Engineering the Human Germline

An Exploration of the Science and Ethics of Altering the Genes We Pass to Our Children

Edited by
Gregory Stock
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Gregory Stock and
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Preface

Germline genetic manipulations are those made to "germinal" or reproductive cells—the egg or sperm—and they can alter both the immediate patient and his or her descendants. This is a major extension of today's genetic therapies and, until recently, most ethicists and scientists have found the idea of allowing such interventions in humans virtually unthinkable. But technology has now advanced to the point where the unthinkable needs to be carefully examined.

This book explores both the prospects for, and the larger implications of, human germline engineering. The book's three sections come at these issues in very different ways. In part I, seven leading scientists lay a solid groundwork by assessing the realistic possibilities and problems of this technology. Too often when genetic engineering is portrayed in the popular media, no distinction is made between fantasy and reality, but the issues surrounding human germline engineering cannot be intelligently debated without a solid grasp of the scientific realities of the technology. These seven essays—each prepared for an audience of nonspecialists—offer us that grasp. Gregory Stock and John Campbell, coeditors of this volume, begin with a vision for practical germline engineering. Leroy Hood, a key figure in the human genome project, describes the relevance of our rapidly expanding understanding of human genetics. Daniel Koshland, editor of *Science* magazine for more than a decade, offers his perspective on issues of safety and ethics. Mario Capecchi, a leading researcher who manipulates the genetics of mice, describes how germline engineering might take place in practice. French Anderson, the father of human gene therapy, lays out his misgivings about near-term use of germline technologies. Michael Rose, an expert in aging research, discusses the feasibility of

eventually retarding the aging process. And Lee Silver, an architect of the reprogenetic vision, describes the tight linkages between germline genetic engineering and advanced in vitro fertilization technologies.

Part II is a looser look at the implications of germline engineering, a lively discussion in which the seven scientists from part I are joined by an ethicist, a public policy expert, and Nobel-laureate James Watson, codiscoverer of the structure of DNA and founder of the human genome project. Words are not minced in this extraordinary conversation that opens revealing windows into the issues surrounding the technology of germline engineering as well as the personalities and attitudes of key figures shaping the debate.

Part III—"Other Voices"—takes a broader perspective, through a diverse collection of short essays by scientists, ethicists, lawyers, theologians, and public-policy makers from both the United States and abroad who have thought deeply about these issues and contributed to discussion of them. Together, these essays show the breadth of opinion about the arrival of these genetic technologies looming at our doorstep. Each contributor was asked a specific question, either his or her concerns about widespread use of this technology, or his or her attitude about germline engineering were it ever shown to be safe and reliable. These thought-provoking responses are nuanced by their response to an additional and very personal question that each of us may one day face—"Would you be willing to genetically alter your own child-to-be, given a safe reliable technology offering a tempting possibility?" Their views may help us prepare for that day.

Many people were critical to the creation of this volume. Above all, we would like to thank the speakers at the "Engineering the Human Germline" symposium at UCLA in March 1998. Without the willingness of French Anderson, Andrea Bonnicksen, Mario Capecchi, John Fletcher, Leroy Hood, Daniel Koshland, Michael Rose, Lee Silver, and James Watson to speak publicly and forthrightly about this difficult and challenging topic, our volume could never have been produced. At present, there is considerable discussion of the challenges of human germline engineering in both scientific circles and the popular media. At the time of that conference, however, the climate contained much paranoia about frankly discussing these topics. Indeed, we were even warned that disruptions or demonstrations might well accompany the event. Thus, the speakers' courage in leading the way toward opening up this topic to reasonable discussion can only be applauded.

The book would also not have been possible without the help and support of a number of others. The funders of the symposium—William Stubing from the Greenwall Foundation and Doron Weber from the Alfred P. Sloan

Foundation—were not only generous in their support; they took a personal interest in the project, which was of tremendous value. Their desire to foster increased public dialogue and awareness of the emerging technology of human germline engineering was instrumental in supporting our work. Professor William Schopf provided critical assistance in many ways, but above all we would like to thank him for his faith in the project and his willingness to put the resources of the Center for the Study of Evolution and the Origin of Life at our disposal. The role of Donald Ponturo, the Special Projects Manager of the Program on Medicine, Technology, and Society, cannot be overstated. Not only was he intimately involved in coordinating the symposium and making it a success—he played a major role in editing and organizing this manuscript. Without him, the book could never have happened.

The support of the UCLA administration was also important, and we wish to acknowledge in particular the role of Vice-Chancellor Patel, Provosts Jerry Levey and Brian Copenhaver, and Dean Lenny Rome, who threw the weight of UCLA behind this effort and helped make it a success.

Finally, we wish to thank our agent, Joe Spieler, for his ongoing counsel and support in bringing this book into its current form, and our editor, Kirk Jensen, for his guidance and commitment to making this book all that it could be.

Los Angeles, California G.S.
March 1989 J.C.

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Contributors

Chapter Authors and Panelists

W. French Anderson is Director of Gene Therapy Laboratories and a professor of biochemistry and pediatrics at the University of Southern California School of Medicine. It was Dr. Anderson's pioneering efforts that led to the first human gene therapy trial in 1990. Dr. Anderson holds an M.D. from Harvard Medical School. He has published extensively, holds many board and editorial positions, and is the editor-in-chief of *Human Gene Therapy.*

Andrea Bonnicksen is a professor in the Political Science Department at Northern Illinois University. Dr. Bonnicksen has written various articles on preimplantation genetic diagnosis of human embryos, germline therapy, and other reproductive issues. She is the author of *In Vitro Fertilization: Building Policy from Laboratories to Legislatures* (New York: Columbia University Press, 1989), coeditor of *Emerging Issues in Biomedical Policy,* and a member of the Ethics Committee of the American Society for Reproductive Medicine.

Mario R. Capecchi received his doctorate from Harvard University and is Distinguished Professor of Human Genetics in the Department of Human Genetics at the University of Utah School of Medicine. His techniques for generating mice with specific targeted genes inactivated ("knock-out" mice) established a new way of exploring how genes work in mammals. He is a member of the National Academy of Science, and his honors include the Bristol-Myers Squibb Award for distinguished achievement in neuroscience as well as the 1996 Kyoto Prize.

John Fletcher received his Ph.D. from the Union Theological Seminary, New York. He researched his dissertation, "A Study of the Ethics of Medical Research," at the Clinical Center of the National Institutes of Health, where he later served as the first chief of its bioethics program. In 1980, French Anderson and he coauthored an influential article on the criteria for any trial of human gene therapy. He was one of the first in bioethics to explore the issues of germline gene therapy. In 1993, he was named Kornfeld Professor of Biomedical Ethics at the University of Virginia.

Leroy Hood received his M.D. from the Johns Hopkins Medical School and his Ph.D. from the California Institute of Technology. He has been a member of the National Academy of Sciences and the American Academy of Arts and Sciences since 1982, and he coedited *The Code of Codes* (Cambridge: Harvard University Press, 1993). Dr. Hood was Bowles Professor of Biology at the California Institute of Technology until he joined the University of Washington in 1992 as William Gates Professor of Biomedical Sciences and the founding chair of the Department of Molecular Biotechnology.

Daniel Koshland, Jr., received his doctorate from the University of Chicago. A professor of molecular and cell biology at U.C.-Berkeley since 1965, Dr. Koshland was the editor of *Proceedings of the National Academy of Sciences* from 1980 to 1985 and of *Science* magazine from 1985 to 1995. He has been a member of the National Academy of Sciences since 1966. Among his many honors are the Waterford Prize from the Scripps Institute and the National Medal of Science.

Michael R. Rose is a professor in the Department of Ecology and Evolutionary Biology at the School of Biological Sciences, U.C.-Irvine, and received his doctorate from the University of Sussex. He is the author of *Evolutionary Biology of Aging* (New York: Oxford University Press 1991) and editor of *Darwin's Spectre.* Dr. Rose's major research focus has been experimental tests of evolutionary theories of aging and fitness. Among other awards, he received the Busse Prize for research on aging from the World Congress of Gerontology.

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James D. Watson, who shared the Nobel Prize with Francis Crick and Maurice Wilkins in 1962 for the discovery of the structure of DNA, received his Ph.D. from Indiana University. He joined the Harvard faculty in 1956 and became Director of Cold Spring Harbor Laboratory in 1976. From 1988 to 1992, Dr. Watson functioned as Director of the National Center for Human Genome Research of the National Institutes of Health, where he helped established the Human Genome Project. Dr. Watson has won numerous honorary degrees and awards and has been the president of the Cold Spring Harbor Laboratory since 1994.

Editors

John Campbell received his Ph.D. from Harvard University and postdoctoral training at the Institut Pasteur, Paris, and the Commonwealth Scientific and Industrial Research Organization (CSIRO) in Canberra, Australia, which runs the main government supported research laboratories in Australia. He is an elected fellow of the American Academy of Sciences, first holder of the Robert Wesson Fellowship on Scientific Philosophy and Public Policy, and the professor of neurobiology at the UCLA School of Medicine. Dr. Campbell's fields of research are genetics and evolutionary theory.

Gregory Stock received a Ph.D. from Johns Hopkins University and an M.B.A. from Harvard. In his 1993 book, *Metaman: The Merging of Humans and Machines into a Global Superorganism* (New York: Simon and Schuster), he examined the evolutionary significance of humanity's rapid technological progress; and at Princeton's Woodrow Wilson School he looked at the implications of recent breakthroughs in molecular genetics. Dr. Stock is now the director of the Program on Medicine, Technology and Society at UCLA's School of Medicine.

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Lloyd R. Cohen holds a Ph.D. in economics from the State University of New York and a J.D. from Emory University. Dr. Cohen teaches law and economics at George Mason University in Virginia. As an outgrowth of his specialization in the application of economics to law, he has written and spoken extensively on his proposal to create a market in transplant organs as well as on a variety of other health-care issues.

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Alex Mauron initially trained as a molecular biologist and is now an associate professor of bioethics at the University of Geneva Medical School. He has published widely on the ethical issues of genetics and reproduction, as well as on clinical ethics. He is a regular contributor to the daily *Le Temps* and is a member of the Swiss Federal Ethics Commission on Genetic Engineering and of other ethics committees at various research institutions and health-care organizations.

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Erik Parens is now the associate for philosophical studies at The Hastings Center, a bioethics think tank in Garrison, New York. He has published extensively on the ethical and social questions raised by biotechnological advances; he is also the editor of *Enhancing Human Traits: Ethical and Social Ramifications* (Washington, D.C.: Georgetown University Press, 1998) and coeditor of *Prenatal Genetic Testing and the Disability Rights Critique* (Washington, D.C.: Georgetown University Press, forthcoming).

Gregory E. Pence wrote *Who's Afraid of Human Cloning?* (Lunham, Md.: Rowman and Littlefield, 2000 [3rd ed.]) and has taught for twenty-three years at the University of Alabama at Birmingham, where he is a professor in the Department of Philosophy and the School of Medicine. He wrote *Classic Cases in Medical Ethics: Accounts of the Cases that have Shaped Medical Ethics*, (Boston: McGraw-Hill, 1995) and edited *Classic Works in Medical Ethics* (Boston: McGraw-Hill, 1998).

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Engineering the Human Germline

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Introduction

An Evolutionary Perspective

Germline engineering is not a common expression, so it's important to make sure we understand it. Human germline manipulations are those made to the genes of our "germinal," or reproductive, cells—the egg and sperm. In practice, this today means altering the fertilized egg—the first cell of the embryo-to-be—so that the genetic changes will be copied into every cell of the future adult, including his or her reproductive cells. Normally such changes would also be passed forward to future generations; but as we shall see in Mario Capecchi's essay, "Human Germline Gene Therapy: How and Why," this need not always be the case.

Germline technology stands in sharp contrast to the genetic therapy of today, which is "somatic" in that it targets cells of the "soma," or body; for example, genetic insertions to treat cystic fibrosis are directed at cells in the lining of the lung mucosa. Somatic interventions do not reach beyond the patient being treated, so their potential scope is obviously more limited than a germline intervention; but one still might wonder why *germline* therapy is viewed as so consequential a step for humanity. After all, when we use contraceptives, fertility drugs, in vitro fertilization (IVF), or artificial insemination, or even when we choose our mates, the consequences reverberate through future generations.

As manipulations, however, all these actions seem indirect or at least nonspecific when compared to human germline engineering—which, by giving us the capacity to intentionally change the genes of our children-to-be, promises to harness the full power of molecular genetics and turn it back upon our own selves. Germline engineering touches the very core of what it means to be human: It palpably extends human power into a

sacred realm, once mysterious and beyond reach. It forces us to look at the degree to which our genetic constitutions shape us. It brings up questions about the adequacy of our collective wisdom. It makes us look at how far we wish to intrude in the genetic flow from one generation to the next.

Even now the evening news routinely features breakthroughs from the Human Genome Project and from work on in vitro fertilization, animal cloning, and artificial chromosomes; human germline engineering will increasingly become a major focus of discussion, soul-searching, and legislation. With human germline engineering, we are beginning to seize control of our own evolution, and yet we have barely begun to grapple with the consequences. Ultimately, we will have to face the question lying at the heart of the emerging international debate about the application of molecular genetics to humans: How far are we willing to go in reshaping the human body and psyche?

By raising the possibility of meaningful human design, germline engineering uniquely captures the challenge of our coming era. Though other technological advances may immerse us in a radically different world, they will by and large leave the essentials of our biology unchanged.

Our lifetimes are so short, our human perspective so narrow, and the changes going on around us so enormous that it is challenging to appreciate just how extraordinary is this moment of time in which we are living. But things are happening today that are absolutely without precedent in the entire history of life on this planet. To see the larger implications of human germline engineering, it helps to step back and consider two other momentous developments underway. The first is space travel: We may be getting blasé about it, but for 3.5 billion years life has been constrained to a thin film on the surface of our planet, and now—through us—it has quite suddenly begun to move out towards the stars. A second is the arrival of the computer chip. It is beginning to seem almost commonplace now, but nonliving material (basically sand) is being imbued with a complexity that rivals that of life itself. These breakthroughs will define our future. And genetic engineering is comparable to them.

As we unravel our own blueprint and begin to tinker with it, we are becoming subject to the same powerful forces of conscious design that have already so completely reshaped the world around us. And as these forces reflect back upon us, life is entering a new phase in its history. Quite literally, we are seizing control of our own evolution, taking the reins, so to speak. How can this not be fraught with controversy? It is mind-boggling to try to imagine the shape of the human enterprise and of our own selves even a millennium from now, much less in the hundreds or thousands of millennia that have been meaningful in traditional evolutionary terms.

To what extent will we transform ourselves? We cannot know, but we can be relatively confident that we will eventually gain the power to do so. Of course, speculation about the shape of the distant future is unprovable, and it is certainly not the subject of this book. We bring it up merely to emphasize the larger implications of the unraveling of our biology. In this text, we will largely direct our attention towards potential human germline interventions that might become feasible in a time frame that is meaningful to us and our children, therapeutic possibilities that may exist or be under serious consideration within a few decades. Trying to look further would almost certainly reveal more about our own hopes and fears than the eventual shape of the future, because critical developments we do not foresee are bound to have major consequences. Even twenty-five years ago, no geneticists imagined that breakthroughs in gene sequencing, molecular genetics, and computers would put us where we are today.

The real question about germline engineering is not whether the technology will become feasible, but when and how it will. The fundamental discoveries that will enable this technology will occur whether or not we actively pursue them, because they will emerge from research deeply imbedded in the mainstream, research directed not towards the goal of achieving human germline engineering, but towards other less controversial goals. Four such arenas of research stand out:

- *Medicine.* The somatic genetic engineering pioneered by French Anderson and others has yet to bring significant new treatments, but it has brought exciting possibilities and is generously supported. Such therapy offers entirely new approaches for treating diseases that have hitherto been untreatable. Society could not easily relinquish such clinical possibilities, and many of the advances developed to achieve them will be readily applicable to germinal cells.
- *Fertility research.* Babies born by in vitro fertilization were once labeled "test-tube" babies and were a subject of serious concern. But now, some twenty years later, IVF has become the obvious choice for tens of thousands of couples who could not otherwise have children.[1] Enormous energies will continue to be devoted to these technologies because they are in serious demand and because society generally approves of giving couples additional reproductive options. When germline engineering appears, it will necessarily be as an adjunct to IVF, so this research effort—driven by its own powerful dynamics—cannot help but lay a foundation for eventual human germline engineering.
- *The Human Genome Project.* Whether the human genome is completely unraveled in the two years now being discussed[2] or in the five years originally projected, it is clear that eventually the information will revolutionize biology and medicine. There will be no turning back from

this grand project, and its fruits cannot help but lay the foundation for both somatic and germline therapies. When coupled with genechip technology, which will provide rapid and inexpensive genetic profiling, and genomics, which will elucidate the relationships between our genetics and our physiology, the Human Genome Project will almost certainly yield a host of enticing ways to intervene in our own genetics.

- *Animal research.* Basic research to explore the underlying biology of life is taking place not only in academic institutions all over the world, but also within corporations trying to produce better pharmaceuticals or improve crops and livestock. Cloning was developed for use on animals, not humans, but that will hardly prevent its eventual extension to humans. The same will be true for other breakthroughs in our ability to manipulate the genetics of laboratory organisms, because there is no gulf between human and nonhuman biology.

If it is inevitable that we will gain the capacity to engineer the genetics of our germinal cells, then it is critical to begin to ask who should be allowed to use the technology, when, in what circumstances, and in what ways. In the past, many scientists and ethicists have dismissed serious discussion of this by asserting either that it is not a journey we should begin, or that the technology is so distant that we can let our grandchildren or great-grandchildren grapple with it. But recently we have witnessed the birth of Dolly, the creation of stable artificial human chromosomes, and the culturing of human embryonic stem cells. Molecular biology and genetics are progressing rapidly, and human germline engineering no longer looks so distant. Indeed, rudimentary procedures could be done today—though not with the safety any responsible physician would demand.

The popular media tend to focus on the more lurid and dangerous distant possibilities of human germline engineering, rather than the mundane therapeutic ones that may develop in the immediate years ahead. This is not surprising, for the ghosts associated with the idea of altering the genetics of our children are haunting ones. The pseudoscience of the eugenics movement of the 1920s and Hitler's brutal attempts to create a master race are far too vivid to ignore, but they should not determine our future in a realm where the possibilities and challenges are so enormous. Now, while the technology is still nascent, is the time to examine germline engineering in a frank, intelligent way. The goal of this book is to lay a solid foundation for that examination and move us toward a broad discussion of the technology's implications.

PART I

THE REALITIES OF HUMAN GERMLINE ENGINEERING

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JOHN CAMPBELL
GREGORY STOCK

A Vision for Practical Human Germline Engineering

This essay looks as concretely as possible at the practical aspects of engineering genetic changes in the human germline. Engineering our genomes often conjures up science fiction images of turning people into Supermen and Star Trek creatures. In light of the enormous cataclysms of the past century, such vivid pictures cannot help but influence us, but they do not reflect reality. Hollywood scenarios are as irrelevant to evaluating the merits of germline engineering as worries of computers taking over the world are to deciding whether to put computers into the schoolroom. The foreseeable prospects which concern us are for discrete, relatively uncontroversial improvements in our health. For the next decade or two, germline genetic engineering might best be thought of as "germline gene therapy," because most changes that can realistically be expected will be "therapeutic" in one way or another.

Already, genes are being manipulated to fight disease. Somatic gene therapists are currently treating illnesses by putting corrective genes into the body cells of patients. Injecting genes into a fertilized egg will extend gene therapy to the germline. This is an important extension, because it will automatically introduce the genetic changes into every cell of the body without having to intervene in each cell individually. Effects can be limited to the cells that need them by controlling the expression of the altered genes so that they are active only where they should be. This is how the genome operates during normal development. The simplicity of introducing genes through the germline makes it not just another type of gene therapy, but the *ultimate* form of such therapy.

Extending gene therapy to the germline will demand two technical developments: The first is a practical procedure to introduce changes into a

human egg. The procedure must be safe, reliable and, above all, practical. Ideally, it should allow us to introduce many improvements into an egg at one time and to do so without interrupting the rest of the genetic program. The second is the creation of genetic improvements with enough promise to inspire us to use them. These two prerequisites are difficult, but geneticists are substantially closer to both of them than is generally appreciated. First, consider how to deliver the genes.

