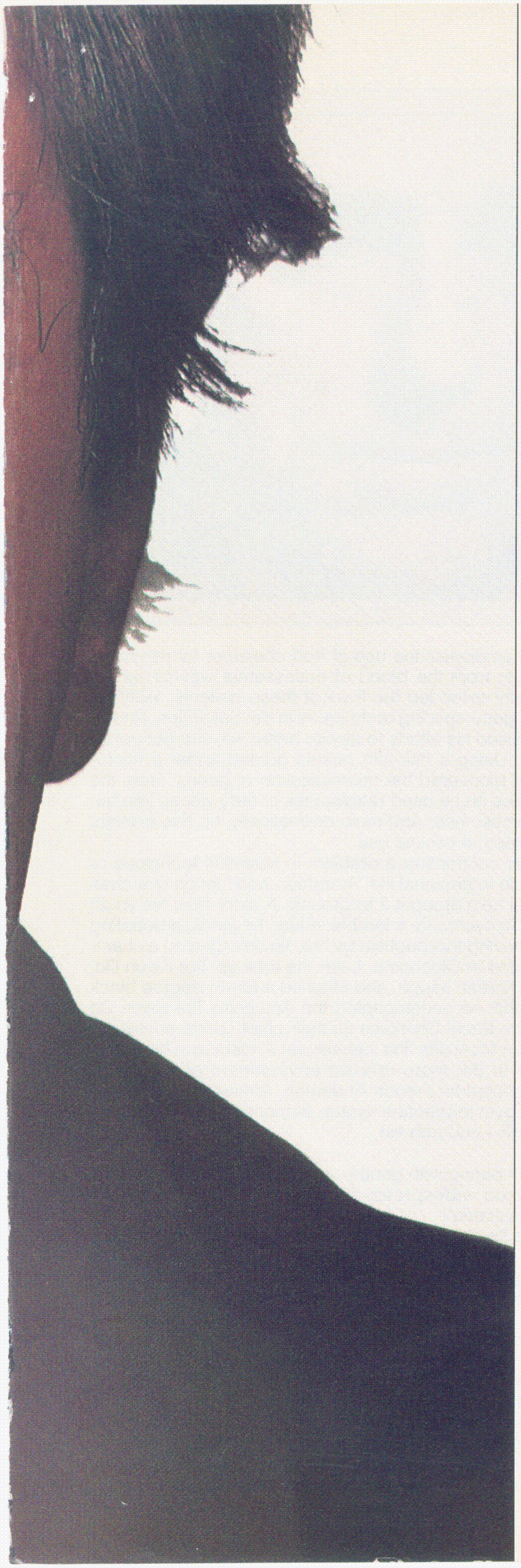




The pioneer who conducted
the first human gene therapy is looking toward
gene transfer to treat diabetes
and heart disease and maybe even double
life span. In a thousand years,
he adds, you may *have* to augment your DNA

INTERVIEW

W. FRENCH ANDERSON

He always knew what he wanted to do. In the late Fifties, before recombinant DNA technology was drawing-board theory, he vowed to cure hereditary disorders by repairing faulty genes. His Harvard professors laughed at the aspiring genetic surgeon with the Okie accent and cowboy boots. But W. French Anderson, now chief of the Molecular Hematology Branch at the National Heart, Lung, Blood Institute in Bethesda, Maryland, never wavered in his mission to bring gene therapy from the laboratory bench to the patient's bedside. And in September 1990, Anderson and his colleagues ushered in a new era of medicine with the first human gene procedure aimed at correcting a hereditary disease.

The patient, a four-year-old girl, was born with an adenosine deaminase (ADA) deficiency. She lacked the same key immune cell enzyme as David the bubble boy, whose defenses were so im-

PHOTOGRAPHS BY JOHN STUART

NAME:
W. French Anderson

AGE:
Fifty-four

HOMETOWN:
Tulsa, Oklahoma

DEGREES:
M.D. (pediatrics), black belt Tae Kwon Do (fourth-degree)

OCCUPATION:
Gene surgeon

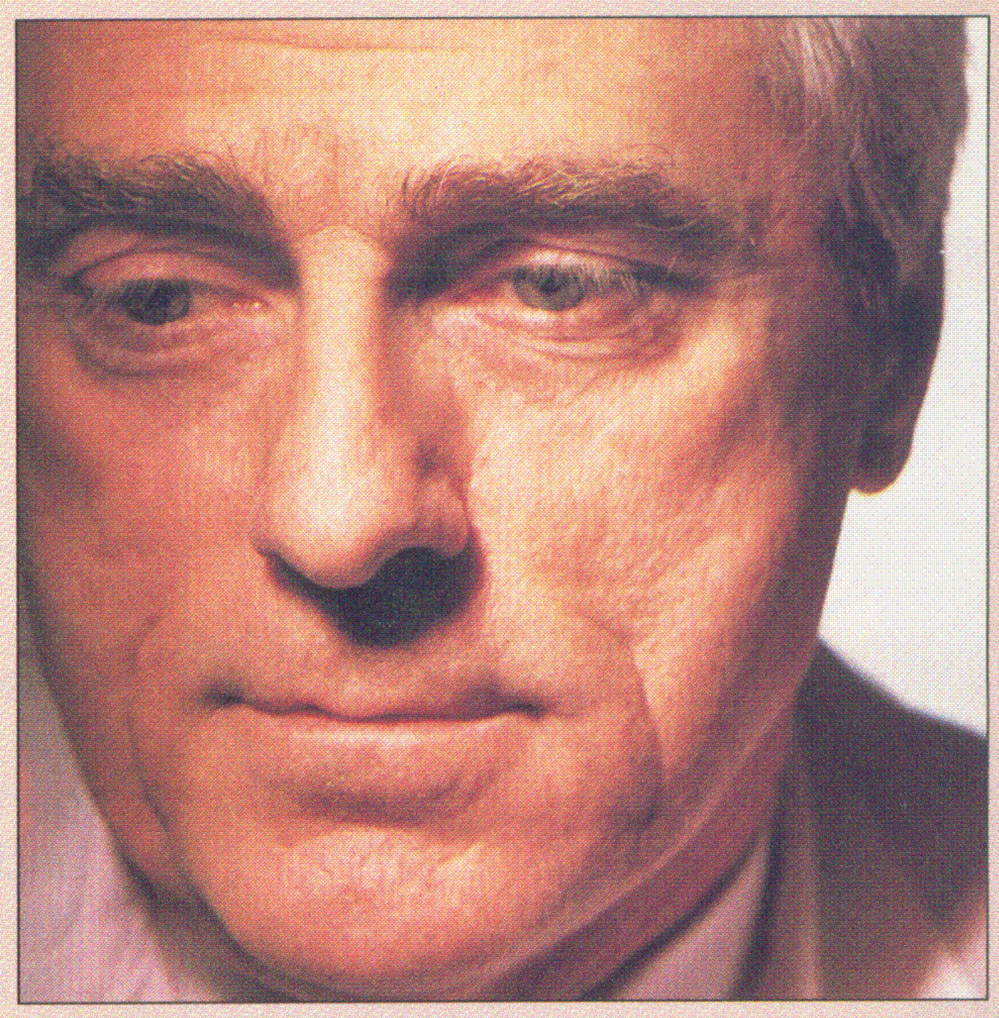
"OPERATIONS" DONE:
Nine for hereditary diseases, 12 for cancer patients

FAVORITE BOOK:
Self-Renewal, by Gardner

ADVICE TO LAB SCIENTISTS, I:
Molecules have minds. Get inside the minds of molecules; master them. Sooner or later they will give up and do what you want them to.

ADVICE TO LAB SCIENTISTS, II:
If your laboratory gets too big for you to do your own science, then make it smaller.

FUTURE OF GENE THERAPY:
If there are many benefits and few risks, gene therapy might eventually become as commonplace as antibiotic therapy is today.



paired that he was forced to live inside a germ-free capsule. Anderson and collaborators R. Michael Blaese and Kenneth Culver of the National Cancer Institute (NCI) combined some of the girl's white blood cells with those of an engineered virus. These genetically modified cells were then reintroduced into her bloodstream, where it was hoped they would multiply over the coming months, gradually restoring the functioning of her immune system.