Currently, geneticists manipulate the germline of animals by adding or changing a gene in an existing chromosome of a germline cell. A new approach just becoming feasible is to introduce a new gene on a new additional chromosome. Adding new genes on a newly added chromosome—*double addition*—is the least intrusive strategy, because it leaves the original genome entirely untouched. Furthermore, the technology is rapidly developing. Geneticists already have artificial chromosomes that will persist for repeated divisions when injected into human cells.[1]

A chromosome for double-addition germline engineering (fig. 1) would have no genes of its own but, instead, a series of "docking" sites where designed genes could be inserted using enzymes. It would serve as a universal delivery vehicle for cassettes of genes that medical geneticists fashion for various therapeutic purposes. Initially, only a few safe and effective genetic cassettes will be available, but eventually hundreds might be incorporated into a germline cell, each offering its own particular improvement. The chromosome could be offered to prospective parents in an infertility clinic. These clinics now routinely collect eggs from a woman, fertilize them in vitro, and implant the zygote into her womb. In the future, techicians

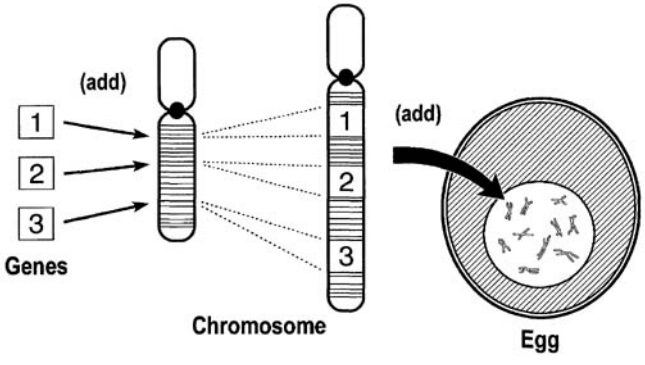

Figure 1. Human germline engineering by double addition. Cassettes of specific genes and their regulatory sequences are loaded at preset docking sites along an artificial chromosome that is then injected into a fertilized egg.

might inject a loaded artificial chromosome into the eggs as an optional extra step.

Chromosomes for human eggs will need other ancillary features. It will be desirable to keep certain gene cassettes inactive until their recipient grows into an informed consenting adult who can decide whether to activate them. It also will be useful to specially design the chromosome to be easy to handle, easy to introduce genes into, and easy to verify that the chromosome and its genes have been properly incorporated into an egg. Most importantly, a mechanism will be needed to prevent the chromosome from being inherited by future generations. Clearly, our earliest genetic modifications should not become permanent parts of the human gene pool. Even were germline engineering perfectly safe, children who received auxiliary chromosomes would one day want to give their own children the most up-to-date set of genetic modifications available, not the outdated ones they themselves had received a generation earlier. It would be difficult to prevent the inheritance of changes scattered throughout the genome, but if changes were confined to an auxiliary chromosome, that chromosome could simply be designed to be nonheritable. Chromosomes could be blocked in a variety of ways from passing through the sexual cycle to the next generation.

Considering the rapid pace of development of artificial chromosomes for the construction of transgenic animals and for human somatic gene therapy, very sophisticated chromosomes will likely be available for human germline engineering within a decade.

A more extensive task than constructing an auxiliary chromosome for human germline engineering will be to design the gene cassettes to place on it. Our understanding of human genetics is still fragmentary; even so, we know enough to begin designing a variety of worthwhile cassettes. Here are two concrete possibilities.

The first protects a person from AIDS. The AIDS virus, HIV, infects only certain cell types made in a person's bone marrow, most notably, T helper cells. AIDS workers are testing a variety of artificial genes which might make engineered T cells resistant to the virus. They include genes for a ribozyme, an antisense RNA, a dominantly defective viral protein, and a truncated anti-HIV immunoglobulin, among others.[2] Gene therapists hope to insert one or another of these genes into bone marrow stem cells of AIDS patients so that they would produce HIV-resistant T cells.[3] Engineering the bone marrow of an adult AIDS patient to produce new T cells is an extraordinarily ambitious goal and might not be possible at all in view of the complex way that mature T cells are formed. It would be far more feasible to introduce the resistance gene into the germline. This would prevent AIDS rather than treat it.

For safety, any resistance gene introduced into the germline should be regulated so that it is expressed only where it is needed, namely, in the T helper cells and their relatives. It seems unlikely that the sorts of molecules used in this case would be harmful to other cells, but the first safety principle for germline genetic engineering should be to express a new or altered gene in the minimum range of cells needed.

Genes are highly amenable to regulation.[4] Chromosomes have two types of genetic elements along their DNA: genes themselves, each of which codes for a unique protein that contributes in some way to the functioning of the organism, and regulatory sequences, which control when and where particular genes are expressed. There are many different classes of regulatory elements. The best understood is the promoter, a short stretch of DNA at the beginning of a gene. Promoters are attachment sites for special proteins that enable the gene to be expressed. These proteins are called transcription factors, because transcription is the first step in gene expression. Every promoter requires one or more particular transcription factor that specifically recognizes that promoter, attaches to it, and initiates the transcription process. If a cell does not make a particular transcription factor, the genes that are dependent on it will not be expressed. Our genome codes for thousands of different transcription factors. Each cell type makes its own unique subset of them for the proteins it needs.

HIV enters only those cells that make a protein called CD4 for their surface.[5] Therefore, an obvious strategy to regulate an introduced HIV-resistance gene is take the promoter (and other regulatory sequences) from the CD4 gene and paste it in front of that gene. That way, the resistance gene will be expressed only in the cells, such as T cells, that the virus can enter.

Actually, the CD4 gene's regulatory sequences are far more complex than just a single promoter. Multiple sites that bind multiple transcription factors are scattered across a long segment of DNA in and around the CD4 gene.[6] Fortunately, vast quantities of DNA shouldn't be a problem for engineering with an auxiliary chromosome, so the inserted HIV-resistance gene could be surrounded by tens of thousands of base pairs of DNA copied from the CD4 region. This would give the inserted gene the expression pattern of the CD4 gene without even identifying the individual controls that were copied.

HIV is a useful example because it is the focus of so much research. The first viral resistance genes developed for antiviral gene therapy may well be for this virus. The general approach we have outlined for HIV could be extended to other intractable viruses as well, admitting, of course, that each will present its own unique challenges. Imagine, for example, a child never getting a cold during his or her entire life. For millions of years, cold viruses

have evolved strategies to evade our immune systems, but they will be naive to strategies that genetic engineers can use against them.

Cancer is a second important target for germline engineering. It presents a complex challenge. The key to one strategy for treating cancer is that certain transcription factors activate their promoters only in the presence of a hormone, such as testosterone.[7] Such transcription factors are called hormone receptors because they function only when they bind a hormone molecule. The bound hormone bends the shape of the receptor so that it can attach to its promoter and activate the gene. Without the hormone, the receptor will not even bind to the DNA. The testosterone receptor is, in essence, a switch that testosterone flips on or off. Add the hormone and the gene goes on; remove it and the gene goes silent. Estrogen and other steroid hormones work the same way, each binding its own specific receptor to activate its own hormone-dependent promoters. Even lower animals control gene expression with steroid hormone/receptor systems. For example, ecdysone and ecdysone receptor constitute a system unique to insects.[8]

Figure 2 shows how the ecdysone switch of insects can be fashioned as a cocked gun that could be triggered, when necessary, to surgically excise cancer cells. The gun is the gene that codes for Diphtheria toxin, a lethal cellular poison. The gene is activated by ecdysone, through an ecdysone-dependent promoter. This promoter will be snipped from an insect genome and pasted in front of the toxin gene.

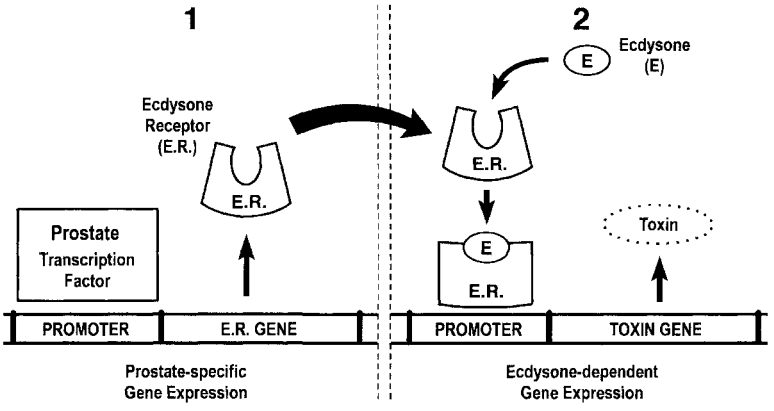

Figure 2. A two-gene cassette to protect against prostate cancer. Gene 1 codes for ecdysone receptor, which is expressed from a prostate-specific transcription factor. Ecdysone receptor functions as an ecdysone-dependent transcription factor to control the expression of gene 2, which codes for diphtheria toxin. When ecdysone is present, the toxin gene is expressed in prostate cells and the cells die. The toxin gene is not expressed in any other cells, because no other cells synthesize the ecdysone-dependent transcription factor.

Humans do not make ecdysone receptor, so its gene must also be taken from an insect genome and supplied in a second module of the cassette. Here, the gene is given a promoter that is active only in the glandular cells of the prostate, which are the ones vulnerable to cancer. This is the same sort of cell type–specific regulation we saw with the CD4 promoter, which was active only in T cells.

This is how the cassette operates: Ecdysone receptor will be synthesized continuously in the glandular cells of the prostate, but nowhere else. It will remain inactive because no ecdysone is present. If prostate cancer were ever diagnosed, or even suspected, a man would get an injection of ecdysone. The hormone would activate the ecdysone receptors in his prostate glandular cells, which would "turn on" the diphtheria gene, resulting in diphtheria toxin that would kill the cells. One shot and the cancer would be gone. Ecdysone would be present throughout the body, but only prostate cells would have the ecdysone receptor to which it would bind, because ecdysone is not a natural hormone of humans.

This strategy is generalizable to other sites. By changing the promoter for the ecdysone receptor gene, this same cocked gun could be aimed at the breast, pancreas, or other vulnerable tissues. These germline engineering approaches for treating AIDS or cancer are not fantasy. They are realistic procedures and strategies that geneticists are already using to create valuable transgenic animals.[9]

The flip side to killing rogue cells is to prevent the death of cells we do not want to lose, for example, neuronal cells in Alzheimer's disease, Lou Gehrig's disease, Parkinsonism, macular degeneration, and stroke. Geneticists are already beginning to test gene insertions in animal models and human cell lines to find ones that might retard these neurodegenerative pathways.[10] When protective genes are finally identified, it will probably be more practical to reach all cells of the nervous system by inserting the genes into an egg than by trying to deliver them to billions of neurons individually.

It is intriguing that neuronal death in patients with neurodegenerative diseases is usually preceded by various combinations of the same common pathologies: oxidative damage, deposition of insoluble proteins, excitotoxicity (excessive stimulation), or induction of programmed cell death.[11] Health providers are especially interested in whether blocking one or more of these pathologies might prevent neurons from dying. If so, it might be that for neurodegeneration, as for cancers and viruses, one basic cassette type could eventually protect against a range of diseases.

Naturally occurring genes in the human gene pool will provide another source for germline improvement. There is enormous genetic variation

among humans. Most genes occur in several alternative forms, called alleles, that constitute the genetic differences among people. For example blue and brown eye colors come from alternative alleles of the eye-color gene.

Some mutant alleles are worse than average, as we all know, but some rare gene forms have especially beneficial effects. We suggest the name "superallele" for an uncommon gene allele that notably extends a beneficial trait in the few lucky people who carry it. Geneticists are now developing methods to find superalleles in the chromosomes of particularly favored persons, for example, longevity superalleles in people who are very old and healthy, or protective superalleles in people who have high serum cholesterol levels but little coronary artery disease.

Superalleles are ideal genes for germline engineering. By definition, they have already demonstrated their effectiveness in humans. We can discover if they cause any undesirable side effects simply by examining the people who already have them. Finally, we only need to find superalleles, not understand how they work. Using superalleles for germline engineering holds the promise of enabling any prospective parents to endow their children with selections of the best gene variants our species has evolved.

Of course, we cannot just add a superallele to a fertilized egg, because the egg already has copies of that gene. The introduced superallele must substitute for the copies already present. To do this by double addition, a gene cassette would need a second module to block expression of the existing copies of the gene. Silencing genes is feasible; indeed, this is what the presumptive HIV-resistance genes discussed above would do—silence an essential HIV gene in an infected cell.

How many possibilities are there for germline improvement? No one knows, but when geneticists, pathologists, other biologists, and clinicians—especially experts in aging—put their minds to this problem, they will probably come up with hundreds. Devising these germline improvements on paper is important, both because it could lead to therapeutic interventions and because at this time it is the only way to concretize the immediate possibilities of human germline engineering. The next step is to actually construct DNA cassettes. This would have been a Herculean task fifteen years ago. Now, a good Ph.D. student might handle the challenge. An exciting, if ambitious, thesis project would be to conceive of a germline improvement, make the DNA cassette for it, and insert it into a mouse egg to show that it works. This entire project could be done without in any way using people or human embryos as subjects.

What scientists and the public need to realize is how close human germline engineering may be. The two research efforts needed to bring it into

being—one to develop gene therapy strategies, the other to develop a system for their delivery—are rapidly proceeding in parallel. In a decade or two, they will come together, and human germline engineering will suddenly become feasible. Now is the time to begin broad public discussion of what we can, should, and will do with this challenging technology.

LEROY HOOD

The Human Genome Project—Launch Pad for Human Genetic Engineering

Human germline engineering is a discipline of the future. Its objectives will be to reverse genetic defects or to enhance desirable human traits such as emotional stability, intelligence, or longevity. Genetic defects may occasionally be encoded primarily by a single gene and will, accordingly, be simpler to engineer than more complex traits that are encoded by many different genes. It is important to stress that complex traits encompass most of the interesting human features including intelligence, attractiveness, and many other physical and behavioral attributes. Three issues are important with regard to germline genetic engineering. First, what are the technical limitations of germline genetic engineering? Do we have the tools to carry out germline engineering in an effective, safe, and reasonable manner? These questions are covered in other essays. Second, to what extent do we understand the networks of genes that operate in concert to control interesting human traits? We cannot engineer humans without more or less fully understanding the gene systems that control the traits that we would like to engineer. Finally, society must make decisions based on the ethical and social issues surrounding germline engineering. The imperative is to have an informed and thoughtful public that can both understand the issues that germline engineering raises and make rational decisions about the alternatives it presents society. This essay will focus on the Human Genome Project, for this project provides the necessary tools and information for launching attempts to decipher interesting human traits. We will also examine the paradigm changes that the project has catalyzed to lead us to the systems biology that will be the central approach to biology and medicine in the twenty-first century.

Human Genome Project

The Human Genome Project is about deciphering human heredity.[12] Human heredity is encoded by our genomes—the twenty-three pairs of human chromosomes (of twenty-four distinct types, since there are two different sex chromosomes, X and Y) that are present in each and every one of our cells. The fundamental core of each human chromosome is a long string of DNA composed of 50 million to 250 million letters of the DNA language. The DNA language has four different letters, G, C, A, and T, and it is variation in these letters down the long strings of our chromosomes that encode one key type of information: the 100,000 or so human genes necessary for building humans. Indeed, our genome may be viewed as the most incredible software program ever written. It is a program that has been fashioned by 3.7 billion years of evolution, and it dictates the most fascinating of all biological processes, human development—the process whereby we all start as a single cell, the fertilized egg, and after many cell divisions emerge as an adult human organism of 10^{14} cells. There are many different types of human cells—muscle cells, brain cells, and bone cells—each of which carry out distinct functions. These distinct cell types or phenotypes are produced by a chromosomal choreography that specifies the appropriate subset of those 100,000 genes that must be expressed for each cell type to generate its particular functionalities.

The Human Genome Project is about two types of maps—genetic and sequence. To construct a genetic map, chromosomal markers, termed *genetic markers*, are identified across our chromosomes. It is these markers that give us the ability to locate genes which predispose to interesting physiological and/or disease traits. The Human Genome Project has identified 20,000 such genetic markers scattered across the human genome, and this genetic map has been used to identify more than 800 individual genes which predispose to a variety of human diseases, most quite rare.

The second type of map is termed a *sequence map*. It shows the order of each of the letters of the DNA language all the way across each of the twenty-four human chromosomes. It is proposed that the sequence map will be finished by the year 2003.[13] The sequence map is the ultimate map, because it gives us the information necessary to begin deciphering the human book of life, a task which undoubtedly will take one hundred or more years.

If we look back at the Human Genome Project in twenty years, it is apparent that three major benefits will have been achieved. First, we will have determined the periodic table of life. The periodic table of chemical

elements, which was established in the nineteenth century, revolutionized our understanding of chemistry by providing insights into the fundamental relationship of the elements to one another. The periodic table of life now being provided by the Human Genome Project will, in the same way, provide the information necessary to gain insights into the fundamental elements of life—the genes and the regulatory machinery that turn genes on at the appropriate time in human development, in the appropriate cells, and express the genes at appropriate concentrations. This periodic table will allow us to take the 100 thousand or so human genes and deconvolute them into their basic building blocks, which are called motifs. These motifs will be important in understanding how the products of the genes, their proteins, actually execute their function. Finally, the periodic table of life will give us the ability to identify and begin to understand the nature of the variation in the DNA letters (polymorphisms) that occur between similar positions on the chromosomes of different individuals. For example, approximately 1 letter in 500 varies between the same chromosomes from two different individuals. Most of this variation has no effect on human traits because genes occupy only about 5 percent of our chromosomes—hence, most mutations lie outside genes. A very few of these polymorphisms modify genes which encode trait variations—for example, some people are tall and others short, some people are fat and others thin. More important, these polymorphisms encode, in part, the entire spectrum of human diversity with regard to interesting physiological and disease-predisposing traits. Therefore, identifying all the human genes, their regulatory machinery and polymorphisms, and their contributions to human traits will be a fundamental aspect of launching the germline engineering of the future.

The second contribution to come from the Human Genome Project will be the development of tools that can decipher biological information at very high rates of speed. Many genes or proteins will be able to be analyzed very rapidly with what are termed *high-throughput analytical* or *global tools*. I'll discuss two of them later.

The third and the most important contribution of the Human Genome Project will be the union of information we obtain from the periodic table of life with very powerful global tools for deciphering biological information; already this union has catalyzed a series of paradigm changes in biology that are leading to what is termed *systems biology*. These paradigm changes provide fundamental insights into how we will go about understanding the complex networks of genes that are engaged in most of the interesting human traits—a fundamental requirement for germline genetic engineering.

Paradigm Changes Arising from the Human Genome Project

Biology is an informational science. This insight is a fundamental revolution in our view of biology. Biological information is of three different types. The first type is the linear or digital language of our chromosomes. As noted earlier, DNA employs a four-letter alphabet, and it is variation of these letters across the strings of information termed chromosomes that encodes genes, programs the regulatory machinery of genes, and specifies the other types of information necessary for chromosomes to execute their functions as informational organelles. The language of our genes is a code very similar to the digital code of our computers, but it has four rather than two letters. The units of information on our chromosomes, the genes, are expressed in a quantified manner; that is, different genes can be expressed in different cells. For different types of cells, different subsets of genes are expressed, and this leads to the features that distinguish, for example, brain from muscle cells.

The second type of biological information is the final product of the expressed gene information. Proteins are three-dimensional molecular machines that catalyze the chemistry of life and give the body shape and form. In looking at an individual, virtually everything one sees is protein. Proteins are initially synthesized as a linear string with a twenty-letter alphabet. The order of these letters in the string dictates how that string folds into three dimensions to create a molecular machine. Two challenges about proteins are fascinating. First, from the order of letters in the linear protein strings, can we actually predict how the string folds into three dimensions to make a particular molecular machine? The problem is partly experimental and partly computational, and we will have to enlist computer scientists and applied mathematicians to help solve it. Ultimately, however, the solution will rest in our ability to obtain the lexicon of motifs—or building block components—of genes and proteins that will come from the Human Genome Project. The second question about proteins is even more fascinating: Given a particular three-dimensional shape, how do we determine what function that protein executes? Once again, this is partly an experimental and partly a computational problem. Once we have solved these two problems, we will be in a position to carry out protein engineering—that is, the design of diagnostic, therapeutic, and even preventive reagents that may revolutionize medicine in the twenty-first century.

The study of individual genes and individual proteins has been the substrate of biology for the last thirty years or so. It has led to the striking successes of molecular biology. In a sense, the information about both individual genes and proteins is joined to create the third type of biological

information—that which arises from complex biological systems and networks. For example, the brain is a complex network of 10^{12} brain cells joined by 10^{15} connections. This network generates fascinating systems or emergent properties such as memory, consciousness, and the ability to learn. In order to understand how these systems properties arise, one can no longer look at single genes, single proteins, or single cells. One has to look at the network of elements as they operate together in the system as a whole. One must be able to take this systems information and create mathematical models that can accurately predict the systems behavior and properties—for it is only through this modeling that we will come to truly understand systems properties. Again, for this, biologists must solicit the help of computer scientists and applied mathematicians. This is the challenge for the future. Global tools will be needed to look at many elements and connections at one time. These global tools will be illustrated shortly.