Although still too soon to predict the ultimate success of this much-heralded trial, the physicians are very encouraged by the child's progress. She is better clinically and many of her immune function studies are improving, some into the normal range. Another ADA patient, a nine-year-old girl, began treatment on January 31, 1991. Early results suggest that she, too, is improving thanks to gene therapy. The investigators now believe this general strategy promises to have applications far beyond the treatment of rare hereditary diseases. Since genes code for vital body chemicals, Anderson thinks gene transfer techniques will eventually be used to "trick" cells into releasing drugs useful in the treatment of almost any disorder—from AIDS and cancer to heart disease and ordinary aging. Inserting the gene for insulin into the B cells of the pancreas might enable the diabetic patient to synthesize his own internal source of the hormone, eliminating the need for daily injections.

Raised at the edge of the dust bowl in Tulsa, Anderson was a prodigy. His passion for science burgeoned at age three, and by the end of grade school, he'd consumed every technical book he could find, including college-level medical texts. As a Harvard University senior at seventeen, he took one of the first courses linking DNA to genetics. The instructor was James Watson, the Nobel laureate who only four years earlier had codiscovered the chemical structure of DNA with Francis Crick. A year later, Anderson went to Cambridge, England, to continue his genetic studies with Crick. He completed his M.D. at Harvard in 1963 and two years later moved to the National Institutes of Health, where he's been ever since.

At NIH Anderson discovered the specific factors cells use to initiate protein synthesis, while his clinical studies led to breakthroughs in the treatment of deadly hereditary diseases. He championed the use of iron chelators for removing excess iron from the blood of thalassemia victims, which dramatically extended the lives of these patients. With the advent of gene-splicing techniques in the Seventies, Anderson intensified his efforts to devise better ways to get genes into cells. Using a hair-thin needle guided under a microscope, he pioneered the microinjection of genes. From the mid-Eighties on he used retroviruses to ferry genes into human chromosomes. And most dramatically, he has brought gene therapy to clinical use.

Whether confronting a problem in scientific technique or an obstacle in personal life, Anderson won't let go of a challenge until he's brought it to ground. A story from his youth is telling: To overcome a terrible stutter, he joined a debating team. Surviving this baptism by fire, he emerged as a champion debater in Oklahoma. Later, he took up Tae Kwon Do, a form of Korean karate, and attained a fourth-degree black belt. In 1988 he accompanied the American Tae Kwon Do team to the Seoul Olympics as their chief sports physician.

Kathleen McAuliffe first interviewed Anderson in his office, and later in the more relaxed environment of his home. Well. . . relaxed for French Anderson. Afterward, he went to his cellar gym to practice karate, demonstrating once again his iron will—and iron fist.

Omni: Tampering with genes—even for treating diseases—has aroused widespread concerns. Do you think those fears are inflated?

Anderson: It's clearly an emotional issue. Jeremy Rifkin [outspoken critic of genetic engineering] has fanned those concerns by exaggerating the risks. But he wouldn't attract so much media attention if society didn't have fears in the first place. Yes, I am concerned. My mother is concerned. The athletes I accompanied to the Olympics are concerned. It's bad enough to have your mind manipulated through advertising, or into eating artificial substances in foods. So the notion of manipulating genes—which make us who we are—is frightening. I feel strongly that gene therapy should be applied only for the treatment of disease. Very firm lines should be drawn to ensure that genetic engineering is used for no other purpose. That's been my position for twenty-five years.

Anderson: I believe an excellent system is in place for reviewing protocols and that doctors in this area are following a very ethical path. The long, involved process of gaining approval for the first human gene therapy trial is testimony to the numerous safeguards in place. This [he points to a document bigger than a Manhattan phone book] was the earliest draft of the protocol for the experiment. The Recombinant DNA Advisory Committee and half a dozen other regulatory committees studied it. Several reviewed the experiment twice, and numerous public hearings took place with TV crews present. In the end, virtually every reviewer voted to proceed with the experiment. Even Rifkin complimented us on the care we took in preparing the Informed Consent Document that lays out for the patient all the risks and benefits of the procedure.

Omni: Why did you choose a patient with ADA deficiency, a very rare disorder, for the first gene therapy trial?

Anderson: In the Seventies I initially targeted a more common hereditary disorder—thalassemia—for the first trial. Kids with the disease produce abnormal hemoglobin [the blood molecule that transports oxygen]. Those pictures on the wall are of Nick and Judy, my first two patients with thalassemia. It's a fatal disease, and both died years ago. Unfortunately, thalassemia turned out to be too great a challenge for us then because the instructions for producing hemoglobin are encoded in several different genes.

Omni: Isn't it distressing talking to these desperately ill children?

Anderson: I'm much more comfortable with children than adults, who tend to maintain a protective front. Kids talk about things important to them. Death and suffering are very real issues. Yes, I'm very comfortable talking to them about dying. I interact well with sick children. I can just feel with them.

Omni: Why was ADA deficiency a better disease to target than thalassemia?

Anderson: ADA, which stands for the enzyme that malfunctions in these children as a result of their genetic defect, involves only one gene. Without adenosine deaminase, the body cannot produce new T and B lymphocytes. So ADA kids suffer from severe combined immunodeficiency and need to be protected from infections.

Omni: How is gene therapy done?

Anderson: We withdraw the children's white blood cells and put into each cell a healthy copy of the gene for the ADA enzyme. We'd already genetically modified monkeys' immune cells, and after we reintroduced the white blood cells intravenously, the animals actually produced human ADA in their bloodstreams. That positive result convinced us we were ready to begin treating a human with the disease.

Omni: Could you be guilty of rushing ahead too quickly, as critics claim?

Anderson: Some patients with ADA might have been helped had we proceeded three years earlier. Richard Mulligan [at the Whitehead Institute for Biomedical Research in Boston] is the main scientist opposing our group. And from his perspective, he is right. But as a Ph.D., he doesn't have the experience of an M.D. doing rounds on a pediatric ward every day who knows that ninety percent of medicine is an art—not a science. That makes a scientist uncomfortable. So he felt our ADA gene protocol was premature. But the science was actually much further developed at the outset than is the case for most successful therapies.

> "The child's T cell count is normal for the first time in her life. And we can isolate gene-corrected cells making ADA directly from her bloodstream. We could not be happier."

Omni: Were you nervous on the day of the trial?

Anderson: Extremely. Even though the event itself was very anticlimactic. I mean, hanging up a bag of blood cells and intravenously dripping them into a patient happens ten times a day in that intensive care unit. And that's just one of many medical wards here, and we're just one of thousands of hospitals.

Omni: Didn't you worry she might die?

Anderson: Not from anything related to the procedure. I did worry that she might get a blood clot in her lungs or develop some other rare, life-threatening condition during the trial, which would have been an absolute disaster. I mean, if the first patient died while genetically modified cells were going into her body, who would agree to be the second patient? It could have set gene therapy back a decade.

Omni: What are the indications that the gene treatment helped?

Anderson: At this stage, there is every indication she is doing well. No, better than well—she is doing beautifully. In every way we can measure she is improving. Her parents are delighted because she is no longer sick all the time. In fact, she's just been sick once and that was when the whole family came down with flu. She was the first to get better! Her parents couldn't believe it. They were still sick in bed and she was running around playing. They say she smiles and laughs a lot more than before. As far as laboratory measurements are concerned, her T cell count is normal for the first time in her life, most of her immune function studies are improving, and some are now in the normal range. And we can isolate gene-corrected cells making ADA directly from her bloodstream. She has never shown any serious side effects from any of the infusions. We could not be happier about the way things are going. Our second patient, a nine-year-old girl, has had two infusions. She is also doing very well and the first preliminary data on her appear to show that she is improving.

Omni: How many more patients are you going to treat?

Anderson: That's Mike Blaese's decision, since he is the PI [principal investigator] on the protocol. But our plan is to add another patient at the end of the summer and maybe one more at the end of the year.

Omni: Does the treatment carry risks for problems later on?