It is important to understand that there are two meanings to the words "decipher biological information." For example, the Human Genome Project proposes to determine the order of the letters of the DNA alphabet across each of the twenty-four human chromosomes—that is, to sequence the human genome. But determining the order of the DNA letters in human chromosomes is deciphering the DNA language at only one level. Understanding the actual information that 3.7 billion years of evolution has embedded in our chromosomes is another level of deciphering. These efforts will occupy perhaps the next 50–100 years. The following analogy is apt. The human genome contains 3 billion letters of the DNA language. If translated into an encyclopedia of how to construct a human, this text would require 500 volumes, each containing 1,000 pages that each average 1,000 six-letter words of the DNA language. To the biologist, reading this book now would be very much akin to your reading a book of atomic physics. You could understand some words, but most of the meaning would be undecipherable. Thus, biological experiments must be carried out to translate the DNA sequence into knowledge of human biology. In a similar vein, it is one thing to know the three-dimensional structure of a protein and quite another to understand how that three-dimensional structure permits its functions to be executed. Likewise, it is one thing to define the elements and connections of a biological system and quite another to understand how systems properties emerge from this network. Once again, it will be necessary to involve applied mathematicians and computer scientists in creating models to understand how systems properties emerge from the complexity of biological systems. The deciphering (in both senses) of biological information from complex biological systems and networks will constitute the most compelling challenge for biology and medicine as we move into the twenty-first century.

A second paradigm change is the realization that high-throughput analytic or global technologies for studying genes, proteins, and even cells are going to be critical to deciphering biological systems. Let me provide two examples of global tools. In the early 1980s, our group developed an automated machine for sequencing DNA that color codes the four different letters of the DNA language with four different fluorescent dyes.[14] The most advanced form of this machine can sequence almost 40 million letters of the DNA language in a single year.[15] Indeed, within six months, an even more advanced sequencing machine will be able to analyze approximately 150 million letters of the DNA language per year.[16] Large genome centers working on the Human Genome Project may have anywhere between 10 and 100 of these DNA sequencing machines. Thus, one can understand the incredible speed with which DNA sequence analysis can be carried out by this global tool—the automated fluorescent DNA sequencer.

DNA chips provide a second example of a global instrument. Over the past six or so years at the University of Washington, we have developed a technology using commercial ink jet printers whereby we will eventually be able to synthesize up to 100 thousand small fragments of DNA on a glass chip approximately the size of your thumbnail.[17] Other scientists have used the technique of photolithography to create DNA chips.[18] If each of these 100,000 fragments of DNA represents a different human gene, then once the human genome is sequenced, we have the capacity to look quantitatively at all of the genetic information that is expressed in human cells. For example, we will be able to compare the expression patterns of the 100,000 human genes in a normal prostate cell and in a cancer prostate cell to determine how the expression patterns of these genes change when the cell is transformed from its normal to a cancerous state. This global high-throughput analytic technology, accordingly, gives us the capacity to analyze all human genes simultaneously. These chips will also play an important second function by giving us the capacity to look simultaneously at many human genetic markers for polymorphisms.[19] Thus, in a similar manner, 100 thousand fragments of human DNA may let us look simultaneously at 50 thousand different polymorphisms (each genetic marker has two alternative forms). This ability to create very dense genetic maps is going to revolutionize human genetics and give us even more effective means of identifying the genes that control human traits. Obviously, both large-scale DNA sequencing and genetic marker analysis are key technologies for understanding human genes and the roles they play in human traits.

A third paradigm change is the imperative to recruit computer scientists and applied mathematicians into biology. The language barrier between these scientific disciplines presents an enormous challenge in bringing sci-

entists from other disciplines to biology. Curiously, if biology is taught as an informational science, the language barrier can be greatly ameliorated. Computer scientists and applied mathematicians must bring to biology the ability to acquire, store, analyze, model, and ultimately disseminate the enormous amounts of information now being deciphered at all three levels of biological information.

The fourth and final paradigm change relates to the universality of biological information and the unity of life. The Human Genome Project proposes to sequence the genomes of five model organisms: bacteria, yeast, nematode (a simple roundworm), fly, and mouse. The genomes of the first three of these organisms are finished (9, 10, 11).[20] Remarkably, many human genes have identifiable counterparts (homologues) in bacteria, yeast, and the nematode. Therefore, one can study the function of these human homologues in biologically and genetically manipulable organisms to understand how these genes work and to delineate the informational pathways within which they operate. These insights can then be brought to human biology because of the common origin of all living organisms and the universality of their basic biological information pathways. It is proposed that the mouse genome will be finished by the year 2005, at which time we can use the mouse as a model system to understand complex traits shared only by higher organisms (e.g., nervous system, immune system, and so forth). Thus, the model organisms will be Rosetta stones for understanding human biology. Just as knowledge of the Greek language in the original Rosetta stone allowed the Demotic and hieroglyphic languages to be translated, so a knowledge of the bacterial, yeast, nematode, fly, and mouse genomes will allow the human genome to be deciphered.

In summary, four paradigm changes will propel us toward a systems biology that will be the launch pad for germline genetic engineering:

- biology is an informational science;
- global tools are the keys to deciphering biological systems;
- computer science and applied mathematics are critical to deciphering and modeling biological information; and
- model organisms are the Rosetta stones for deciphering human biology.

Germline Genetic Engineering: Simple and Complex Traits

Some human traits may be dominated by a single gene—examples include susceptibility to infectious diseases such as AIDS and certain types of cancer. This does not mean that the corresponding genes are not parts

of complex informational pathways, rather that they exhibit a dominant effect in these pathways. In the case of these simple traits, one could think about germline engineering once the technical and ethical issues have been resolved. The interesting question is, how many such simple human traits exist, and which are appropriate for germline engineering?

Complex human traits are encoded in many genes representing complex informational pathways. Thus, complex traits include most interesting human traits—the ability to learn, memory, consciousness, physical attractiveness, and so on. It would be inappropriate to consider engineering these fundamental human traits before we understand the informational pathways and biological networks that encode them. For some of these traits, that may take decades or more.

Germline Genetic Engineering: Ethical Issues

The general public has a general concern, perhaps even distrust, about where human genetics (and the Human Genome Project) is taking us. This distrust arises, in part, from a vague apprehension about where science is taking society (e.g., weapons of mass destruction, the ambiguities of the benefits of atomic power, and so on) and in part from a conviction that genetic engineering of humans is unnatural and therefore wrong. To think rationally about ethical issues in germline engineering requires a basic understanding of inquiry-based analysis and a general scientific (biological) background. Most citizens lack one or both of these educational experiences. My own feeling is that scientists can play a catalytic role in educating society in these regards by making a commitment to helping school grades K–12 science education. Children are excited by hands-on, inquiry-based science experiences, as are their teachers. If all scientists were to make a commitment to improving K–12 science education in their local communities, we might eventually have a society capable of thinking analytically and rationally about the challenges and opportunities of science—including germline engineering.

This education of society is essential, because the Human Genome Project will be a launching pad for understanding systems biology, and once the technical and ethical issues surrounding germline engineering are resolved, humans will be in a position to direct their own evolutionary changes—for better or worse.

DANIEL KOSHLAND, JR.

Ethics and Safety

From what I read in the press about the state of human germline genetic engineering, there is a large vocal group that says, "Scientists are the heroes of today; they brought us automobiles, pesticides, genetic engineering." And then there is another group, equally vocal, who say, "Scientists are the villains of today; they brought us automobiles, pesticides, and genetic engineering."

Some say that genetic engineering opens an enormous vista for mankind, and others say it's the beginning of a catastrophe, that even a small step such as curing a defective gene is also the first step down a slippery slope to disaster. There is talk of a moratorium before we do any more work on cloning, and there is fear of doing anything to the human genome, even curing a genetic defect.

All agree, however, that no serious catastrophe can result if we start thinking about the subject. Pericles in the glory days of Greece said to his troops, "Let us march." I say, "Let us think."

My aim in this chapter is to tackle the subject of safety and ethics. Unfortunately, there are probably as many ideas about appropriate standards of safety and ethics as there are readers. With so many different moral and safety standards in our population, my job is to try to pave the way to a possible consensus on these subjects. I shall start with safety. There is no such thing as absolute safety in this world, even though some in our legal profession believe that doing anything more dangerous than getting out of bed in the morning must have somebody responsible and financially liable. Yet most of us know that risks are relative and will take them if the potential gains seem to warrant them. So, perhaps a start on the design of safety standards in germline engineering is to ask that the technology be

no more risky than the normal process of birth and conception. You might say that this is too tough a standard for a new therapy, because it doesn't allow room for error. But when you think it over, the normal process of conception and birth is really a very risky and dangerous proposition. If our criterion is that the children should turn out to be at least as good as their parents, my guess is that germline engineering will compete very well with those conceived the natural way. And if we make our criterion that the children should be up to their parents' expectations, then I think the engineered child may have a good edge over the child conceived the normal way.

Safety will require, first of all, that there be extensive experiments on animals to be sure that the techniques we would use to correct a defective gene carry only known risks and side effects and do not create any more problems for the mother than would a natural birth. We should expect the treated child to have a better chance of living a longer and more disease-free life than a natural child who has inherited the defective gene.

We must also figure out the dangers to the mother during the implantation, because natural childbirth can bring unforeseen complications, whether or not the child is engineered. Of course, the natural way of conception is going to be more fun, but we will be very solemn and only consider legal and moral risks. The safety issues are not solved yet, but the hurdles are technical and should be solvable in the not-to-distant future.

Now we come to the question of ethics. I looked up the Webster's dictionary definition of ethics. It says, "The study and evaluation of human conduct in the light of moral principles. Moral principles may be viewed either as the standard of conduct which the individual has constructed for himself or the body of obligations and duties which a particular society requires of its members." That struck me as pretty easy. If the standard of moral principles are my own, they are clearly the best. But the definition implies that everyone is entitled to his own set of moral principles. I guess the second part of the definition—that we have to find a set of responsibilities by which society will live—is a better goal. We should start, perhaps, with the question raised by those who say we shouldn't tamper with the germline. I frankly don't understand these people. Where are they living? We are already altering the germline right and left. When we give insulin to a diabetic who then goes on to have children, we are increasing the number of defective genes in the population. No one is seriously suggesting we refuse to give life-saving drugs to genetically disadvantaged people.

We attempt to treat cystic fibrosis, yet we are damaging the germline every day by doing so. Are we doing something terrible by ameliorating the illnesses that our compassionate policies of the present and past have helped create?

I had 20/400 vision when I was a child. If I had been living in the jungle and a saber-tooth tiger had come up fairly close, I would have reached out and said, "Nice kitty," then tried to pet it. I wouldn't have survived for long. But I was nurtured by parents who gave me glasses and kept me in a home free of saber-tooth tigers, so some of my children have inherited my bad vision. If that could be corrected in subsequent generations, should we prevent it?

There are technical difficulties to germline manipulation, and endless problems to be solved, but certainly the emotional statement, "We can't modify the germline," means we must stop all therapies and alter the survival of the less fit as well as block new future germline treatment. As I said at the beginning, "Let us think."

We next come to the question of cloning. There are a number of technical research problems here, too, that must be solved before we can really begin cloning, including, of course, the issue of safety that I mentioned above. But it would be foolish to ignore the high probability that technical problems will be solved. So, we should think about whether we should clone humans if we are able to. If we shouldn't, there's no use even doing the research to make it possible.

My first reaction when I heard the idea of human cloning was: "Oh, that's terrible. This time those scientists have gone too far." Then I started to think a bit, and I thought, "Well, if they had eight people just like me and we were all on the Supreme Court, it would really save the United States." So I thought further.

One of the complaints we hear periodically is that it is the egotists, the megalomaniacs, and the rich who will want to clone themselves, and that isn't fair or good. I am skeptical of this notion. Individuals, and particularly egotists, are usually interested in establishing a life record that is not only considerable but also unique. Some people like to win an Olympic gold medal, be an upstanding leader of the community, be a devoted patriarch of a family, and so forth. Others yearn to be a famous bank robber, or a charming swindler, or a distinguished artist—different goals for different souls, but unique for each. Would they really want to clone themselves? My guess is that people's demands for self-cloning will be very low.

The demand for gene enhancement therapy in order to try to give your children a better chance of success in the world will probably be very large. So outlawing the cloning of one's self seems to me a little like outlawing ballooning around the world. A balloon flying around the world may land in your backyard and do some damage, but the frequency of this really doesn't require that we pass a law against ballooning around the world. And similarly, we should not try to outlaw research on human cloning before any indication of widespread use is apparent.

Cloning, in my opinion, is likely to be most appealing to those who want to emulate someone more clever or more handsome or more athletic than themselves. That will require humility, not egotism. One is saying, "My children will be better with somebody else's genes rather than mine."

Let us imagine an infertile couple faced with the need for artificial insemination. If that's the only way they can get a child, would they be better off taking a natural child with a stranger's genes than a clone from a known person of the family who led a commendable life? As we know, children of even the best parents can turn out to be quite peculiar disappointments. Some just don't care to study and go to college—the same college that Dad and Grandpa or Mom and Grandma went to. Or some child of a long line of clergymen will decide to go into the theater and disgrace the family and run around with loose people. Or others smoke pot and live a wild life and become president of the United States.

It would surely be safer and surer to clone good old Uncle Ebenezer, who paid his bills, went to church, stayed married to the same woman, and voted the straight party line all his life. That would certainly be better than taking part in the gene lottery.

On thinking it over, though, I begin to worry that cloning might be the most conservative thing society could do. We'd all pick successful, humdrum, middle-of-the-road people to ensure that our children turned out all right. We wouldn't take a chance on the new, different, quite strange person that our children might become.

Before we take up the slippery-slope argument, let's think carefully about it, because all human progress can be negated by this argument. I'm sure that in the Middle Ages, if citizens in the time of Henry VIII had been told that serfs would someday ride around in horseless carriages and would someday have enough money to go off on their own and do crazy things like read books and vote, they would have said, "That will be the end of civilization, the family as we know it, and the village as we know it."

There is nothing you can think of that would be worse than having serfs loose all around the world getting educated and voting. It reminds me of the statement made in the early days of aviation by some of its opponents, "If God had wanted us to fly he would never have made railroad tracks."

What strikes me as missing from the doomsday scenarios regarding the ethics and safety of human cloning is the incredibly gradual timetable of events if we allow it. We are not talking about an atomic bomb or a bubonic plague. Procedures for cloning will be expensive and individualized. If we had a few clonings, and people started abusing it, we could always pass a law and stop the procedures.

A few new people can hardly be threatening to society. On average, they would probably be no better or worse than the children who are now pro-

duced by statesmen, thieves, scientists, embezzlers, philanthropists, artists, and even politicians—in short, everyone who is now allowed to have children of their own.

If we do go ahead with germline engineering, as I think we should, I can't see any possible reason for not allowing enhancement therapy. We are facing monumental problems with the population explosion, environmental pollution, the shortage of fossil fuels, and the serious lack of leadership. Our science and our compassion prevents us from using survival of the fittest as a process of selection even though it has guided us through evolution up to this point. Should we turn our back on new methodologies that might bring us smarter people and better leaders who are more responsible in their lives? It's going to be tricky, but it seems silly to shut our eyes to a new technology like this.

If, for example, we could clone an Abraham Lincoln or an Einstein or a Beethoven, should we say No? I'm going to use dead people just to illustrate the kind of people to consider, but I'm not hinting we have their DNA. If we could help the common man have children who could more easily get jobs and do better in a computer society, should we say No?

In a democracy, the government of the people must make the final decision on genetic engineering. But we need to discuss how intrusive the government should be in individual matters of genetic engineering and in the cloning of people. If an ordinary person like me wants to clone Franklin D. Roosevelt for one of his children, will he need a license? Will the government say, "No, you really run a terrible household. It's disorganized and you don't take out the garbage on time. Very bad early training for a Franklin Roosevelt."

Or even if they approve it for him, suppose twenty other people want to clone Franklin Roosevelt. Would that be too many in the population? We'd have to make some kind of ruling that if somebody is a Franklin Roosevelt he can't advertise that when he runs for office. If he said, "I have the genes of Franklin Roosevelt," that might get him elected even if he's no good.

If someone wants to clone Jack the Ripper, do we really have anything to say about that? The government is not allowed to say "yes" or "no" on having children now, but cloning presents new problems and, possibly, like driving an automobile, you will need some kind of a license.

So, I think there are major problems, but I think it would be absolutely ridiculous to stop now. It is correct to have a temporary moratorium. We need to think seriously about the consequences from all the angles, assembling people with different thoughts and ideas. We don't need political stump speeches by either scientists or politicians; we need to come together and say, "What are the major problems and how are we going to solve them?"

The easy slogans, such as "It will cure all genetic disease" or "It's a slippery slope to Armageddon" are much too superficial to guide our thinking. These genetic engineering technologies have real benefits and risks, and we'd better think long and hard about them.

I'm reminded of a story about a Maine farmer who'd built a nice-looking farm, in the rather hostile countryside. The farm was in a lovely valley, along a hillside. There were nice furrows plowed in the ground and a stone fence around the property, which clearly showed the generations of toil that had made it a beautiful farm. As the farmer was working, a minister came by and said, "My, that's a beautiful farm you and God have put together." And the farmer scratched his head and wiped the sweat from his brow and said, "You know, that's right, I guess. But you should have seen it when God was handling it alone."

This is an issue that tries men's souls. And all of us are going to have to work together to come to a reasonable solution. Genetic engineering has enormous possibilities for the benefit of mankind, but it also has real dangers of abuse. It is time to take steps, measured steps, to learn the kind of things that are necessary to make it safe and ethical. It is not time to stop even before we start.

MARIO R. CAPECCHI

Human Germline Gene Therapy

How and Why

In this essay I consider technical issues associated with the implementation of human germline gene therapy, as distinct from human somatic gene therapy. Since, in the latter case, only selected somatic cells are genetically modified, the effects of gene therapy are restricted to the patient. However, in germline gene therapy, all of the cells of the patient, including the patient's germ cells, receive the genetic modification. As a consequence, the newly-introduced genetic change(s) can be transmitted to the patient's progeny. This critical difference between germline and somatic gene therapy makes the issues associated with the merits and justifications for embarking on germline gene therapy much more complex. We need to consider the effects of the therapy upon the health and welfare not only of the individuals directly involved in the procedure, but also of their potential progeny who are not directly involved in the therapeutic protocol. Germline gene therapy is a controversial, complex topic; only through many open discussions of this topic by a broad spectrum of our society will we gain the wisdom needed for proper evaluation of the factors that must be considered before we contemplate initiation of these protocols.

Technical issues directed at evaluating the feasibility, the merits, the ratio of benefits to risks, and the safety of human gene therapy procedures should be part of this discussion. But I want to emphasize that even among the technical issues there is ample room for broad divergence of opinion, because new medical procedures are often introduced without an adequate data base to effectively predict all the consequences, even when there is extensive data from animal models.

Before discussing potential scenarios for human germline gene therapy, it is important to consider the goals of human germline gene therapy and where the pressures for its implementation are likely to arise. In many cases, the justification to use human germline gene therapy is likely to be made in terms of genetic enhancement, rather than in terms of ameliorating a medical problem resulting from a genetic defect. This is because for genetic diseases involving mutations in single genes, there are simpler, cheaper, and more effective means than the use of germline gene therapy to guarantee that a child will not receive a debilitating genetic defect. These methods rely on voluntary abortion of postimplantation mutant embryos or on selection of unaffected preimplantation embryos for implantation. There are rare cases where the above alternatives to human germline gene therapy will not work. Consider, for example, a parent that possesses two defective copies of a gene, such as the dominant mutation associated with Huntington's disease (HD). With dominant mutations, even a single copy of the mutant gene is sufficient to cause the disease. Under these circumstances, all of the embryos produced by that parent will give rise to children with the disease. Although the onset of this disease occurs in adulthood, it is extremely debilitating and leads to early death. Currently there are no known cures for this disease. The only current option for a parent with two copies of the defective HD gene to have healthy children is adoption. However, the drive to have your own biological children can be extremely strong. A small measure of this desire is evident in the extreme monetary costs, as well as physical and mental sacrifices, that parents are willing to tolerate to overcome problems of infertility. In vitro fertilization (IVF) clinics are a booming business. Since approximately 12 percent of couples are infertile, the services provided by IVF clinics will continue to be in strong demand.

It is conceivable that human germline gene therapy could be used to correct the defective Huntington's disease gene, thereby providing the parent who has two defective copies of the HD gene the option of having his or her own healthy biological children. Much of the technology that would be required to perform human germline gene therapy is available in private IVF clinics. Further, should parents desire to implement human gene therapy, and should they find an IVF clinic that is willing to undertake the procedure, there are no laws in place prohibiting it in the United States.

I have brought up this particular example of the use of human germline gene therapy to make two points. The first is that the pressure to initiate germline gene therapy will not likely come from governments or dictators with a desire to make a super race, but rather from parents who desire to improve the chances for their biological children to function effectively within our society. The second point is that, although germline

gene therapy is technically demanding, it is not outside the expertise of existing IVF clinics. With a coupling of recombinant DNA technology and the ability to manipulate preimplantation embryos, the core expertise required for doing human germline gene therapy would be at hand.