Anderson: To introduce genes into the patient's cells, we use a vector derived from a retrovirus that can cause leukemia in mice. We snip out most of the retrovirus's genetic material so it can't cause disease. But there is always a remote possibility that when the new gene is inserted inside the patient's cells the process might cause cancer many years later.

Omni: Before the ADA trial, your group introduced a foreign gene into ten adults with advanced melanoma. The gene itself was not intended to have therapeutic benefits, so was this early trial done basically to show that gene transfer was safe?

Anderson: In part, yes, since the risk to a terminal patient is almost infinitesimal. But another major motivation was to obtain information that could help medicine better develop cancer treatments in the future. Mike Blaese, our ADA expert at NIH, saw that our gene transfer techniques could help Steve Rosenberg at NCI refine his new cancer therapy and got us all together. Rosenberg removes cancer-fighting white blood cells called TILs [tumor infiltrating lymphocytes] from the patient's tumor. In the lab those cells are multiplied ten-thousandfold using the growth factor

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interleukin-2. Then the TILs are given back to the patient. About forty percent of patients show at least a fifty percent reduction in tumor size. Ten percent have a complete response; there's no evidence of any remaining tumor.

Omni: For terminal patients, isn't that an incredible response?

Anderson: Yes. But why does the treatment work for some and not others? Rosenberg needed some way to get a handle on what was happening inside the body. He needed to know where those TILs were going. What they were doing. That's where our technology could help. We tagged the TILs removed from the patients with a retroviral vector carrying a bacterial gene. When those gene-marked cells were returned to the body, they functioned a lot like a radio transmitter attached to a dolphin. We followed the TILs, saw how long they lived, where they went. It worked beautifully and perhaps has helped us to identify a subpopulation of lymphocytes more effective in fighting tumors. These findings may help us develop more powerful treatments against some types of cancer.

For example, Steve Rosenberg has already started treating two patients with advanced malignant melanoma by infusing TILs that contain the gene for tumor necrosis factor, an anticancer compound. Although it's too early to see any clinical response—we are still in the phase one safety trial—these patients have shown no toxicity from the gene transfer. Other approaches for using gene transfer to treat cancer are now being developed.

Omni: When did you know retroviruses would work in gene therapy?

Anderson: By around 1983, I became convinced that they were the way to go. It was not a sudden revelation. I'd been talking with Ed Scolnick, then at NCI, about retroviral vectors since 1979–1980. But there were so many apparent problems with them. By late 1983, thanks to the work of Gilboa, Mulligan, Verma, Friedmann, Miller, Bernstein, and others, I developed a deep instinctive conviction that retroviral vectors could be made to work in human gene therapy protocols.

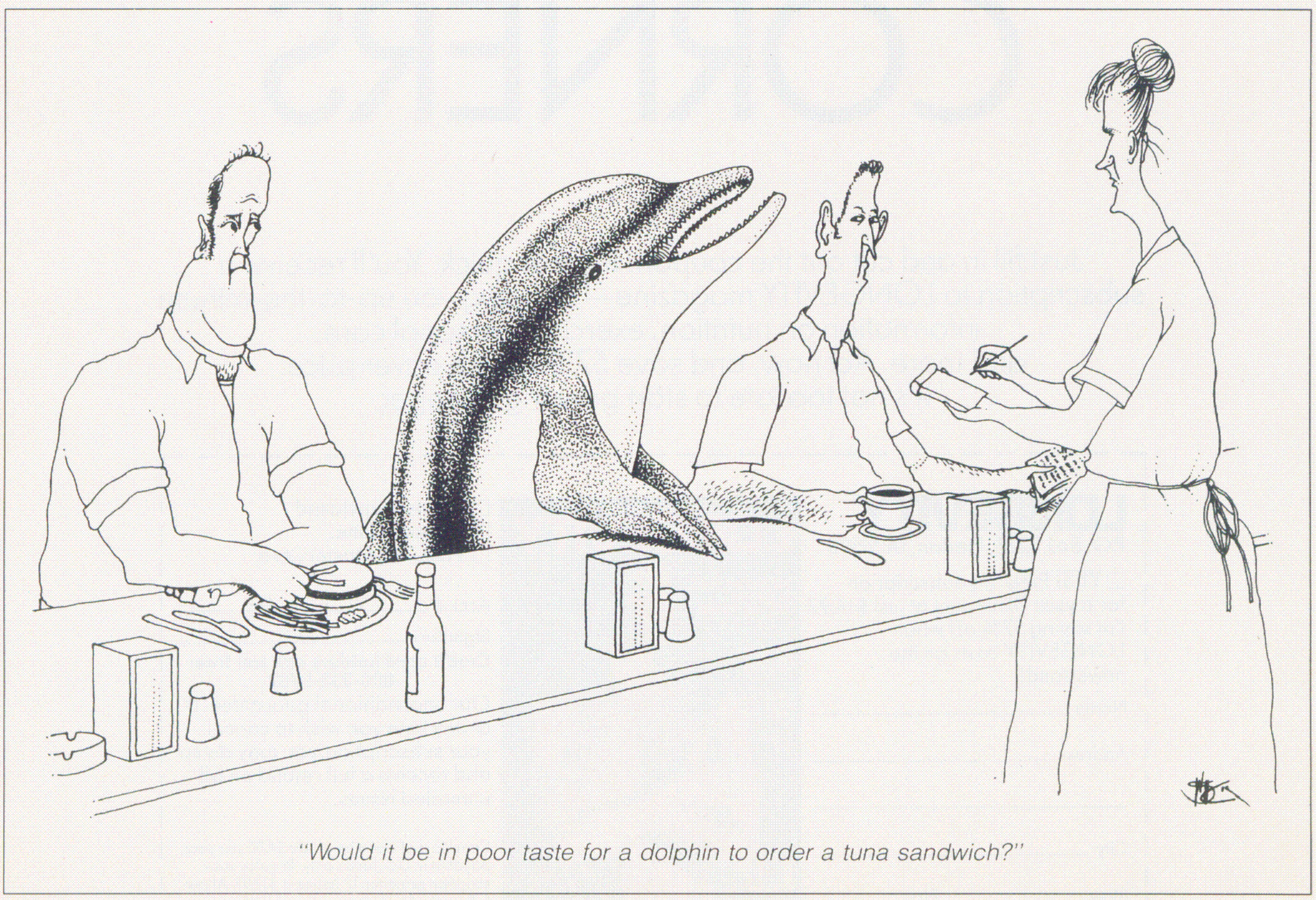
Retroviruses normally carry genetic information into cells; that's how they reproduce themselves. They evolved to do just that, so they're much more efficient than microinjection. With retroviruses we could get into millions of cells in one step. I should make it clear that I'm not the only person to have this idea. But, yes, most of the rest of the world thought we would never make it work in patients. Of course there were technical problems. There always are. But to me, the important thing was that I knew what ought to be done.

Omni: Why are you so confident your experiments will work?

Anderson: I've always had that ability. My conscious mind isn't so bright. I have trouble following lectures unless I know something about the subject. But when I get really interested in a problem, I take in all the information and totally immerse myself in it. My subconscious works on it all the time, and sooner or later it comes out. Sometimes I'll wake up at three A.M. with the idea for an experiment.

Omni: And it works?

Anderson: Ninety percent of your "brilliant" ideas don't work the first time. And don't work for a long time—the experiment may drag on for months or years. Francis Crick once said if there's a conflict between theory and data, the theory's more likely to be correct. Most scientists think just the opposite, but I'm more like Crick. If an experiment ought to work, I'm convinced it will work, and stick with it until it does.



"Would it be in poor taste for a dolphin to order a tuna sandwich?"

I'll tell you something more bizarre. Molecules have minds. They can tell if you're not comfortable with them, if you're not really in control. So they just won't work. You have to get inside the minds of molecules and master them. Sooner or later they will give up and do what you want them to. You can try and try to no avail. But once you finally get the system working, you can drop the experiment on the floor, scrape it up, and it will still work.

Omni: How did you see the idea for gene therapy so long before the advent of genetic engineering technology?