The example I have chosen—a parent with two copies of the defective HD gene wanting to have his or her own healthy biological child—is obviously a very special, rare case. But it is a plausible case, since over a dozen HD mutant homozygous individuals (i.e., with two defective copies of this gene) have been identified, and many of them have had children.[21] (Surprisingly, the life expectancy of individuals with two defective copies of the HD gene is not measurably different from that of individuals with only one mutant copy of the gene.) Should such a case arise, I believe that few people within our society would question the right of the parents to pursue human germline gene therapy as a means of having their own healthy child. We hold very dear the right of parents to bear their own children. For this reason, we have imposed very few restrictions on IVF clinics. As long as they are run professionally and safely, we allow them to implement new procedures with very few restrictive guidelines. As a result, new innovations are introduced at a remarkable pace by these clinics in efforts to overcome a myriad of infertility problems.

As previously stated, in many cases the proposed goal of human germline gene therapy will be "genetic enhancement." This does not mean that the child will be provided with new human powers, but rather be provided with alleles (i.e., different forms of a given gene) having desirable properties that are not present in either of the parent's genomes. An example would be resistance to HIV infection. Approximately 1 percent of people in our society show remarkable resistance to infection by the AIDS virus. The altered genes (alleles) responsible for conferring resistance to this deadly virus are being identified and characterized. Parents, neither of whom has alleles for such HIV resistance, may nevertheless desire their children to have such alleles. Should the AIDS virus, through recombination with another virus, acquire routes of transmission in addition to those now known, the demand for resistance to HIV would rise dramatically. Although multidrug treatment, particularly involving protease inhibitors, has made significant progress in arresting HIV infection, the ability of these viruses to rapidly generate drug-resistant variants is dramatic. It is still unclear whether the pace of new drug development will outrun the virus's capacity to generate new resistant variants. One can imagine many other examples of alleles present within the human gene pool that, could we choose our parents, we would be happy to have. This would include alleles that reduce rather than increase our risk of acquiring diseases such as diabetes, heart failure, stroke, cancer, neurological pathologies, and so

on. We must keep in mind, however, that susceptibility to disease is a complex process usually involving the interactions between several genes. Thus, the beneficial effects of alleles that cosegregate with a lower incidence of a disease, such as atherosclerosis, may depend on the presence of other alleles within the fortunate carrier. As a consequence, the transfer of that allele to a new individual may not confer the same benefit.

Before the cloning of the sheep Dolly by Wilmut and his colleagues[22] and the cloning of mice by Wakayama and his colleagues,[23] human germline gene therapy was a theoretical possibility, but its implementation faced so many technical hurdles that we could safely dismiss its potential use on pragmatic grounds alone. However, the demonstration that a nucleus from a differentiated cell could be completely reprogrammed by immersion into the cytoplasm of an enucleated oocyte and that this hybrid embryo could produce viable offspring has potentially eliminated the pragmatic arguments.

Vast experience with the mouse as subject has demonstrated that the safest, most versatile means of altering the genome in a mammal is to use gene targeting to modify an existing gene.[24] However, the process of gene targeting is not very efficient and must be done on a population of cells in order to allow the investigator to identify the rare cells that carry the planned modification. Because of the need to work with populations of cells, it is not practical to do gene targeting directly on one-cell embryos, because these embryos can be obtained only in relatively small numbers. In mice, we circumvent this problem by using embryonic stem (ES) cells. ES cells, which can be cultured in vitro, are derived from the early mouse embryo and are pluripotent.[25] That is, they are not committed to a particular differentiated cell type such as liver cells, bone cells, nerve cells, and so on. When ES cells are returned to an early embryonic environment, they participate in making all of the tissues of the mouse, including the germ cells. Using this technology, a genomic modification introduced by gene targeting into mouse ES cells can be transmitted to the mouse germline. By breeding, we can then generate as many mice as we want with the desired genetic change which had been originally introduced into the ES cells. Gene targeting in mouse ES cells is now used routinely, in hundreds of laboratories all over the world, to generate mice with designed genetic alterations. All of these mice, in effect, are generated by mouse germline gene therapy.

ES cells, however, are not an attractive option for human germline gene therapy. The reason that ES cells are a good route in mice, but a poor route in humans, is that genetic diversity plays a very different role in these two situations. In our experimental mouse population, we normally try to reduce genetic diversity. Any genetic alteration that we introduce into these

mice can then be evaluated on a uniform genetic background. For this purpose, we utilize inbred lines of mice that were generated by brother-sister crosses for over twenty successive generations. In the human population, on the other hand, we treasure genetic diversity. One of the pleasures of having children is that, with the exception of identical twins, each child receives a very different complement of genes from each parent, thus contributing to the child's uniqueness. With one's own children there is a pleasant blend of resemblances and differences.

In our desire to maintain overall genetic uniformity in our mouse experiments, we use the same starting ES cell line to generate many mouse lines, each containing a different genetic alteration. To use the ES cell route for human germline gene therapy, and also maintain the same degree of genetic diversity that is generated during normal human conception, would require preparation of individual ES cell lines from each embryo. This would be prohibitively labor intensive. However, the nuclear transfer technology used to clone Dolly provides an alternative route that could be applied to individual embryos (see fig. 3).

In vitro fertilization using sperm and eggs donated by each set of parents would be used to generate one-cell embryos (fig. 3). In culture, the embryo would be permitted to progress to the four-cell stage. The embryo would then be separated into four cells; three of these cells would be frozen for later use. These are procedures routinely carried out in IVF clinics. Each of these four cells, frozen or unfrozen, would have an identical set of genes and would be capable of generating a normal child. The fourth cell would be allowed to divide in culture until a million cells were generated, taking approximately twenty cell divisions to achieve this number. Different embryonic cell types would be present within this cell population, but this diversity should not affect the procedure. One million cells is an ample population size to permit the use of technologies, such as gene targeting, to introduce the desired genetic alteration into a subset of these cells. The subset of cells containing the desired genetic alteration would be isolated from the remaining cell population and carefully characterized to ensure that the genetic modification was accurate. At this point, the nucleus of one of the mother's oocytes would be removed and replaced with a nucleus from the expanded pool of cells containing the prescribed genetic modification. In this cytoplasmic environment, the modified nucleus would receive instructions to commence making an embryo. The cells would be allowed to divide in culture once or twice, and then the embryo would be surgically transferred to the mother's womb to allow pregnancy to continue. A child produced in this way would contain the genetic modification, introduced in cell culture, in all of his or her cells, including the germ cells.

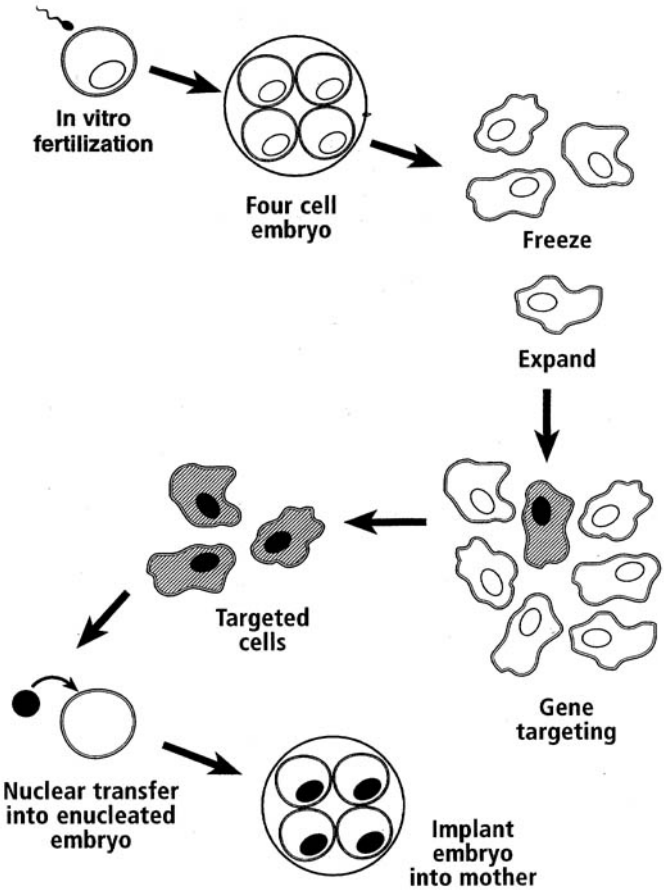

Figure 3. A scheme for human germline gene therapy using nuclear transfer. The first step is to generate the one-cell embryo by in vitro fertilization. Next, the embryo is incubated for two cell divisions to generate the four-cell embryo. The zona pellucida is removed and the four cells are dispersed. Three of these cells are frozen for later use; the fourth is expanded in culture to produce a population of cells to be used for gene targeting. A clone of cells, containing the desired genetic modification, is isolated and synchronized in culture to arrest them at Go. A nucleus from a cell containing the desired genetic modification is then transferred into an enucleated embryonic cell, this being any of the three original embryonic cells frozen in step 3. In the new cytoplasmic environment, the nucleus is reprogrammed to initiate embryogenesis (I. Wilmut, A.E. Schnieke, J. McWhir, A.J. Kind, and K.H.S. Campbell, "Viable Offspring Derived from Fetal and Adult Mammalian Cells," *Nature* 385[1997]:810–13.). The embryo is cultured in vitro to form a four-cell embryo and then transferred into the mother's fallopian tube to allow development to progress from implantation, to formation of the fetus, and finally to the newborn child. Every cell in the newborn child, including the germ cells, will have the genetic modifications introduced in culture by gene targeting.

In the above scenario, I suggested using gene targeting to introduce the desired genetic modification. There are alternative procedures for introducing genetic modifications, which I will discuss shortly, but gene targeting has a number of clear advantages over other approaches. Modifications introduced by gene targeting take place at the gene's normal chromosomal location. The activity of a gene is normally controlled by the interactions of regulatory transcription factors with DNA sequences surrounding the gene. The pertinent DNA sequences can be located hundreds of thousands of DNA nucleotide base pairs away from the gene. Placing a gene in an inappropriate chromosomal environment can result in perturbation of the gene's activity or in no gene activity at all. Modification of a gene in its normal environment, on the other hand, allows the gene to be properly regulated so that it functions in the right cells, at the right time, and at the right level.

A problem with the use of gene targeting to introduce genetic modifications is that it is normally employed for only one modification at a time. With the view of being able to introduce many concurrent modifications, investigators are developing artificial chromosomes that could simultaneously carry many modified genes with their appropriate regulatory sequences to ensure proper gene expression. This technology is currently in its early infancy but has a potentially promising future.

A potential problem with the use of artificial chromosomes as a route for human germline gene therapy may occur in the second generation. Pairing of chromosomes is an important step during meiosis (i.e., during the formation of germ cells). To ensure proper chromosome pairing, two artificial chromosomes can be introduced during the human germline gene therapy procedure. This will also ensure that each germ cell will receive one artificial chromosome. However, in the second generation, the only way to ensure proper chromosomal pairing is for both parents to contribute related artificial chromosomes (i.e., capable of pairing) to the embryo. The inability of chromosomes to pair may lead to sterility. Should this be the case, the problem may be solvable in an IVF clinic by introducing the artificial chromosome into the oocyte (female egg) or spermatocyte (precursor to the sperm) of the parent that does not harbor the artificial chromosome.

Whereas the ethical issues associated with human germline gene therapy are more complex than those of somatic gene therapy, some of the technical hurdles are actually less complex. Though considerable effort has gone into somatic gene therapy, the success has been meager. Three major obstacles have been encountered: gene delivery, gene expression, and immunological nontolerance. For example, if the genetic defect results in the absence of a particular enzyme normally produced in the

pancreas, then the ideal somatic gene therapy protocol would be to deliver a nondefective gene encoding the enzyme to a majority of the pancreatic cells. Further, gene activity in the pancreas would be modulated in a normal manner in response to metabolic need. Instead, what is often observed is that a minority of cells of the appropriate tissue receive the gene and further, that the transgene (gene of exogenous origin) is expressed at suboptimal levels because it is located in a foreign chromosomal environment. However, this small amount of gene product is still sufficient to elicit an immune response, so even what little that has been produced is cleared from the body. These difficult technical hurdles would not be encountered in germline gene therapy since the altered gene would automatically be delivered to all cells in the body. If, as already discussed, gene targeting were used to introduce the genetic alteration, then the altered gene would also be in the proper chromosomal environment to ensure proper expression. Finally, since the gene is likely to be expressed during fetal development prior to the establishment of the host immune system, the altered gene product will be recognized as self and not elicit an immune response.

A major consideration with human germline gene therapy is that the genetic alterations would be transmitted from generation to generation. It would become a permanent record within the family. Because human germline gene therapy would be mediated by human beings, and we are far from perfect, there is a potential for error. In addition, no matter how much thought went into the process, twenty or thirty years henceforth the procedure may appear naive in the context of the technology available at that time. Furthermore, whatever improvements could be made at that future date, they too would be subject to being outmoded. For these reasons, it is important that whatever procedures we might adopt for human germline gene therapy, they should, at the very least, be reversible. Fortunately, this can be accomplished.

An example of how genetic information added to the patient's genome could subsequently be deleted is illustrated in figure 4(A). This selective deletion takes advantage of a site-specific recombinase known as CRE.[26] This enzyme performs recombination (i.e., exchanges) between specific thirty-four-base-pair sequences known as *loxP* sites. The consequences of activating CRE-mediated recombination between two *loxP* sites oriented in the same direction (i.e., head to tail) is deletion of all intervening DNA sequences (fig. 4[A]). Note that, in this approach, at the same time as new information is introduced into the germline, the *loxP* sites and CRE recombinase gene needed to reverse the change would also be introduced. This would, at the patient's discretion, allow subsequent deletion of all information introduced into his or her germline, leaving only one *loxP* site behind. This single *loxP* site does not have a coding or regulatory potential

on its own and therefore could be placed within the genome so that its presence remains neutral. The CRE recombinase could be accompanied by control elements to allow it to be activated in response to a drug taken by the patient, which would result in deletion of essentially all of the added the information from his or her germ cells. Thus, the added information would not be transmitted to subsequent offspring.

For other experimental objectives, we have tested this procedure in mice under conditions designed so that the exogenous information flanked by the *loxP* sites was automatically deleted from the germ cells in the first generation of mice.[27] Under these circumstances, the genetic alteration was restricted to the somatic cells of the first generation mouse and not transmitted to any progeny. We tested over 100 second-generation offspring and none received the exogenous information, which was, by design, intended to be deleted. As planned, however, the CRE recombinase was not activated in any of the mouse's somatic cells.

The procedure described above works to delete added information. Germline gene therapy may, however, require replacement of one piece of information with another. For example, we could replace the HD mutation with the normal sequence, or replace a more common allele with the allele that confers HIV resistance. Could replacement processes also be done so as to be reversible (i.e., permitting restoration of the original replaced sequences)? The answer is yes, one approach to this end being outlined in figure 4(B). The open arrow in that figure represents an exon (coding sequence) of a gene containing the sequences that we want to replace (the HD mutation). It is drawn as an arrow because exons have a functional direction. In the opposite orientation, an exon loses its function, that is, it is not seen by the cellular processing machinery as an exon. The introduced targeted sequence (second line) contains the replacement exon (arrow with cross hatch) plus the original exon, with the latter in the opposite orientation, so that it is not functional. In addition, the gene targeting event introduces three *loxP* sites, two in the same orientation, the third in the opposite orientation, as well as the coding sequences for the CRE recombinase. In the absence of activation of the CRE recombinase, the only functional unit within this construct is the new exon (cross-hatch) that replaces the old. On activation of CRE, the new exon would be deleted and the orientation of the old exon would be reversed and therefore become functional again. The reason that the orientation of the old exon would be reversed is that CRE-mediated recombination between *loxP* sites in the opposite orientation (head to head) results in inverting the intervening DNA sequences, rather than deleting them. It may be asked how the CRE recombinase knows which pair of *loxP* sites should be recombined, but, in fact, the order of these events does not matter. In either case, the final

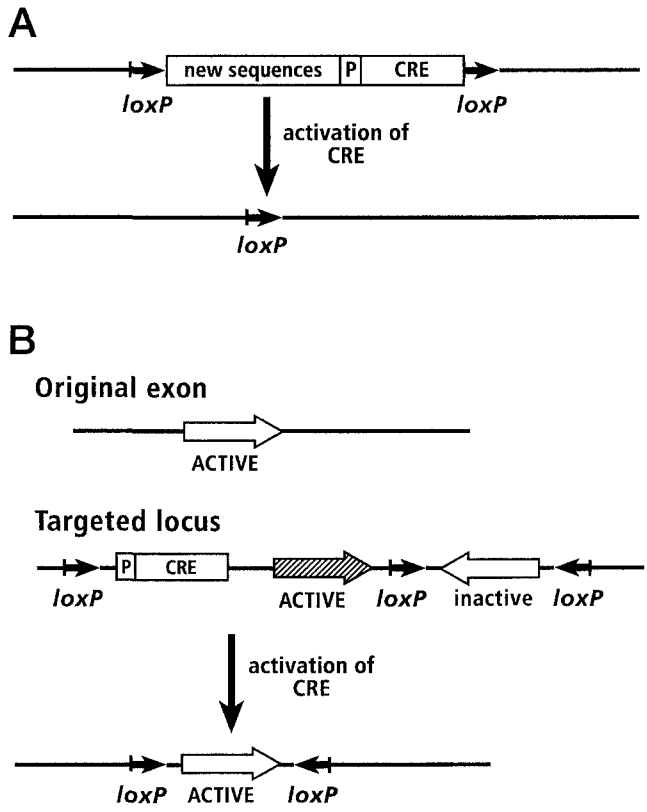

Figure 4. Human gene therapy can be designed so as to be reversible. A: An approach permitting deletion of added information from the germline. The new sequences added by the germline gene therapy procedure could encode a single gene or multiple genes present on an artificial chromosome. These new sequences would also include the gene encoding the CRE recombinase. All of the sequences would be flanked with *loxP* sites oriented in the same direction. On activation of CRE, recombination would take place between the flanking *loxP* sequences resulting in the deletion of all of the intervening DNA. Activation of the CRE recombinase gene could be made dependent on a drug taken by the patient in order to delete the exogenous information from his or her germ cells. B: A procedure for reversing the consequences of a replacement reaction. In this sceme, rather than deleting newly added information, the objective is to revert to the original information which was replaced by the gene-therapy procedure. For simplicity, the scheme illustrates the replacement of one exon (gene coding sequence) with another. The top line represents the exon to be replaced. It is drawn as an arrow because exons have a functional direction. In the opposite orientation, an exon loses its function—that is, it is not seen by the cellular processing machinery as an exon. The second line represents the targeted locus generated by the gene therapy protocol. It contains the new exon (arrow with cross-hatch) which will replace the old exon, plus

(continued)

result of these two reactions is the same. It may be noted that continued inversion reactions can yield half of the cells with the old exon in the correct orientation and the other half with that exon in the opposite orientation. In further refinements of this scheme, the sequences of the *loxP* sites can be designed so that they allow the initial recombination reactions to occur, but discourage further reaction. With such refinements, the recombination reactions can be directed so that restoration of the original exon in the correct orientation is greatly favored.

Unless an error were made, it is difficult to envision a situation in which once a defective gene, like the one for Huntington's disease, had been corrected, it would be in the patient's interest to reverse the procedure. However, procedures involving the incorporation of alleles conferring HIV resistance may be more complex. Although such alleles do provide resistance to HIV, they might also compromise the immune system such that carriers of these alleles may be more sensitive to other, as yet undefined, pathogens. This latter case points out the importance of having a full understanding of the biology of a system before attempting to change it.

In summary, I have tried to underscore the fact that plausible scenarios can already be envisioned for methodologies by which human germline gene therapy could now be accomplished. I have also outlined examples of problems that could be approached by this technology. The contemplated procedures are not overly complex and are within the expertise of existing IVF clinics. Ironically, many of the technical hurdles encountered in human somatic gene therapy are obviated in the apparently more radical human germline gene therapy. I have also argued that any procedure utilizing human germline gene therapy need not be, and should not be, regarded as an inevitably permanent alteration but can, and should be, designed from the outset to be reversible.

The pressures to undertake human germline gene therapy are likely to come from the desire of parents to provide their children with improved opportunities to function more effectively within our society. While there remain many technical issues to be explored before germline gene therapy

Figure 4. *(continued)* the original exon in the opposite orientation so that it is now nonfunctional. The targeted locus also contains three *loxP* sites, two oriented in the same direction, and the third in the opposite direction, as well as the coding sequences for the CRE recombinase. In the absence of activation of the CRE recombinase, the only functional unit within this construct is the new exon (cross-hatch) that replaces the old. On activation of CRE, the new exon would be deleted, the orientation of the old exon would be reversed, and therefore the old exon would become functional. The orientation of the old exon would be reversed because CRE-mediated recombination between *loxP* sites in the opposite orientation results in inversion of the intervening DNA sequences.

is actually implemented in humans, it seems likely that most of these can readily be approached with animal models. Eventually, the difficult questions will not involve the methodology by which human gene therapy can be accomplished, but whether to initiate the procedures and, if so, for what purposes. The technology, though now relatively straightforward, is extremely powerful. With recognition of this power comes a responsibility for social deliberation to seek ways to ensure that human germline gene therapy can be used in productive ways that keep the interests of individuals and of society in balance.

W. FRENCH ANDERSON

A New Front in the Battle against Disease

At the center of this discussion of the potential for genetic engineering of human beings over the next twenty years is the question of germline gene therapy. Let me present my position at the beginning. I believe that it would be unethical to attempt germline gene transfer at this point in time. We have neither the scientific ability to do so safely, the medical knowledge to do so effectively, nor the ethical competence to do so wisely. However, we do now have the expertise to attempt in utero gene therapy of somatic cells and this new approach does offer a new front in the battle against disease.

Genetic engineering of human beings can be classified into four categories:[28] somatic cell gene therapy, germline gene therapy, enhancement genetic engineering, and eugenic genetic engineering.

Somatic cell gene therapy is a treatment procedure whereby a therapeutic gene is inserted into a patient's somatic (body) cells in an attempt to treat a disease. In contrast to somatic cell therapy is germline gene therapy, whereby the gene is inserted into the germline cells, the egg or sperm. Inserting a gene into somatic cells affects only the patient being treated, similar to when a patient undergoes surgery, takes a medication, or receives a limb prosthesis. However, with germline gene therapy, a gene is inserted into the DNA of an egg or sperm so that children of the patient will have the inserted gene. There are two proposed ways to attempt germline gene transfer. One is to insert the gene into the pre-embryo, perhaps even at the four-to-eight cell zygote stage. The other is to target germline cells in the fetus, child, or young adult. The technology to carry out either procedure in a safe manner does not now exist.

The third category, enhancement genetic engineering, would involve an attempt to "improve" or "enhance" a normal individual, for example by inserting extra copies of a growth hormone gene to try to make him or her taller. A line can be drawn between therapy and enhancement. Therapy occurs in response to illness, when a person is below what is considered a healthy state, and the attempt is to bring the patient up to normal. Enhancement is the idea of trying to go from "normal" to above normal. As I have discussed elsewhere,[29] I am strongly opposed to attempts at enhancement genetic engineering for a number of reasons: scientific, philosophical, and societal.

The final category, eugenic genetic engineering, is defined as the ability to modify complex human traits such as body structure, personality, intelligence, and so on. In 1982, when I put this classification scheme together,[30] I thought that eugenic genetic engineering was so difficult that modification of complex traits would not be possible for many decades. And yet, only seventeen years later, the incredible pace of gene discovery and genetic research is such that attempts to "redesign human beings" have become a distinct possibility in the next twenty years.

Ethical Considerations Involved in Human Genetic Engineering

What are the ethical considerations that should be taken into account before attempting a new therapeutic procedure with a human being? In 1980, John Fletcher and I attempted to answer this question with regards to somatic cell gene therapy.[31]

The medical abuses that occurred in Germany during World War II led to an in-depth analysis of what ethical rules should be followed before initiating experimental therapy with human beings. Beginning with the Nuremberg Code, a body of ethical guidelines has accumulated. Central to these ethical guidelines is Rule 3 of the Code:[32]

> The experiment should be so designed, and based on the results of animal experimentation and a knowledge of the natural history of the disease or other problem under study, that the anticipated results will justify the performance of the experiment.

Henry Beecher summarized the ethical considerations governing the initiation of a new experimental treatment with a patient by stating: "A study is ethical or not at its inception; it does not become ethical because it succeeds in producing valuable data. . . ."[33]

The report of the Belmont Commission[34] is the most definitive statement of the ethical guidelines that govern experimental clinical research. The Belmont report stressed that the paramount question to ask is: Is the risk/benefit ratio acceptable for the patient? To assist in assuring that this question is appropriately answered, the Belmont report recommended two new procedures which, although controversial at the time, are now considered mainstays of clinical research: the establishment of local review committees called "institutional review boards" that must approve any experimental procedure before it is carried out with a human being, and the requirement for a written informed-consent document.

For any new procedure to be carried out with a human being, whether it is a new surgical operation, a new drug, a new medical procedure, or gene therapy, the issues are the same. What are the potential risks for the patient? What are the potential benefits for the patient? Is the ratio of risks to benefits appropriate for the patient? These questions can best be answered, in most cases, by carefully-conducted studies in animals. Two categories of data need to be obtained: One, efficacy—will the new procedure be effective in treating the disease? And, two, safety—how significant are the risks of harm from the procedure itself? Whether the new procedure is medical, surgical, pharmaceutical, or genetic, these requirements need to be met. Thus, there are no unusual or new criteria for genetic engineering that are different from any other new experimental procedure.[35] The issue is to evaluate, on a patient by patient basis, the risk/benefit ratio.

The determination was made in 1990 by the appropriate government regulatory groups (the National Institutes of Health Recombinant DNA Advisory Committee [NIH-RAC] and the Food and Drug Administration [FDA]) that the animal and other data justified an attempt at human somatic cell gene therapy.[36] If we replace the phrase "somatic cell gene therapy" with "germline gene therapy," we can use the somatic cell gene therapy review process as a means to determine what needs to be done before an attempt at germline gene therapy should be approved.

Ethical Considerations Involved in Germline Gene Transfer

We do not have the expertise to attempt germline gene therapy.[37] There are three criteria that need to be satisfied prior to any attempt at modifying the germline of human patients.

First, there needs to be long-term experience with somatic cell gene therapy. Before attempting to manipulate the germline of human beings

by genetic engineering, we need to know what are the long-term consequences of carrying out somatic cell gene therapy in patients. At present, we have only limited experience with somatic cell gene therapy: nine years of experience with the first two girls that were treated in 1990 and early 1991, a number of cancer patients who have survived, and a few other surviving patients. But this represents only several dozen patients over a short number of years. We need to have experience for ten or fifteen years, with hundreds if not thousands of patients who have undergone somatic cell gene transfer, to be certain there will not be serious long-term negative effects. It is possible, though highly unlikely, that patients who have exogenous genes placed into their cells might have a very high risk for cancer ten years later. Lack of data does not constitute negative data. We simply do not know what the long-term risks may be from genetically engineering human cells. Consequently, it would be ethically inappropriate to attempt an irreversible and multigeneration procedure such as germline gene transfer without initially having long-term experience indicating that there is a low risk with somatic cell gene transfer.

Second, there needs to be a reliable, reproducible, safe procedure.

We read about new transgenic mice that have been developed, new "knock-out" mice that mimic human disease, and about Dolly, Polly, and other cloned and transgenic livestock. The impression is that it may be a simple step to go from germline genetic engineering in mice and livestock to germline genetic engineering in humans. This impression is incorrect. Ninety-five to 99.9 percent of all "engineered" embryos are damaged; most are lethally damaged and do not lead to live births, but even those that do are frequently deformed and later die. Even in mice, where separate inbred strains of animals can be optimized for each step of the procedure, the success rate has not improved that much over the past fifteen years. Only a few percent of animals are born as "healthy" transgenics, and these are the ones we read about in the press; the failures are often reported only in the scientific literature. In livestock, which are partially inbred, the success rate is down to less than 1 percent. In humans, who are totally outbred, the success rate with the present procedures would be expected to be extremely low. What this means in practical terms is that the vast majority of attempts at germline gene transfer would result in deformed or dead embryos. It would be unethical, I believe, to attempt such a procedure in humans until the success rate in animals is significantly improved.

Successes in the field of in vitro fertilization and reproductive biology are indeed impressive. It is becoming possible to take one cell from a eight-cell zygote and analyze it for a range of genetic defects. Perhaps, over the next twenty years, it will become possible to safely insert a functional gene

into one of the cells in a mammalian zygote and, thereby, carry out germline gene transfer efficiently. The technique would then need to be shown to be reproducible, reliable, and safe in nonhuman primates, since these animals are the closest to humans. If healthy baby monkeys carrying a functional gene can be born, then, I believe, it would be ethical to transfer the procedure to human beings for the treatment of serious disease.

It could be argued that injection of a therapeutic gene into a human zygote may be possible without any apparent ill effect, so why not try it? Unfortunately, one can only know that there is a problem when one knows how to look for it. But we do not know what to look for. The only way to measure an effect now, with our present state of ignorance, is either to have a gross defect or death. We simply cannot know what the effect is in the zygote when an exogenous gene is injected, whether we "see" any problems or not.

Third, there needs to be societal approval prior to the first attempt at germline gene transfer. Almost all medical decisions are made between the patient and his or her physician, whether it is with regard to tranquilizers for nerves or cosmetic surgery for personal pride. Our rationalization for this freedom is that "my body belongs to me." But our genes do not belong to just ourselves. The gene pool belongs to all of society. No individual has a right to intentionally change the gene pool without the consent of society. Thus, the final criterion is that there should be societal awareness and approval before germline gene transfer is initially attempted.

In Utero Gene Therapy

Expertise in the area of gene transfer has now attained a sufficient level to consider an attempt at in utero gene therapy.[38] A gene transfer procedure into the mid-trimester fetus would be into somatic cells, although there is a potential for a low level of inadvertent gene transfer into the germline cells. Therefore, the criteria outlined above concerning societal approval may also apply to fetal gene transfer. The purpose of developing in utero gene therapy is to attempt to treat those genetic diseases that cause irreversible damage before birth and for which there is no other therapy available.

My colleague, Esmail Zanjani, and I, together with our collaborators, have developed two different procedures as possible techniques for carrying out in utero gene transfer. After twelve years of study in sheep and monkeys,[39] we believe that there are sufficient animal data to consider developing clinical protocols.[40] To this end, we submitted two "preprotocols" to the NIH-RAC for discussion at their September 24–25, 1998, meeting. The committee agreed that the time was appropriate to begin

the discussion and that animal work should proceed with regular public review. We anticipate that it will be at least three years before sufficient data will be available to justify the submission of clinical protocols.

The two pre-protocols we submitted to the NIH-RAC can be summarized as follows. The first is in-utero gene therapy for the treatment of adenosine deaminase (ADA) deficiency. We propose a direct injection into the 13–15-week fetus of a retroviral vector carrying a normal copy of the human ADA gene controlled by human genomic ADA regulatory sequences. Because it is a direct in vivo injection, an occasional vector particle may enter an egg or sperm, thereby resulting in germline gene transfer. The magnitude of this risk will be determined by animal studies over the next two to three years.

The second is in-utero gene therapy for homozygous alpha-thalassemia. Homozygous alpha-thalassemia is a particularly tragic disease, because the fetus dies in utero and produces toxic symptoms in the mother. The standard therapy is an abortion at 24 weeks to protect the mother. We propose to remove blood cells from the fetus at 17–20 weeks, insert ex vivo a copy of a normal human alpha-globin gene controlled by human genomic alpha-globin regulatory sequences, and then transplant the gene-engineered cells back into the fetus. Because the gene transfer would occur outside the fetus in this procedure, there would be less danger of germline gene transfer, but the cell transfer approach is not as efficient as direct vector injection.

Because of the concern relating to inadvertent germline gene transfer in these in utero procedures, the ethical issues surrounding germline genetic engineering are now under active public discussion.

Conclusion

We know so little about the human body and so little about living processes, we would be unwise to attempt genetic engineering to try to treat, much less "improve," the human zygote or embryo. What our society may want to do 100 years from now is its business. It will not care what we think any more than we care what people 100 years ago thought we should do. However, it is our duty to go into the era of genetic engineering in as responsible a way as possible. This obligation means that we should utilize this powerful new technology cautiously until we learn its problems, and even then, use it only for the treatment of disease and not for any other purpose.

MICHAEL R. ROSE

Aging as a Target for Genetic Engineering

This essay is divided into three parts. I begin by discussing the interesting nature of the problem of aging, continue by looking at the new promise of aging research, and conclude by considering whether at this point aging is an appropriate target for genetic engineering.

The Problem of Aging

One perspective on aging is that it concerns death and when you get to die. Right now, in the United States, life expectancy averages about seventy-five years. If your're male, it's about four years earlier than that; if you're female four years later, which some might take as yet another indication of which sex is superior.

By contrast, we can look at the demographic pattern of a nonaging human population. Such populations don't actually exist, but we can estimate their properties using the low mortality rates of humans between the ages of ten and fifteen in the United States and other OECD (Organization for Economic Cooperation and Development) countries. The survival of this age group is better than that of any other, and if every American, irrespective of age, could have and maintain these optimal survival statistics, a cohort of such Americans would have a life expectancy of 1,200 years,[41] and a few people would live some 2,000 years. These are just numbers, since no one is now in a position to make people nonaging, but this simple calculation reveals that, if we didn't age, we'd have an order of magnitude greater life span. Yet it might be said, "Well, who needs more than that? Seventy-five years is plenty."

So, what is enough of a lifespan? There is a spectacular pediatric disorder known as Hutchinson-Guilford's progeria, which is thought to be a genetic disease. Sometimes this disorder is called "accelerated aging," though this label is controversial. Afflicted children live about ten to twelve years, with a variety of symptoms that become progressively more severe. They "look old," and come to lack the physical abilities even of children, but they remain cognitively normal. Could it be said that their lifespan is perfectly acceptable? Most dogs live about that long. Most rodents don't even approach such an age. Nonetheless, most people regard progeria as a tragically curtailed lifespan.

But why is the lifespan of a progeric tragically short, while that of the present average American is not? Do contemporary citizens of OECD countries live a perfectly appropriate life span? Do they enjoy their "God-given life span"? Would it be appropriate to extend present-day lives, or is this something too Promethean to contemplate?

Even if you aren't interested in when you die, you may still have some interest in how you die. It's one thing to imagine dying climbing Mount Everest or sky diving. It's another thing to die of cardiovascular disease, stroke, or cancer, which is how most of the elderly die. As time goes on, the health of the elderly deteriorates until, by eighty-five years of age, only 30 percent are ostensibly free of a major disease. And the elderly have any number of aggravating diseases like gout, diabetes, and impotence. As time goes by, it's not true that you're getting older but getting better. You are deteriorating.

There is much you can do to change when you will die. You can die sooner by a variety of pretty reliable methods: acute physical stress, hypoxia while climbing Mount Everest, hypothermia. Those are fast ways to die sooner. Almost as reliable, but somewhat slower, is smoking, but it has the fringe benefit of addiction to make you less likely to change your mind. Exposure to contagious disease is making a comeback thanks to HIV, though there are also resurgent disorders from the nineteenth century, such as tuberculosis and influenza. Still common are various sources of fatal injury, from driving without a seat belt to drunken navigation of watercraft. As long as we are willing to truncate our lives, we can certainly control when we die.

What is unclear is what we can do to die later. Many people suppose that, if they exercise fanatically for ten or twenty years, they're adding years to their life span. But there's very little evidence for that. Exercise does improve your short-term morbidity, your short-term likelihood of developing a variety of diseases, but it does not appear to radically transform your life expectancy. The nostrums and prescriptions gleaned from health magazines are not likely to change the essential numbers. As we get older,

after forty or so years of age, we are more and more likely to die, to contract a disabling disease, and to look bad in bright light. For the fatalist, this is as it should be, and everyone is entitled to this point of view. But for those who are interested in amelioration or extension of their lives, this prospect must seem pretty grim.

New Hope for Aging

Despite the scenario just sketched, there are reasons for thinking that there may be some new hope coming from basic biological research. In fact, it might be argued that aging is now a solved biological problem. We know why aging occurs, and from that we know how to shape it, at least on the level of basic science.

The solution to the scientific problem of aging is that aging is caused solely by a decline in the force of natural selection with increased age, in adult organisms that reproduce using eggs or seeds, which is what most organisms do. This seemingly enigmatic statement deserves some explanation.

Consider an organism that reproduces strictly by splitting in two as, for example, bacteria do. This organism practices binary fission, in the terminology of science. If, through successive divisions, the descendant cell lineages deteriorate, you have a process that's somewhat like aging, but the lineage eventually will terminate. For these organisms, aging and extinction are the same, so the process of natural selection is going to strongly select against aging. And it doesn't matter whether an organism is unicellular or multicellular. It's all the same. Sea anemones provide examples of multicellular organisms like this; quite a few anemones reproduce by strictly splitting in two, and they can live forever, with no signs of aging.

Humans, on the other hand, are organisms that grow from an egg or a seed into a mature organism that, in turn, reproduces using eggs or seeds. When this situation is considered formally, using mathematics, one can calculate the force of natural selection acting, for example, on American males at any particular age.[42] This calculation shows that the force of natural selection is very powerful at early ages. Evolutionary biologists know that this has produced a wonderful adaptation at these early ages, something we might call "health." But once reproductive age is reached, the force of natural selection progressively weakens, hitting zero around age forty, using the simplest assumptions. After this point, metaphorically speaking, natural selection does not care whether you live or die. This causes many males to panic and buy a sports car.

The only upside of this grim conclusion is that it can bring an understanding of the genetic fabric of aging. One possibility is that because the force of natural selection collapses later in life, mutations that affect us only then are unshaped by natural selection. Basically, any genetic garbage can accumulate as long as it doesn't alter our reproductive success. The other possibility—and this is an important issue for genetic engineering—is that of genetic trade-offs. It's also called "you can't get something for nothing." This possibility would come about by natural selection enhancing early fitness through genetic effects that are deleterious later in life. Something may be good when you're young, but bad later. Either or both of these possibilities can lead to aging and all it entails.

But this is just verbal gloss on mathematical theory. Let us consider the data. Most of the data on the evolution of aging are collected on fruit flies, partly because they're easy to study. The bottom line is that we test the validity of the evolutionary analysis of aging by manipulating the force of natural selection so that it postpones aging. If the theory were incorrect, we couldn't do this. But we can. The most elementary experiment is one where you discard the eggs of younger flies and thereby increase the age at which you first allow female fruit flies to reproduce successfully. When this procedure is sustained for many generations, the results are very consistent, as long as there is genetic variation to begin with. Postponing reproduction maintains the force of natural selection at high levels in middle age. Theory predicts that this should eventually cause the evolution of increased longevity. And it does. This has been the result in one experiment after another since I began them in the 1970s.[43]

For example, in an experiment that has been ongoing for about eighteen years, the average life expectancy has doubled, and the maximum life expectancy has slightly more than doubled. We are not just compressing morbidity by getting the flies to die closer to some natural limit. We are, instead, shifting the pattern of aging. Otherwise we wouldn't have doubled the maximum life expectancy.

We know many things about the physiology of the longer-living flies. They are much more robust than their controls. They can survive extremes of starvation and desiccation that kill normal flies. Both males and females can reproduce vastly more when they're older. They have much better endurance at the athletic level. These are not flies that do as little as possible for a very long time; their metabolic and sexual activity is considerably in excess of the meager lives of normal fruit flies.

These points undergird the contention that aging is a solved problem. We not only have essential theory; it has been validated by tests of its predictions. So, the problem of aging is something we can address in theory and resolve—at least in fruit flies.

How to Postpone Human Aging

But what can we do about human aging? How can we engineer postponed aging in humans? There are all kinds of possibilities that would be bad ideas to carry out. One is breeding humans for postponed aging. That would require the forced use of contraception by everyone under age thirty-five, if not forty. This is a *Nineteen Eighty-four* or *Brave New World* fantasy. Not enough people would cooperate, and the coercive system necessary would be worse than aging itself. Like Soviet socialism, it would mainly serve to make the alternative look attractive.

Another idea, which the French are fond of, is to use only human genetic data to unravel human aging. The basic problem with this is that you don't get enough information fast enough. Human genetics, on its own, will never advance as quickly as genetics that uses "model systems" such as fruit flies, nematodes, yeast, and bacteria. Among other difficulties, it is hard to arrange the human matings that are the most interesting scientifically.

Another procedure that would be inappropriate would be the untested injection of fly genes directly into humans. However well we know how the fly works, particularly its genes, we can't assume that all that knowledge will apply to humans. Tests with other mammals will be needed first.

And there is a final, more controversial point: Genetic manipulations that make the cells of our body capable of unlimited division are now becoming available. But what works for cells won't necessarily be beneficial for whole organisms, so I do not support this approach. Unlimited cell division, for example, raises the risk of cancer, even if cell-division controls are added.

Instead of these approaches, I propose the following scenario. Start work with simple animal experiments. We can identify more genes for postponed aging faster using invertebrate "models" such as the fruit fly and the nematode. Then, from those model systems, work must progress first to mice and then to humans. This is a multistage, multimodel approach to postponing aging in humans.