Anderson: By my junior year in high school I was already thinking about the idea in its broadest outlines. I wrote on my application to Harvard that I wanted to study the molecular basis of human disease. Nobody even knew what a gene was at that stage. By my senior year in college, however, we knew about this slimy stuff, DNA, that could alter the appearance and function of bacteria. Working with Julie Marmur, I'd irradiate DNA with ultraviolet light, causing mutations in the molecule, and then introduce it into bacteria. This experimental manipulation would often change a basic property of the bacteria. So it occurred to me then: If I can change how a bacterium functions by giving it new DNA, it ought to be possible to use the same strategy to help people suffering from hereditary disorders. I began to study human genetic disease at NIH, joining [Nobel laureate] Marshall Nirenberg, who was working out the final stages of the genetic code in *E. coli*. When that project was completed, I announced I wanted to study hereditary diseases in man. Marshall was aghast. So little was known about human genetics then, he thought I was throwing my career away. It was only if you couldn't make it in *E. coli* genetics that you worked on humans. But that's what I wanted to do. So I said, "If you won't let me do what I want to do, I quit." Marshall did his best to talk me out of it but finally gave in and let me spend fifty percent of my time doing human work.

Omni: What sorts of advances can we look forward to in the future?

Anderson: We're trying to transfer genes into other types of human cells: hepatocytes [a type of liver cell]; endothelial cells [lining blood vessels and the heart]; and bone marrow stem cells. A host of potential applications could come out of this work. Endothelial cells are especially attractive targets because any protein produced by them will be secreted directly into the bloodstream. One protein we'd like these cells to produce is the anticlotting factor TPA [tissue plasminogen activator]. When a clogged or injured blood vessel needs to be replaced, doctors will graft in an artificial vessel. About three hundred thousand grafts are performed yearly in the United States, and one hundred thousand of them fail because a clot forms in the artificial vessel. David Dichek in my lab plans to line the artificial vessel with endothelial cells that have been genetically manipulated to produce TPA. We've done it with rabbit cells, and others have been successful with pigs and dogs. But the cells tend to wash off after a couple of days. When we find a better way to anchor them, these techniques will improve the success of blood-vessel grafts in humans.

We also hope to engineer insulin-producing cells for the diabetic, or antitumor agents for the cancer patient. Perhaps someday we might genetically engineer cells to produce neurochemicals needed by psychiatric patients.

Omni: So gene transfer could provide a new drug delivery system?

Anderson: Yes. Drug companies now churn out millions of vials of drugs with half-lives of minutes or hours. Some must be injected several times a day or week. Today even diabetics who closely monitor their blood sugar levels still suffer debilitating problems, such as the retinopathy leading to blindness. Perhaps they can't regulate the drug dosage closely enough. By transferring a properly regulated gene for insulin into the B cells of the pancreas, we might avoid such serious complications. We hope to get the body to manufacture and release the appropriate amount of insulin at the appropriate time—the way a healthy body does. Within twenty years gene transfer techniques will give us another drug delivery vehicle.

Omni: Could gene therapy transform us into a new species?

Anderson: No. We have a hundred thousand genes, and even after the Human Genome Project is completed, all we'll know is the sequence of these genes. We won't know what they do in the body; at what stage in our life cycle the gene is expressed; or how one gene interacts with others. The total amount of information contained in the human genome is truly overwhelming. Comparing that knowledge to an ocean, all we're doing is scooping water out of a tiny lagoon. And with each scoop, the inlet fills up with more water. The idea of creating a new species of human anytime in the next century is about as like-

ly as traveling at warp speed to a galaxy millions of light-years away.

Omni: If ninety-eight percent of our DNA matches the chimpanzee's, perhaps you'd have to change only a few genes to transform the species.

Anderson: That's misleading. That figure is based on how much of our DNA will bind to, or "hybridize," with a complementary strand of DNA from a chimp. If you actually look at the bases [the basic components of the genetic code], only about seventy percent of our DNA exactly matches the sequence of a chimp. We probably differ by twenty to eighty million base pairs. That's an enormous difference when you consider that gene therapy usually involves the correction of only one or two genes, or what amounts to a few thousand base pairs.