We have just mentioned fruit fly selection experiments that produced postponed aging. They are only the beginning. There are other manipulations one can use to postpone aging in fruit flies and nematodes. It is possible, for example, to manipulate diet and thereby change their aging patterns. In fruit flies, genetic engineering has been going on for almost two decades. In the nematode, one can use wholesale mutation as well as genetic engineering to postpone aging. With mice, we can select for postponed aging. Once you have mouse lines that have been selected for postponed aging, you can identify the specific genes involved and, very importantly, you

can start to work on physiology. It is not enough just to think genes; you must to think of inparting meaningful physiology to the organism, particularly if you are to avoid problems with side effects.

Once we learn enough about aging in the mouse, we will be able to genetically engineer postponed mouse aging. We are not at this point yet, but we could easily get there someday, and then some will undoubtedly say we should proceed to genetically engineer postponed aging in humans.

But there's another alternative. We might also figure out how to emulate the effects of genetic interventions using more conventional therapies such as oral provision of hormones or protein injections. This would be the more cautious strategy, and I think that at this stage there's a lot to recommend caution. For example, once we have shown that tweaking a particular hormone in a mouse gave postponed aging, we could try tweaking that hormone nongenetically in humans. Indeed, at present, there are a number of physicians having their patients try out hormone antiaging interventions before there are proper results in well-understood laboratory experiments or appropriate clinical trials. The fact that these people are operating more on hope than knowledge doesn't mean that someday we won't have useful hormone interventions for aging. The present approach suggests the need for more research at the preclinical level, but there are, in fact, very good reasons for thinking that conventional medicine may fail to address the problem of aging correctly. The conventional medical model is about the alleviation or amelioration of specific conditions, effects of specific pathogens, and specific genetic defects. That's the way medicine works. It cures disease.

But aging has no such disease status. We are all going to age. Approximately 70 percent of the United States population will die of an aging-related disorder such as cardiovascular disease, cancer, or stroke. Aging is not something weird. It's something that's predictably going to happen to us unless we get hit by HIV or a big RV on the freeway. So aging is not a disease in the traditional sense.

Aging is a failure of adaptation. In aging, you are seeing the effects of natural selection abandoning you. In aging, you are seeing the power of evolution by natural selection in reverse, namely, when it stops working. When you look at what an eighteen-year-old can do, you are seeing the power of what natural selection can accomplish. When you look at yourself in the mirror and you're sixty-eight years old, you're seeing what happens when natural selection just doesn't bother.

To address this kind of problem, you need different approaches. Serious antiaging medicine, if it can be called medicine, depends on addressing problems that involve many genes, some of only minor effect. These problems will require powerful, complex, and well-balanced interventions. But

that's not how medicine works; medicine is specifically targeted. One possible technological need created by the polygenic nature of aging is for artificial chromosomes, so that numerous genetic alterations can be brought together in one physical structure. Artificial chromosomes will allow the assembly of many genetic loci to do a variety of things that our aging bodies fail to do. What may be required is "genomic" engineering, well beyond genetic engineering.

The timing of intervention is an important issue when considering the genomic engineering of aging. One approach would be to wait until the last minute. So you are sixty-seven years old and you say, "Okay, Doc. Shoot me up with all the latest artificial chromosomes." A good thing about that is that you wouldn't pay any earlier physiological price for the treatment. All of the physiological costs would be paid at that time. On the other hand, there may be a lot of medical problems you can't solve at that point. At least with this last-minute, desperate approach you wouldn't have any effect on future generations.

Then there is the hard-core germline approach. Let's say you went after the gametes because you wanted your descendants to have the best possible genes. So right from the start—right from the zygote or close to it—you intervene. The advantage is that the benefits will go to all your descendants, but there's a disadvantage in that early problems associated with your artificial chromosome would be expressed through growth and development. It is very fashionable for genetic engineers to say, "Ah, yes, but we will only turn on those genes later." Well, indeed, they may be able to turn on transcription at high levels later, but there will still likely be some genetic side effects at early ages even though they tried to shut everything down until later years. There is also the problem of evolutionary instability, of permanently having in your germline an artificial chromosome that is simply not going to be as stable as a regular chromosome. And then, finally, you have the problem of possible homogenization, which is like all of us driving Toyota Camrys. If we all have exactly the same antiaging chromosome and, as it turns out, that makes us prone to infection by a virus we've not yet seen epidemiologically, then we could all be stricken and the consequences might be dire.

So it seems reasonable to conclude that hard-core genetic engineering presents us with some very substantial problems. A compromise might be appropriate. One such compromise might be to supply any artificial chromosomes to the adult body before aging really begins, in the hope of alleviating much of the damage of the aging process, so that when you do hit age sixty-seven or sixty-eight you're in relatively decent shape. Not all disorders associated with aging will be preventable using this kind of intervention, because some later medical problems may arise from growth

patterns established in the fetus, such as patterns of vascularization. However, this does leave the germline free, and it avoids deleterious effects during childhood. Therefore, early adulthood intervention is the most reasonable choice for prudent genetic engineering to postpone aging. Now, if only we could get people to quit smoking.

LEE M. SILVER

Reprogenetics

How Reproductive and Genetic Technologies Will Be Combined to Provide New Opportunities for People to Reach Their Reproductive Goals

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The Impact of In Vitro Fertilization

A singular moment in human evolution occurred on July 25, 1978, with the birth of Louise Joy Brown to Lesley and John Brown in the Oldham and General District Hospital in Oldham, England. Nine months earlier, a single egg had been removed from Lesley's ovary and placed into a small plastic dish by Patrick Steptoe. Sperm obtained from John Brown were added to the same droplet of culture fluid, and the dish was placed under the microscope where Steptoe's colleague, Robert Edwards, watched as fertilization took place. The fertilized egg was allowed to divide three times and was then placed into Mrs. Brown's uterus. At the end of July 1978, Louise Brown was born.[44] Why did I call the birth of Louise Brown a "singular moment in human evolution"? Medical science in the twentieth century has had enormous success developing cures for many once-fatal illnesses. Why should a cure for infertility—and an imperfect one at that—be singled out as more important than all of the hundreds of other medical advances that have occurred during our lives? Aren't cures for diseases that used to kill or lame children, in particular, more significant to our society?

I don't think a cure for infertility should be placed on a higher pedestal than the development of a polio vaccine or cures for childhood cancers. But this isn't what I had in mind when I used the phrase *singular moment.* Rather, it was the conviction that although in vitro fertilization, or IVF, was developed as a means for treating infertility, it will now serve as a stepping

stone to many reprogenetic possibilities that go far beyond its original purpose. By bringing the embryo out of the darkness of the womb and into the light of day, IVF provides access to the genetic material within. And it is through the ability to read and alter genetic material inside the embryo that the full force of IVF will be felt.

Most people are aware of the impact that reproductive technology has had in the area of fertility treatment. Louise Brown is already nineteen years old, and the acronym IVF is in common use. The cloning of human beings has become a real possibility as well, although many are still confused as to what the technology can and cannot do.[45] Advances in genetic research are in the limelight, with almost weekly identifications of new genes implicated in diseases such as cystic fibrosis and breast cancer, or personality traits such as novelty seeking and anxiety.

But what has yet to catch the attention of the public-at-large is the incredible power that emerges when current technologies in reproductive biology and genetics are brought together in the form of reprogenetics. With reprogenetics, parents can gain complete control over their genetic destiny, with the ability to guide and enhance the characteristics of their children, and their children's children as well. As the editors of *Nature* put it in 1996, "That the growing power of molecular genetics confronts us with future prospects of being able to change the nature of our species is a fact that seldom appears to be addressed in depth."[46]

The development of IVF marks the point in history when human beings gained the power to seize control of their own reproductive and evolutionary destiny. In a very literal sense, IVF allows us to hold the future of our species in our own hands. The possibilities that open up with the use of IVF as a foundational technology can be grouped into two broad categories. The first is the enhancement of reproductive choice. In addition to providing a means for infertile heterosexual couples to overcome their infertility, extensions of the IVF technology will soon allow single adults to reproduce completely alone (through the procedure commonly referred to as cloning) and homosexual couples to reproduce children that share their genetic inputs. Although these alternative methods of reproduction will never be used by more than a fraction of the population, they will provide a benefit to society as a whole by allowing this group to reach their reproductive goals and achieve happiness through the birth of children who will be loved and cared for.

The second category is based on the fact that IVF and its associated protocols will provide access to the genetic material within the embryo. And it is through the ability to read and alter genetic material inside the embryo that the full force of IVF will be felt ultimately.

Will the Technology Be Used?

Before I describe the reproductive and reprogenetic possibilities made possible by IVF, it is important to consider whether people would actually be willing to sever the link between sexual intercourse and babies in an attempt to achieve some sort of reproductive goal, also whether they would be able to find professionals willing to work with them on the task. It depends, of course, on what the goal is. There's a big difference between curing infertility, on one hand, and trying to make sure your child inherits your curly hair, on the other. More than 75 percent of Americans now feel that IVF is an acceptable solution to infertility, while many fewer accept its use for purely cosmetic reasons.[47] But there are many reprogenetic goals that lie between these two extremes. Where will people draw the line?

No matter where it is drawn today, it will almost certainly be drawn to include more reprogenetic possibilities in the coming years, and more still in later years. This is because breakthrough technologies are always viewed as alien when they first appear—many people are instinctively opposed to things they are not accustomed to. But as the physicians Kleegman and Kaufman observed in 1966:

> Any change in custom or practice in this emotionally charged area [of assisted reproduction] has always elicited a response from established custom and law of horrified negation at first; then negation without horror; then slow and gradual curiosity, study, evaluation, and finally a very slow but steady acceptance.[48]

The public's opinion of IVF has evolved in this very way. When news of its development by Steptoe and Edwards reached the media during the 1970s, there were editorials calling for the abandonment of all further research on "test tube babies." And when the first IVF baby was born, most Americans found the notion so bizarre that they couldn't think about using it themselves. Over the period of a decade, however, IVF has been transformed from an alien concept to a broadly accepted medical approach for treating infertility.

Let's consider the arguments that can be made against the possibility that IVF will be used for purposes other than the alleviation of infertility. One argument is that people will not be willing to subject themselves to an alien technology that separates sex from reproduction just for the purpose of providing their children with some advantage that they might not otherwise have. Either ethical or emotional concerns, or both, could be at the root of this unwillingness.

A second argument concerns cost. Even if people had no objections to using the technology per se, they might not be willing to spend $30,000 or more for this purpose. A third argument is that even if people were willing to pay, they wouldn't be able to find clinics that were willing to provide the nonessential reprogenetic services that they desired. This could be because the technical expertise itself might not be available, or because those with the technical expertise have ethical objections to using it in this manner.

There is no doubt that in Western societies today, many people have a strong "gut reaction" against the use of reprogenetic technologies for nonmedical purposes. I observed this "gut reaction" when I asked a class of about 100 senior college students in a 1996 "Biotechnology and Society" course at Princeton whether they would ever consider the use of genetic engineering on their own children-to-be for any reason. More than 90 percent said no. But when I presented a hypothetical scenario in which genetic engineering might be used to provide absolute protection against AIDS, and posed the question again, half changed their minds. In a matter of minutes, they switched from rejecting a reprogenetic technology to accepting it.

What about the cost? Would $30,000 be too much to pay to ensure that a child would be born healthier or wiser in some way and better able to compete in the world? In fact, it is not uncommon for American parents to spend more than five times $30,000 to provide a child with four years of college education. And what is the point of this expenditure? It's to increase the chances that their child will become wiser, in some way, and better able to achieve success and happiness. If parents are willing to spend this money after birth—with no guarantee of a return on their investment—why not before? Parents might be willing to spend this money, you might say, but only the wealthy will be able to afford it. This notion is belied by the entry of so many middle-class couples into current IVF programs. In one well-known case, a Tennessee couple with a joint annual income of just $37,000 was able to come up with the money required for seven separate IVF attempts at pregnancy over a four-year period.[49]

Finally, there's the question of whether there will be clinics that are willing to provide these nonessential services. In this regard, there can be no doubt of the answer. IVF practitioners are expanding so rapidly that they are bound to reach a point where the pent-up demand from infertile couples is satisfied. When this point is reached, if not sooner, some will go looking for new customers.

Many practitioners, including those associated with major medical centers, may worry about political backlash from conservative political groups before proceeding. But consider the countries where IVF is being practiced

successfully today; consider as well the hundreds of private clinics that operate in the United States; consider the amount of money to be made; and consider the fact that as of January 1999 there are no federal laws that regulate the services that private IVF practitioners can offer to their clients. If there are people who desire reprogenetic services, there will be others willing to provide them.

"Cloning"

The first method of alternative reproduction that I will discuss is cloning, which became a real possibility with the announcement in February 1997 that a healthy sheep named Dolly had been cloned from an adult cell.[50]

On January 6, 1998, less than a year after this announcement, an unemployed physicist named Richard Seed told a radio interviewer in the United States that he planned to set up a private clinic for cloning human beings. The media response to Dr. Seed, with television coverage and front page newspaper articles, was as immediate and nearly as explosive as the response to Ian Wilmut's announcement of Dolly. And yet, the actual accomplishments of Dr. Wilmut and Dr. Seed are as far apart as can be.

Dr. Seed did once dabble in fertility work, but that was over a decade ago. At present, he has no laboratory facilities at his disposal, no private or public funding, and no demonstrable commitment from actual physicians or reproductive biologists to perform the work. Indeed, there is no evidence whatsoever—and much to the contrary—that he can set up a clinic, let alone carry out the cloning protocol on human cells. Indeed, Dr. Seed does not even seem to appreciate the overwhelming technical obstacles that currently lie in the way of human cloning.

So why has a man on the street who says he plans to clone human beings garnered so much attention, including a direct response from the President of the United States? I believe the answer lies not in what Dr. Seed himself can, or cannot, do, but rather in the startling realization by the American public, in particular, that human cloning may be pursued in private clinics, no matter how many government officials, scientists, and bioethicists argue against it in public.

Although human cloning is not feasible today, I have no doubt that it will become so one day. Dr. Wilmut and his group proved that the clonal production of a healthy mammal was scientifically possible. The transformation of this scientific result into a usable technology will almost certainly follow the same path as other science-to-technology conversions in the field of biotechnology. In the wake of Dr. Ian Wilmut's announcement, numerous researchers have jumped into the cloning fray, working on a

variety of different animals. Already, a more efficient method for producing cloned animals by somatic cell nuclear transfer (cows, in this case) has been published by an independent group,[51] and live-born monkeys have also been born by a separate cloning technique.[52] Over the next several years, it is very likely that the biotechnical community, as a whole, will resolve the technical problems associated with cloning, increase its efficiency, ultimately demonstrate its safety on a monkey species closely related to humans, and optimize the protocol to the point that it could be used to create human embryos for development into children. The question, in my mind, is not whether this will happen, but when.

The initial reaction to the announcement of Dolly's birth—from the public around the world—was one of hysteria. In retrospect, it's not hard to understand why the public reacted this way. In the absence of scientific understanding of what actually took place in Scotland, people had no choice but to visualize human clones through the images fed to them by popular culture—as full-grown replicate, but perhaps inferior, copies of human beings that already exist. Not surprisingly, these ghoulish images led to a sense of revulsion.

Even with an accurate scientific understanding of what cloning can and cannot accomplish, there are still many who adamantly oppose its human application. First, they worry about safety and efficiency—perfectly legitimate concerns, but ones that will surely be made moot, sooner rather than later, if we use past history of technological advances as our guide. Then they worry about the psychological well-being of the child. They fear that a cloned child will have a reduced sense of individuality, will not be treated with dignity and respect, and will be ostracized by society. To my mind, these fears are mainly based on an exaggerated expectation of what cloning can accomplish as well as an exaggerated notion of genetic determinism.

Right now, there are children being born somewhere in the world who will mature into a "spitting image" of one parent or the other, just by chance. Other children will express a personality and behavior that is a replica of one parent, just by chance. And for a small number of children born every day, it will be both: a "chip off the old block," as the old saying goes. Indeed, there are surely people alive today, around the world, who are actually more similar in both looks and personality to a parent than might be expected, on average, with a child who is a genetic clone! For this reason, observers will never know for sure (in the absence of DNA testing) whether a child is really a clone or just a parental look-alike.

As is so often the case with new reproductive technologies, the real reason that people condemn cloning has nothing to do with technical feasibility, child psychology, societal well-being, or the preservation of the human species.[53] The real reason derives from religious beliefs. It is the sense

that cloning leaves God out of the process of human creation and that man is venturing into places he does not belong. Of course, the "playing God" objection makes sense only in the context of one definition of God, as a supernatural being who plays a role in the birth of each new member of our species. And even if one holds this particular view of God, it does not necessarily follow that cloning is equivalent to playing God. Some who consider themselves to be religious have argued that if God didn't want man to clone, "he" wouldn't have made it possible. Should public policy in a pluralistic society be based on a narrow religious point of view? Most people would say No, which is why those who hold this point of view are grasping for secular reasons to support their call for an unconditional ban on the cloning of human beings. When the dust clears from the cloning debate, however, the secular reasons will almost certainly have disappeared. Then, only religious objections will remain.

But just because something can be done does not mean that it should be done. Will the cloning of human beings provide any benefit to society? The answer is Yes. It will provide a means for a small fraction of the population to achieve their reproductive goals, and by increasing happiness in these people, it will benefit society as a whole.

The desire to have biological children is a deeply ingrained instinct, second only to self-preservation. In the United States, couples unable to have children because of fertility problems can spend $30,000 or more to obtain treatments that can include in vitro fertilization, sperm donation, egg donation, or the services of a surrogate mother. Cloning, better labeled somatic cell nuclear transfer (SCNT), is one more tool that could be used by fertility clinics to help clients achieve their reproductive goals. As one example, SCNT may provide the only means by which a couple that is unable to produce either sperm or eggs could still have a biological child (or two, with one related to each parent). In such a case, the U.S. Constitution might legitimize this couple's right to nuclear transfer as a matter of procreative liberty.

As another example of who might want to use the "nuclear transfer" technology and why, I want to present a fantasy story that takes place fifty years in the future. It is the story of an American woman named Jennifer.[54] Jennifer is single, forty years old, financially secure, and the happy mother of a seven-year-old daughter from an earlier marriage. Even though she doesn't have a man in her life, Jennifer wants to have a second child. She knows that menopause is on the horizon, and she must act quickly. Many other women in her situation have used anonymous sperm donors to achieve pregnancy, but for Jennifer, a new option has become available. A reproductive clinic in Indonesia has recently begun to offer "nuclear transfer" as one of its many services. Although the price is steep at

$100,000, Jennifer knows she can afford it. And so Jennifer compares her options. She could use a sperm donor to fertilize her eggs, or she could initiate a pregnancy with one of her own cells. Which method should she choose? An anonymous sperm donor could bring all sorts of unknown genes and undesirable traits into her child so what would she gain? On the other hand, what would be so terrible about having a child who carried 100 percent of her mother's genetic material, if no one knew?

Jennifer makes up her mind to go abroad for a two-week holiday by herself. One month after she returns, her gynecologist confirms her pregnancy. He knows that she is a single woman, but he doesn't ask—and she doesn't tell—how her pregnancy began. Eight months later a newborn baby is delivered. Jennifer names her Eve. To the nurses and doctors on the maternity ward, Eve is just one more baby, just like all the other babies they've seen in their lives.

Eve will grow up in a loving household like many other children her age. Occasionally, people will comment on the striking similarity that exists between Eve and her mother. Jennifer will smile at them and say, "Yes. She does have my facial features." And she'll leave it at that. And then one day, when Eve is well into her teens, Jennifer will explain to her how her development began. And like other children conceived with special reproductive technologies, Eve will feel . . . special.

No matter what the laws are in Jennifer's home country, they will have no impact on her ability to use the "nuclear transfer" process at a clinic somewhere in the world where it is not illegal (it is illegal in most of the United States at the present time). But in the final analysis, SCNT won't make a bit of difference to society at large. No heads will turn when an SCNT child walks down the street, just as no heads now turn at the sight of a child born through IVF, egg donation, or artificial insemination. And as times passes, in the decades ahead, more and more individuals and couples who must now seek out sperm (or egg) donors to achieve pregnancy, will ask themselves, "Why not just use one of my own cells?"

Shared Genetic Motherhood through Embryo Fusion

Cloning is just one new way in which some people of the future will choose to reproduce. Many happily bonded couples view the birth of a child who brings together their genetic material as the ultimate consummation of their love for each other. And when barriers lie in the way of achieving this goal, many couples will do anything within their power to overcome them. A certain type of happily bonded couple, however, has never even consid-

ered the possibility of joining their genes together in a child. I am speaking, of course, of same-sex couples.[55]

Most people think it is biologically impossible for two unrelated women (or men) to both pass on their genetic material to a single child. But twenty years ago, a Polish embryologist demonstrated the feasibility of a protocol for accomplishing just this result in mice. Tarkowski reasoned that if very young embryos could be separated into individual cells which could then go on to develop independently as identical twins, triplets, or quadruplets, it should be possible to reverse the process and combine multiple embryonic cells to form a single animal. Tarkowski reasoned further that if cells originating from the same embryo could be brought together, it should also be possible to bring together cells from different embryos or even cells produced by different mouse parents.

Tarkowski's simple method worked like a charm, and since his original publication in 1961, the method has been repeated in hundreds of laboratories.[56] When embryos produced by pairs of mice from two strains with different fur colors are merged together, the success of the protocol is clearly visible in the offspring born. If an albino-strain embryo is mixed with a dark-colored one, the resulting offspring exhibit a patchwork coat with alternating areas of dark and white fur.

It is important to understand what is and is not happening inside a merged embryo from two sets of parents. At the cellular level, nothing happens. Each individual cell retains its identity; no fusion between cells takes place. But, as the embryo develops, the cells derived from different parents mix together and communicate with each other as if they are all members of the same team. And when the animal is born, every tissue within it—including the brain and gonads—is a mixture of cells from the original two embryos. Now creating chimeric mice is all well and good, but how do we know that we could actually accomplish the same thing with human embryos? I could remind you that mouse, human, and all other early mammalian embryos are virtually indistinguishable from each other and will almost certainly respond to manipulations in the same way. This is the logic that Steptoe and Edwards followed in their decade-long quest to perfect conditions for in vitro fertilization in humans.

But I don't need to rely on this logic at all, because mother nature has already done the experiment for us. Since the 1950s, more than 100 natural-born chimeric human beings have been identified by medical geneticists. Each of these people emerged from the fusion of two embryos that resulted from the fertilization of two eggs that the mother had simultaneously ovulated. We should not be surprised by this rare, but natural, process because we already know that embryos can spontaneously fall apart to form identical twins. If scientists can get two mouse embryos to stick together on

contact in the lab, then the same thing should occasionally happen spontaneously in a woman's reproductive tract.

In almost all respects, a chimeric person—like a chimeric mouse—is indistinguishable from other human beings. But, like mice, there are two ways to recognize some chimeric humans. If the two embryos that merged together had genetic makeups programmed toward very different skin or hair colorations, then the chimeric person could have a patchy complexion or hair color. Among naturally-born chimeric humans, this type of abnormality is rarely observed.

The second distinction occurs when an embryo with an XX genetic constitution merges with an embryo having an XY genetic constitution. During fetal development, the tissues that differentiate into the sex organs will be bombarded by conflicting signals. More often than not, signals from the Y chromosome predominate, and the individual develops normal, or nearly normal, male genitalia. But the gonads themselves will often develop as mixtures of ovarian and testicular tissues. In some cases, the combination of male and female signals can cause the external genitalia to develop into an intermediate configuration with an enlarged clitoris (or reduced penis) and other tissue intermediate between a scrotum and a vulva, with perhaps a shallow vagina or none at all.[57] In fact, intersex chimeras can have genitalia ranging anywhere from normal female to normal male. And perhaps surprisingly, intersex chimeras can be fertile and have children, sometimes as a father, sometimes as a mother.

It is only when their genitalia are what physicians call "ambiguous" that chimeric human beings usually are detected. However, for every chimeric person identified through ambiguous genitalia, there are likely to be four or more other chimeric individuals who have gone through life unnoticed. These include essentially all of the chimeric people formed by the merger of two same-sex embryos as well as many intersex chimeras who have developed as normal men or women.

With intentional embryo fusion, the possibility of intersex formation can be eliminated by pre-sexing the embryos and choosing two of the same gender. Thus, embryo fusion technology could provide a means for same-sex couples to combine their "bloodlines" in a single child, just as heterosexual couples do all the time.

Reprogenetics

Amazingly, as the world's attention has been focused on the prospect of so-called human cloning, other powerful technologies with a much greater potential for altering the nature of the human race have been developed

without much fanfare over the last twenty years. This enormous potential will emerge when current technologies in reproductive biology and genetics are brought together in the form of "reprogenetics." With reprogenetics, prospective parents will gain the power to select which of their genes to pass down to their children and whether to add in other genes to protect their children from diseases, both inherited and infectious.

Already, embryos produced in the laboratory can be genetically screened so that parents can begin their pregnancy with one free of a particular disease—such as cystic fibrosis or Tay-Sachs disease. And, in fact, children have been born disease-free this way.[58] But this technology can just as easily be used to select for the presence or absence of any known gene. And within twenty years, we will know every one of the 100 thousand human genes. The implication of this knowledge is profound. It means that parents will be able to select genes that provide their children with resistance to what many consider to be less-serious diseases such as obesity, alcoholism, or clinical depression. Ultimately, it means that parents might be able to select for positive traits like height, happiness, or inborn talents in one realm or another.[59]

Some scientists don't believe that the technology of embryo screening will ever become this powerful. These scientists claim that the genetic component of these positive and negative traits is too complex and that the technology of embryo screening is not powerful enough to do such complex screening.

But these same scientists would have told you just twelve years ago that DNA screening of embryos would forever be impossible. Indeed, every scientist thought it was impossible, and now there are children alive today based on the use of this so-called impossible technology. Thirty years ago, scientists thought we might never be able to characterize all 100 thousand human genes, and now we are only a few years away from accomplishing the feat. Just five years ago, most scientists still thought it would be impossible to rapidly screen all those genes in any individual, and now the technology to accomplish this very task—based on DNA chips—is already in use. As the physicist and visionary, Freeman Dyson, says in this regard: "The human species has a deeply ingrained tendency to prove the experts wrong."[60]

But there is an inherent limit to what embryo selection can accomplish by itself. All it can ever do is allow a couple to choose from among their own genes to give, or not give, to their children.

Germline Genetic Engineering

A reprogenetic technology that will allow prospective parents to go beyond their own genes is called germline genetic engineering. It could

allow parents to enhance their embryos with genes that they themselves do not carry. Genetic engineering is already routine in laboratory animals such as the mouse.[61] and it has been performed with success in pigs, sheep, cows, and goats as well.[62] There is no limit to the kind of genes that can be added to the embryo. Genes from one species can be manipulated before they are placed into another to carry out their designated task. So a cow, for example, can be engineered with a manipulated human insulin gene to produce human insulin in its milk.

This ultimate reprogenetic technology has not yet been applied to human embryos for two reasons. First, it has not been very efficient. Second, apart from issues of efficiency or safety, the idea of manipulating human genes is deeply troubling to many people.

Once again, problems of safety and efficiency may soon be resolved. Indeed, probably the most important implication of the nuclear transfer technology is that it provides a means for solving the efficiency problem.[63] Thus, there is every reason to believe that genetic engineering could become feasible on human embryos in the near future.

What reason might people have for wanting to use this technology? One answer is to provide protection against disease. In fact, we can already imagine a way to use genetic engineering to provide absolute genetic protection against infection with HIV, which causes AIDS.[64] And as we learn more and more about our own genetics, it will become possible to develop more and more sophisticated genetic enhancements for parents to use to give their children other health advantages.

The Final Chapter: Extending the Human Mind

"Have you ever imagined what might become of our race in the future?," asked the bright young man. "Do you think future people could have intellectual powers far, far beyond our own?" The village elders shook their heads as they smiled in unison, seeming to say, "Been there, thought that." "No," they explained, "it is not possible. The problem, my bright young man, is that our brains are so unbelievably complex that any tinkering meant to improve one aspect of mental processing would surely diminish another. *We are the final chapter.* We are exactly what God intended us to be."

Beginning almost two centuries ago with Mary Shelley's *Frankenstein*, countless works of fiction have focused on the theme of humans who succeed in creating human life or enhancing known human life beyond its "natural" form. While the stories differ in detail, the moral is always the same: Anyone who tries to play God is not only doomed to fail but to cause

ghastly pain and destruction. We humans are the final chapter, these stories assert. We are exactly what God intended us to be. Given the complexity of our bodies and brains, not to mention our *souls*, there is not merely a possibility of unintended consequences for attempting to usurp God's power—there is a natural *law* to prevent it.

Although the creation of humanoids has a long history in literature, it was impossible for anyone—scientist or nonscientist—even to imagine the genetic enhancement of natural-born human beings before the discovery of the molecular structure of the gene by Watson and Crick in 1952. Since the 1970s, there has been a rapid increase in the number of science fiction writers who have taken a stab at this idea, often in ways much less fantastical and more realistic than previous portrayals of humanoids.

Nevertheless, the moral remains the same. In two excellent examples from this genre—*Brain Child* by George Turner[65] and *Beggars in Spain* by Nancy Kress[66]—genetic engineering is used to provide children with superior abilities. But—and there's always a but—these "superior" children are deficient in some way. In both novels, as in Philip K. Dick's *Do Androids Dream of Electric Sheep?*,[67] which gave rise to the film *Blade Runner*, genetically enhanced children lack empathy, and their "race" is doomed. In the 1997 movie *Gattaca*, the most fully developed, genetically enhanced characters are actually weaker in body and mind than the unenhanced protagonist and hero. Indeed, there is a common, if unspoken, implication in all these works that genetic engineering for the purpose of enhancement is, and always will be, morally wrong. And it's not just the fiction writers who moralize. Dean Hamer, one of the top scientists studying genetic links to such human behaviors as homosexuality, curiosity, and anxiety, agrees with this point of view in his recent book, *Living with Our Genes*.

What exactly is the moral objection to genetic enhancement? Well, that's not always clear. Writers' and scientists' views on this subject are laden with emotion; when all else fails, they fall back on the assertion that it shouldn't be done because *it won't work*. As Hamer says, "Using genes to select elaborate traits in children before they are born will *always* be an exercise in frustration because of the *inevitable* trade-offs that parents will have to accept."[68] The words *always* and *inevitable* leave little room for maneuvering, yet this respected scientist fails to shore them up with any logical argument.

The *law* of unintended consequences. Yin-yang. What goes up, must come down. The light that burns twice as bright burns half as long. And so on, and so on. These are the clichés that writers, social commentators, and some scientists have long used to pooh-pooh the idea that humans might someday succeed at creating or enhancing human life beyond its "natural" form. As the village elders said, "We are the final chapter."

Old clichés die hard. What goes up need *not* come down—anymore. The so-called law of inevitable trade-offs is based on religion or ideology, not science. This is not to say that there aren't sometimes unintended negative consequences of attempts to improve the human condition. Of course there are, and there always will be. But the twentieth century has witnessed a series of medical and technological advances that have greatly improved human health and increased longevity. We have gone higher and higher without stumbling.

But our minds are different, you might say. They represent the essence of humanity, and it's pure hubris to imagine that we could improve upon them. Really? What if the exchange between the bright young man and the village elders had taken place among early *Homo erectus* individuals, 1.5 million years ago rather than today? Since that time, a doubling in brain size has led to a massive increase in intellectual capacity, which has brought about civilizations in which most people are protected from the cruel hand of nature. The *Homo erectus* elders would have been proven wrong.

So why couldn't we evolve even further in the direction of increased intellectual capacity? Well, for one thing, it won't happen "naturally." The most important evolutionary consequence of civilization is that greater intelligence—no matter what its root basis—does not lead a person to have more children. And only genes that increase reproductive output are "naturally" selected. Thus, the natural evolution of intelligence has come to a grinding halt.

Nevertheless, I am convinced that further evolution of our minds will occur. It's just the driving force that will be different. Instead of evolving naturally, the present-day human species is on the verge of self-evolving. If our civilization doesn't self-destruct, and if our world is not destroyed by an asteroid, the human race has five *billion* years left on the planet earth before the sun burns out. That's a very long time. Can you really believe that we will never figure out how to enhance intellectual capacity *without* any trade-offs, when the technology is practically at our doorsteps today? If not in the next decade, what about the next century, millennium, or million years?

Of course, just because something *can* be done does not mean that it *will* be done. But the driving force behind self-evolution is as transparent as can be. Parents have always wanted to give their children all possible advantages in life, and what could be more advantageous than increased intelligence? And where there's a demand, there will be a market.

Not so, some say. The government will control the use of genetic technology. Look at the massive governmental effort to identify all 70 thousand human genes, an effort molded by public debate on the uses and abuses of the information obtained.

Incredibly, in May 1998, while no one was looking, the Human Genome Project was snatched up by a private biotechnical company that will do it faster, cheaper, and without any oversight whatsoever. How long will it be before clever scientists use the information generated in this project to develop reprogenetic technologies that meet the market demand, which is sure to expand along with the power of the technology itself, for genetic enhancement? Those who condemn any talk of cognitive enhancement as an act of hubris have it backwards. The real hubris is displayed by those who claim confidently that we are the final chapter.

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PART II

THE ROAD AHEAD

A Panel Discussion

This part offers a unique view of the feasibility and significance of germline engineering and a look at where the technology lies within our present medical, scientific, and societal landscape. In addition to the authors of the book's essays, the discussants included John Fletcher, a distinguished ethicist; Andrea Bonnicksen, a public policy expert; and Nobel laureate James D. Watson, codiscoverer of the structure of DNA and founder of the Human Genome Project. Gregory Stock, director of UCLA's Program on Medicine, Technology, and Society, moderated. Though this remarkable discussion took place before a large audience, presentations and questions from onlookers were avoided. The discussion's course went wherever the panel's exchanges led it. The spontaneity of the participants and their candor in addressing even the most controversial issues surrounding human germline engineering make this exchange as provocative and stimulating today as it was in 1998, when it took place at the UCLA symposium, "Engineering the Human Germline," the first major public forum where key scientists and educators openly explored the topic before the public.

GREGORY STOCK: Dr. Fletcher, you have a doctor of divinity degree, so I'd like to ask what role you feel religion plays in our evaluation of the propriety of germline engineering and other sorts of genetic technologies?

JOHN FLETCHER: Actually, I don't have a doctor of divinity degree. I received my doctorate at Union Theological Seminary in 1969, and in those days you studied ethics and received a doctor of theology degree

with a specialty in ethics. But so many of my colleagues who received the degree couldn't get employed that they petitioned Union, which then petitioned the Board of Regents of the State of New York to change the nomenclature, and by action of the Board of Regents we all became Ph.D.s. Also, in the interests of full disclosure, inthe late eighties, after thirty-five years of trying to hold together the beliefs of Christian theology and modern biology, I gave up the struggle and resigned from the Episcopal ministry and became a friendly critic of religion.

I am not an enemy of religion. I recognize its power for good and for evil. My view of religion is that it is an evolutionary program fulfilling a very important function: to make you aware that you're part of the whole. Human beings are the only species who are aware they are part of a whole, and that is an awesome insight that binds us all together. I think the concept of God blurs that insight for the most part, rather than magnifies it. Religion plays a powerful part in the development of peoples all over the world, especially in our culture, where religion is so vibrant and alive and where there are so many types of religious movements.

On the whole, religion plays a very conservative role in response to genetics. And it actually, in its worst features, makes people afraid and passive in the face of terrible things that nature and genetic roulette can do to children.

I think one of the greatest harms of some religions in the world today is the doctrine that unprotected sex is sanctified. The idea behind the doctrine is to promote unity between sexual love and reproduction, but unprotected sex is the greatest threat to women in the world. It's also a threat to men, but it's certainly a threat to women.

In my experience, very few deeply religious people are open to understanding biological evolution. It is not hard to understand why. Evolution by natural selection powerfully answers how we and all living things descended from one source, a tree of life that slowly evolved over billions of years. This answer offends many deeply religious people who attribute all power to a God who, they believe, created them and everything else as Genesis described it. The biblically literalistic churches wage "culture wars" against this answer and misinform children about the development of life on the planet. However, evolution need not offend an inquiring religious mind. It is a very large step from the question, "Why and how did living things come to be?" to "What is the meaning of life?" The second question involves choices between world views and ultimate loyalties, and Darwin's answer to the first question implies but does not dictate a particular philosophy

of life. Noting these differences, moderate and liberal religious traditions make room for evolutionary science in the anterooms of their theodicies and theologies. So, religious views of science and evolution create a spectrum of responses to human genetics and genetic technologies. Although conservatives lack the social power to block advances in human genetics, they have blocked federal funding of genetic research involving living human fetuses or embryos.

Public life in a democracy is like a large table to which parties willingly and openly come for discussion. There is a minority of the religious who shun this table. Among them an even smaller minority dangerously acts out their hatred of science. A so-called Army of God bombs abortion clinics. I know of a scientist in a well-known university who works with stem cells derived from electively aborted fetal tissue. He takes a different way to work every day because he is afraid that somebody with this mindset may harm him.

So, you have posed a complex question about the role that religion plays in evaluating germline engineering and genetic technologies. The answer is complex, but in the public affairs of science, religion is a force with which to reckon. Anyone who underestimates the power of religious groups in this nation is politically naive. If one is involved in the public process, the table had best be set so that all can come, express their views, and have a role in settling questions like germline genetic modifications. Neglect of religion will mean that before the end of the process, hostility will prevail, which comes back to harm you.

GREGORY STOCK: Thank you. I think it's going to be very difficult to come to a consensus on these issues, because they affect us so deeply and fundamentally. Dr. Bonnicksen, you've written about international perspectives on genetics. There are such different attitudes about germline engineering and genetic engineering in general; could you say a few words about the key differences that exist globally?

ANDREA BONNICKSEN: I can best answer this by looking at a few national perspectives, a regional perspective, and an international perspective, because many different voices around the world have been heard about germline manipulations. These voices have come to the forefront of national and transnational governments more vocally than they have in the United States, where the federal government has not created the opportunity to discuss the issues.

One example in Europe of what I would call a permissive climate is the United Kingdom, which has a licensing system for embryo research and in vitro fertilization. The law setting up this system has been in effect since 1990, and it leaves the door open for germline

manipulations and other medical innovations. It states that there will not be germline interventions unless they meet regulations, but this leaves the door open, so I would consider it permissive.

Other nations are permissive by default, not having a national law on embryo research.

And some are restrictive. There are two kinds of restrictive voices: one includes countries that have restrictive embryo research laws that are so broad they would, in effect, prohibit germline manipulations. This leaves the door open, because if embryo research were to reach the point where germline interventions were safe, then perhaps their application would be appropriate.

Another restrictive type has an embryo research law that specifically mentions germline interventions. Germany would be an example of a highly restrictive law. Its Embryo Protection Act has been in effect since 1990. Here there is concern for individual rights. but there is more distrust of the ability to draw lines against technological change. There is also a concern for the human genome as a common heritage of humanity.

On the regional level, the Parliamentary Assembly of the Council of Europe in 1982 issued a recommendation stating that there is a right to inherit a genetic pattern that has not been interfered with, except according to certain principles. What might those principles be? The Council of Europe produced in 1997 a bioethics convention now out for the signatures of the Council's member states. Twenty-two nations have already signed it. This convention looks for principles that would guide such things as the deliberate intervention in the human genome. A key phrase states: "An intervention seeking to modify the human genome may only be undertaken for preventive, diagnostic, or therapeutic purposes and only if its aim is not to introduce any modification in the genome of any descendants." This indicates a more or less closed door, but still only half of the member states have signed the convention.

Another international body is the United Nations Educational, Scientific, and Cultural Organization [UNESCO], which has a global rather than regional orientation. One-hundred-eighty-six nations signed the Universal Declaration on the Human Genome and Human Rights in 1997. This declaration was four years and nine drafts in the making. It was designed to balance individual rights with the promise of genetic inquiry for all people. It did not forbid germline interventions, so it left the door open. It did, however, call for further discussion about practices that "could be contrary to human dignity, such as germline interventions."

There are other organizations as well, but in the interest of time let me make a couple of summary points. First, national laws on germline gene therapy are caught up in broader laws on embryo research and assisted reproductive technologies. We cannot talk about germline therapy without considering the policies on embryo research. And much of the concern relates to the sanctity or the nonsancitity of the embryo. What the embryo is will determine what people believe about what should be done with it.

Second, there is no single approach to germline manipulations. There are polar worldviews, illustrated by differing policies in the United Kingdom and Germany, so this is not a simple matter to discuss. International documents have attempted to bridge these polar views, and the UNESCO declaration is an effective example of that.

Third, germline policies are efforts to protect human rights before the techniques have even been developed, and the result is an odd mixture of definitions and notions. If you look at the different documents and the national laws, you have to scratch your head a bit and say, "What exactly is being forbidden here? And when we hear about all of the things that were discussed today, are they or are they not forbidden?" This is one of the perils of advance regulation.

And a final point, these regulations do not deal explicitly with enhancement. They all deal with germline gene therapy.

GREGORY STOCK: Thank you. You mention how restrictive the laws are in Germany and in a couple of the other countries in Europe. Dr. Watson, you've spoken very eloquently about the legacy of eugenics and the abuses of Hitler. What are your thoughts about the impact that legacy has had on our perception of genetic engineering and germline engineering?

JAMES D. WATSON: I think people are frightened by the term *gene*, frightened that genes are powerful and can be used against people. The main message we need to draw is to keep, insofar as possible, the state out of any form of genetic decision. Consider what happened in Russia, where they essentially banned genetics because the concept of genetic inequality didn't appeal to them. Since there is genetic inequality of all sorts, it's denying reality.