Omni: Still, by introducing extra copies of those genes that possibly encode for enzymes that repair damage done to DNA as we age, couldn't we, say, double our life spans?

Anderson: You're not talking about creating a new species now. The scenario you're presenting is more than possible—it very well may happen over the next hundred years.

Omni: Would it be ethical to alter our genetic endowment to live one hundred and fifty years?

Anderson: No, because society isn't ready to handle the problems that this development would engender. As it is, we can barely care properly for people living into their eighties or nineties. Also, a gene that expands our life span may have twenty other detrimental effects. These individuals may live longer—but might be worse off in terms of their vigor, health, intelligence, memory, and so on. Say, parents of short children might want their offspring to receive the gene for human growth hormone so they could become basketball stars. But who knows what problems that might cause later in life?

Let's say, however, that our knowledge progresses to the point that we can safely expand the human life span, or make kids taller, or who knows. Maybe someone will discover a gene coding for a neurochemical that enhances memory. Then there's the whole issue of equality: Who gets the gene? Who decides who qualifies? And by what criteria? Do we give the memory-booster gene to mentally retarded children, because they need it the most? Do we give it to smart kids, who could make the most use of it? Who deserves to live longer? Be taller? Our society has no answers. I don't think we should use a powerful technology just because it exists.

Omni: Once the technology exists, won't there always be genetic doctors who'll perform surgery for the right fee?

Anderson: Yes, based on what we know is a thriving black market for steroids among athletes.

Omni: We have cosmetic surgery, and a system for deciding who gets it—namely, money. Why is this different?

Anderson: It's considerably more fundamental, something that strikes at the core of who we are. Surgery on the breasts or face is very superficial in the real sense of the word. Why doesn't society permit Olympic athletes to take steroids if what we want is people who can jump higher, run faster, lift more weights? The reason is only partly because of the dangerous long-term health consequences. Steroids give people an unfair advantage.

Omni: What could be more unfair than our genetic endowment at birth?

Anderson: True. And society quite legitimately is concerned that the richest, most powerful, most famous, will get the good genes first. Elite groups could become even smarter, better looking, and richer than people disadvantaged from day one. That's why society is more comfortable with the idea of offering genetic surgery to individuals who, through no fault of their own, suffer from severe diseases. Then it is morally justifiable to at least try to bring them up to a minimum level of quality of life. To take an acceptable quality of life and try to enhance it would be more disruptive to society than beneficial.

Omni: Would it be ethical if we could boost everyone's intelligence or life span or physical prowess through gene transfer?

Anderson: Yes. If it turned out everyone could have a marvelous quality of life for one hundred and fifty years, then everybody ought to have it. But now we're getting into the argument of how many angels can stand on the head of a pin—because for the next fifty years it's not going to be possible to genetically engineer the whole population.

Omni: How do you decide what constitutes a disease? How short is too short? How fat is too fat?

Anderson: You start out with severe cases: the child who'd grow up to be under three feet tall. If the procedure proves safe and effective, then you would gradually extend treatment to people with less serious conditions. Until gene therapy is well accepted by society, we should err on the side of being too conservative and restrict treatment to the most medically needy.

Omni: Might a future generation view gene therapy like cosmetic surgery?

Anderson: If we continue to destroy our ozone layer and pollute the environment with toxins and carcinogens, everybody may need gene therapy in another thousand years—extra genes for DNA repair enzymes to protect against harmful radiation from the sun, extra genes to boost the number of liver enzymes that can detoxify dangerous compounds. A *New Yorker* cartoon shows a spokesman outside a nuclear reactor saying to a TV crew, "Not to worry. The genetic damage caused by the nuclear accident can be corrected by genetic engineering." I hope *that* day never comes to pass, but one cannot be encouraged by how we're handling our environment now. What happens with gene therapy in the long run depends on the risk–benefit ratio to society. But what society does five hundred years from now is not for us to decide. They wouldn't care what we have to say any more than we care what people in 1600 thought about how we should spend our lives. Ethics, after all, is contextual. To a future society, gene therapy may not only be acceptable—it may be essential for its survival.