In the case of the eugenics movement, genes are often used to justify racial, class, and religious prejudice, and in a very awful way. This left a legacy, particularly in Germany, which I think still hasn't really faced up to what they did.

When Benno Muller published his very popular book, *Murderous Science* [Cold Spring Harbor, N.Y.: Cold Spring Harbor Press, 1997], he

only received one review in all of Germany, and he hasn't been elected to any German academy, despite the fact that his work with Wally Gilbert on the lactose repressor was very major science. So Benno has simply been penalized for drawing attention to what happened in Germany.

I think the complexity of genetics makes regulation very difficult. For instance, the term *enhancement.* Should you restrict abortions only to serious genetic diseases? What may be serious to one family isn't serious to another. What's frivolous to some people isn't frivolous to others. Very few cultures are monolithic; and particularly in the United States it's hard to form a consensus for letting people go their own way.

I'm very afraid of the middle class deciding what's best for poor and unfortunate people. I think they're patronizing, and they distrust the notion of trying to improve human beings, because they think they're pretty well off. In reality, they're not really worrying about the people who suffer from what I call "genetic injustice."

Evolution can be very cruel. There's an enormous amount of variation that is there to create the variations that have been necessary in the past for survival in changing environments. We have quite a high mutation rate, so many people are born with very obvious defects where their genes don't let them function as well as other people.

I certainly was very conscious of eugenics and, particularly, the role of my own institution, Cold Spring Harbor Laboratories, in the eugenics movement in the United States. When we started the Human Genome Project, we decided to spend 3 percent of our money for the discussion of ethics, and I think that's been among the wisest money we've spent. We simply tried to co-opt as many people as possible into discussing genetics. I think, as you discuss it, you realize how difficult it is.

My principle here is pretty simple: Just have most of the decisions made by women as opposed to men. They're the ones who bear children, and men, as you know, often sneak away from children that aren't healthy. We're going to have to feel more responsible for the next generation. I think women should be allowed to make the decisions, and as far as I'm concerned, keep these male doctor committees out of action. The French are the perfect example of that. Their policies are a mistake. . . . Keep them away. . . .

W. FRENCH ANDERSON (interrupting): Am I a good example or a bad example?

JAMES D. WATSON: You're a terrible example of trying to tell other people what to do. We will not know whether things work perfectly. You

sounded so conservative I just couldn't believe it. We are going to make mistakes in this world. Mistakes are made all the time. Someone gets a bad surgeon and they die. If the surgeon continues to make mistakes, he loses his license, and at least you know where he is. Some people are going to have to have some guts and try germline therapy without completely knowing that it's going to work.

It seems obvious that germline therapy will be much more successful than somatic. If we wait for the success of somatic therapy, we'll wait until the sun burns out. We might as well do what we finally can to take the threat of Alzheimer's away from a family or breast cancer away from a family. The biggest ethical problem we have is not using our knowledge, . . . people not having the guts to go ahead and try and help someone. We're always going to have to take chances.

It seems to me the question we're going to have to face is, what is going to be the least unpleasant? Using abortion to get rid of nasty genes from families? Or developing germline procedures with which, using Mario Capecchi's techniques, you can go in and get rid of a bad gene.

Right now, abortion, unpleasant as it is, sounds to me a lot easier and more predictable. But assuming that research goes forward, you may reach a situation where people will say that germline modification is safer and causes less stress to the people involved. One doesn't want to justify a procedure on something you can't predict, but having good germline therapy to protect us if a terrible virus suddenly occurred on the face of the Earth might be a very good thing.

We could have these techniques on hand so that we could at least see that the children who are going to be born won't die of a new plague. It's common sense to try and develop it. I think the slippery slope argument is just crap. If you get a Hitler, nothing's going to protect us. Societies thrive when they're optimistic, not pessimistic, and the slippery slope argument sounds like one from a worn-out person who's angry at himself.

And the other thing, because no one has the guts to say it, if we could make better human beings by knowing how to add genes, why shouldn't we do it? What's wrong with it? Who is telling us not to do it? I mean, it just seems obvious now. I think, and Mario Capecchi knows all too well, that these procedures are difficult. But if you could cure what I feel is a very serious disease—that is, stupidity—it would be a great thing for people who are otherwise going to be born seriously disadvantaged. We should be honest and say that we shouldn't just accept things that are incurable. I just think, "What would make someone else's life better?" And if we can help without too much risk,

we've got to go ahead and not worry whether we're going to offend some fundamentalist from Tulsa, Oklahoma.

GREGORY STOCK: Well, I hope Dr. Watson's frankness and openness is a model for everyone on the panel. Let's try and get at the core of these issues in a very concrete way. Safety and reliability have come up a number of times, and Dr. Anderson has stated very stringent requirements—including primate testing—as to what would be safe. I'm not sure all his requirements have been met even for somatic testing, certainly not for some fetal therapies. Does anyone else have some thoughts about the levels of safety that are required and when we might achieve those? Lee?

LEROY HOOD: Mario would be more qualified. I have opinions but not facts.

GREGORY STOCK: Well, why don't you give an opinion then, and afterwards Mario can give us the facts.

LEROY HOOD: I agree with Jim [Watson]. I think science proceeds and succeeds by doing. And I think what we're talking about here are incremental advances with enormous implications. If we're shackled by "You can't do fetal research. You can't do this; you can't do that. . . ." Some of the laws that have come up to ban cloning would ban everything that has anything to do with the word *clone.* That includes DNA as well as cells. I think that's something we can't afford to have in our society. You need to be reasonable and rational. Yes, you should do animal testing, but how far you have to carry it I'm not certain.

Some of the well-known model systems will give us much of the information we need, but it would be a shame if we were really inhibited by society. Again, I agree with Jim [Watson]. The great thing about American society is its enormous diversity. It's the equivalent of what Mario [Capecchi] was talking about regarding genes. An implication of that is that people have to have the right to make decisions based on what their diversity is all about. If we follow that to its logical conclusion, I would say that we have unique opportunities to bring together the kind of things we've talked about today, and we can make enormous changes. In twenty-five years we'll be, as Mario [Capecchi] said, ahead of anything that we can conceivably imagine now.

I think the specific details of what we can do may be answered when we get to the point where we know exactly what tools are available. At that point we can formulate theories on how to proceed, rather than talking well before the fact and trying to set up abstract rules and regulations. So, how about some facts, Mario?

GREGORY STOCK: Mario, do you have any comments?

MARIO R. CAPECCHI: First, in terms of safety, the issues can actually be addressed in fairly simple organisms—for example, mice. How much damage do you do if you micro-inject? Those issues haven't been examined in detail because nobody has had reasons to address such questions. But if we have the impetus, such issues can be addressed. One thing I am afraid of is to set stringent guidelines saying you have to go through animal A, B, C, D, and E. Certain questions can be addressed in certain organisms, and other questions will have to be addressed in other organisms. For example, when you make transgenic animals of domestic quality, you find mosaics much more frequently than when you do it in a mouse. So, doing experiments in different species is of value. But that doesn't mean every time you want to do a protocol you should go through animals A, B, C, and D. What it means is that certain safety tests are done in different species but that most could be done in species such as mice. It saves money, it saves time, and, I think, limits the need for regulation. The criterion should be that you have demonstrated that the procedure is not doing harm. A remarkable fact is that we've been using recombinant DNA technology for twenty-five years, and there's very little evidence any harm has ever been done. That's quite remarkable compared to any other industry. So I think we should be proud that there have not been the catastrophes that people envisioned, and just march forward—but at the research level.

GREGORY STOCK: Thank you. Dr. Koshland, you had a response?

DANIEL KOSHLAND, JR.: I want to come in on the side of more hope and optimism. I was listening to French [Anderson] and it sounded to me that, based on the hazards and the problems, we should give up sexual intercourse for about ten years until we really understand what's going on. To be serious, when you look at something new, the benchmark for safety must be how hazardous the present process is. When you think of childbirth and conception, it really is a hazardous undertaking—let alone how the children grow up.

Absolute safety is never going to be possible. At a certain point, the advantages are going to be clear for an individual. What is good about cloning is that we're not doing it to everybody all at once; we're doing it incrementally. In the case of a childless couple, using a process that will give them a child means an enormous amount; it is very different from a couple with several children interested in a slight enhancement. Individuals are going to have to decide how much risk they'll take to try to get an optimal result. I think we need to be careful about flat prohibitions.

GREGORY STOCK: Dr. Anderson, you wanted a chance to respond?

W. FRENCH ANDERSON: Yes. I'm having a wonderful time, because having endured a considerable number of death threats when we pioneered somatic-cell gene therapy, and now facing another onslaught of these when we announce fetal gene therapy, to be attacked because I'm a fundamentalist from Tulsa, Oklahoma, is extraordinary.

It might sound funny, but I agree with what everybody says. I think the difference is that perhaps my perspective is slightly different in the sense, at least for somatic-cell, and it appears, for fetal gene therapy, I'm the guy behind the eight ball. If we produce a defective fetus, I'm the guy who's going to get sued, and I'm the guy who will have to face the parents and the press. So, yes, I'm a little more conservative than others.

GREGORY STOCK: Another aspect of this is that you had to go through some fifteen committees and present all sorts of evidence to Congress. It must be very difficult to convince officials to allow you to do what you're doing.

W. FRENCH ANDERSON: It does warp the mind a bit, yes.

GREGORY STOCK: Thank you. Now, John Campbell, I've noticed there has been a little sniping at you today. You've proposed a double-addition approach to germline engineering. What are your thoughts about the safety of such procedures?

JOHN CAMPBELL: It's clear that this engineering must be done in the safest way possible. Some of the safety issues are real, but I think some can be looked at as problems to be solved. The crucial factor is to understand the expression of our genes. If genes are expressed only in a very specific cell type, then some of the problems dissolve, especially where you're trying to eradicate a disease. If that construct can be kept silent beforehand, then you need only worry about what it will do when it is expressed in the cells you're trying to eliminate.

As far as keeping the addition silent, we have to study that, but it's the sort of thing that can be assessed. There are special reporter genes we can put in to make sure these constructs are not expressed in cells we don't want. We'll need empirical evidence of that. If they are expressed, you go back and redesign your control systems to add another lock or another safety feature If you can't do that, you say, "Well, that won't work. We've got other opportunities, and we'll just have to put that one back on the drawing board until we can make it safe."

JOHN FLETCHER: This is a question for Mario. I gather you don't agree with French that you would need to do germline gene experiments in higher primates; you think you could stop with the mouse.

MARIO R. CAPECCHI: No. I'm not saying that. I'm saying you don't need to do *all* experiments in primates. It would be good to do a certain number of experiments in nonhuman primates, which then establishes the protocol. Once you've learned what you can from that particular process, you move on. You have to be selective. The problem with bureaucracy is that you set a train of events in motion, saying you must go through these particular hurdles over and over, and it may be a waste of time and resources. So, I'm saying you must do some experiments in nonhuman primates, because otherwise you won't know. The biology may be different in a mouse and a primate, but it should not become a part of the bureaucratic protocol.

GREGORY STOCK: A key aspect of John Campbell's notion of double addition was the ability to turn the added genes on and off. Does anyone have a thought about whether that is really practical or could be practical within a decade or so?

DANIEL KOSHLAND, JR.: It seems to me that when you're repairing a defective gene such as a defective insulin gene, in the long run the more economical and safe method is going to be homologous recombination, which is where we excise the bad gene and put a good gene in its place.

I think there are a lot of clever ideas about the addition of an extra chromosome, and turning it off with a hormone and so forth, but by removing a bad gene and replacing it with a normal gene, you're really bringing back the normal person. Controls in the interactions and the secondary interactions with other systems are minimized. If you had a gene on an extra chromosome, you'd have to turn something off in the bad gene's transcription to be sure the good gene took over. That seems a lot more complicated than homologous recombination.

LEROY HOOD: Yes, I would concur. Further, I think an amazing thing is that the manipulations to do those kinds of experiments are actually much simpler in germline than in somatic therapy. If I had to project, I think fifty years from now we will be doing everything through the germline rather than in somatic tissues.

JOHN FLETCHER: I want to go back to Dr. Watson's appeal for gutsy investigators to go out and just do it. Jim, there's a distinction between being a fool for genetic science and a damn fool for genetic science. I would like to see the best investigators turn their attention to therapy. There's a huge discrepancy between what we can diagnose and what we can treat. The more excellent investigators we have involved in therapy the better. But there is a system out there that has evolved in clinical investigation and human experimentation that you need to respect.

And, although you didn't say it explicitly, the vision I got was that you wish that somebody would just go on and try it and be successful. And that's been tried, Jim, right here in this town, and it didn't work.[1]

JAMES D. WATSON: You know that was premature. It was twenty years ago. I'm just afraid of demanding a consensus of committees of elders to decide whether we should use a new technique. They are always going to say No. So you're going to be as dull as Germans who want the State to make all the decisions. I think the healthiness of America is keeping the State out of it, educating your people well, and not having cowboys doing things they shouldn't. One's not for that. If Edwards and Steptoe had needed to get the consensus of the American public to go ahead with their work, it would not have happened. That's what I'm trying to say. So we've got to be careful about demanding consensus. We should say that it's none of their business.

If there's a terrible misuse and people are dying, then you can pass regulations. That's how society goes. We're in the position of passing regulations without anything bad happening. That's a very different situation, and a very dangerous one, because you don't know your enemies and yet you're passing laws against them. Biology is so complicated that this is a very misguided way to go. I'm afraid of asking people what they think. Don't ask Congress to approve it. Just ask them for money to help their constituents. That's what they want—money to help their constituents. They don't want to deal with diabetes. They don't want Parkinson's. Frankly, they would care much more about having their relatives not sick than they do about ethics and principles. We can talk principles forever, but what the public actually wants is not to be sick. And if we help them not be sick, they'll be on our side.

GREGORY STOCK: There's certainly an extraordinary hesitance to regulate areas that are considered natural, even if they are known to be extremely dangerous. You had a comment, Lee?

LEE M. SILVER: There's an interesting analogy from the fertility field. Until 1992, men who could not produce motile sperm were completely infertile, and nothing could be done for them. But, in 1992, they tried a completely untested technique, which was to inject sperm directly into the oocyte, and it worked. It had never been tested on other animals but it worked. You got babies out. And within three years, not knowing anything about long-term effects, 80 percent of the fertility clinics in the United States were using this technique.

It's important to understand the driving force here. There was a demand from infertile individuals whose only way to have a child was to use this technique, and fertility clinics met their demand using an

untested technique, and children were born from this technique—the oldest ones are not more than five years old. That gives you a sense of what's going to drive this technology. There was a sense that this technique would work, that it shouldn't be bad. But they weren't sure.

GREGORY STOCK: Let's shift gears a bit and discuss genetic patrimony and the sanctity of the human germline. It has been said that our germline is something owned by all of us and that it shouldn't be tinkered with. This was brought up earlier by Dr. Anderson. Do you have some thoughts about this issue, Dr. Watson?

JAMES D. WATSON: I think it's complete nonsense. I mean, what or who sanctifies? I can't indicate how silly I think it is. I mean, we have great respect for the human species. We like each other. We'd like to be better, and we take great pleasure in great achievements by other people. But, saying we're sacred and should not be changed? Evolution can be just damn cruel, and to say that we've got a perfect genome and there's some sanctity? I'd like to know where that idea comes from, because it's utter silliness. We should treat other people in a way that maximizes the common good of the human species. That's about all we can do.

Terms like *sanctity* remind me of animal rights. Who gave a dog a right? This word *right* gets very dangerous. We have women's rights, children's rights; it goes on forever. And then there's the right of a salamander and a frog's rights. It's carried to the absurd.

I'd like to give up saying *rights* or *sanctity.* Instead, say that humans have needs, and we should try, as a social species, to respond to human needs—like food or education or health—and that's the way we should work. To try and give it more meaning than it deserves in some quasi-mystical way is for Steven Spielberg or somebody like that. It's just plain aura, up in the sky—I mean, it's crap.

GREGORY STOCK: Does anyone else have anything they'd like to add to the notion of the germline having some sort of a sanctity that shouldn't be tampered with?

JOHN FLETCHER: The concept of genetic patrimony, or the way that it's put in Europe, is that every individual has a right to an untampered genetic patrimony. If you study the origins of this concept, it's really a way to smuggle natural law into the debate. Its roots lie in theological sources. This is a very powerful motif in the Council of Europe's deliberations. I neglected to say earlier, when I was talking about religion, that traditions of religion supply strong resources and inspiration for morality. They supply stories, parables, myths, and symbols that are tremendously important for civilization.

But the idea of natural law is one that I think is not a viable concept when it comes to the gene pool. One of the first thought experiments I did when I began thinking about this was: Suppose we really knew how to treat cystic fibrosis or some other very burdensome disease and didn't do it because of the belief that people had a right to an untampered genetic patrimony. Then, you met a person twenty-five years later and you did the Golden Rule thing and said, "Well, you know, we could have treated you for this, but we wanted to respect your right to your untampered genetic patrimony. Sorry."

It doesn't take a high-falutin' ethicist to realize that's just plain wrong. You violate one of the basic principles of morality, namely that you want to treat a person as you would want to be treated. And what person who is sick and suffering wouldn't want to avoid it, if it could have been done safely and effectively?

I have lived long enough in this country to know, and Dr. Anderson, who is also coming from experience, knows that, for the well-being of a germline therapy movement, you have to do it as well as you can the first time it is tried. If you get concrete results, you'll see considerable backing and filling in Congress. And those early results are going to come from privately-funded research efforts.

We live in two worlds now. There's a publicly funded world that Congress has got by the throat, and there is a privately funded world that comes through university funds, clinical earnings, foundations, private donors, and pharmaceutical and biotechnical firms. It is that world that is going to supply the money in order to get this done.

W. FRENCH ANDERSON: John [Fletcher] has presented, very eloquently, my exact feeling. Of course, the two of us have been working hand in hand for thirty years, so that's not too surprising.

The fact is that I'm the one who has been in a position to pioneer procedures. Because of the concern that if it's done wrong, the field will be set back, the criteria I've set for myself and the field are conservative. But, as I pointed out in an editorial in the Journal when we did the first somatic-cell gene therapy, if it was successful it would open the door for a vast number of protocols. We are now seven years later, and there are over 300 approved clinical protocols.

The same thing will happen, I hope, if we do the first fetal gene therapy correctly, which I am now proposing. If we are successful, it will open the door, and if nobody else does it, I'll be the first one that does germline gene therapy. But we're going to do it in a safe way, when the time is right, and not when it's premature.

GREGORY STOCK: I think that gets at the issue of how these things should be regulated, if at all. In vitro fertilization presents an interesting model where there are local regulations, sometimes very restrictive, sometimes very loose. There has been tremendously rapid progress in that field, and there are probably some risks as well. Do any of you have thoughts on this? Because there have been strong efforts to try and gain international consensus on a uniform approach of some sort.

JAMES D. WATSON: I think it would be complete disaster to try and get an international agreement. I just can't imagine anything more stifling. You end up with the lowest possible denominator. Agreement among all the different religious groups would be impossible. About all they'd agree upon is that they should allow us to breathe air. But even regarding food, their opinions are not in common. I think our hope is to stay away from regulations and laws whenever possible.

There were all these efforts to get laws about recombinant DNA in about 1977. We fought it, and thank God we did. Efforts like the Council of Europe are dull and ineffective, and all it will do is put Europe more in the backwater.

DANIEL KOSHLAND JR.: I agree with Jim [Watson] in the following sense: When you're dealing with something like global warming, that's a case where you want all nations to come together. In that case an international agreement is important.

With something like genetic engineering, it seems to me there isn't any great potential catastrophe. And I agree with French completely, that what we need to do is have some cases that are really good examples for the public, and then you may have to take some chances. Maybe it won't turn out perfectly, but I have a great deal of confidence in the people who are doing it, and in French's work, and I'm confident they will pick a specific case and do a good job. It seems to me the United States will be in the forefront of this research. We're more likely to carry it out successfully than almost any nation in the world. To try and get all the nations of Europe to agree with us, let alone all Africa and Asia, will significantly hinder us.

If we go ahead and set a successful example, most people will want to follow that example. We also have to set some priorities. For instance, I really loved Dr. Rose's talk, but I was really against putting any priority on lengthening our life span.

The one way I personally don't want to go is by dying of natural causes. I mean, who needs to be eating oat bran and sitting away from

a draft? I want to die in an open roadster going eighty miles an hour and getting hit by a truck. That's the way to go.

We're living long enough, and the bad thing at the moment is that some of us are not living so well in our current lifespan. We have bad diseases: arthritis, which is painful; Alzheimer's, which is emotionally awful. Anybody who has a good idea should be considered, and I thought John Campbell's ecdysone suggestion was just terrific in terms of getting at prostate cancer and breast cancer. One of the things scientists can do is to make priorities of the conditions that are going to be most important and most efficacious. And, of course, in a democracy, the people as a whole have to decide whether we're going to go ahead.

MICHAEL R. ROSE: Can I respond to that?

GREGORY STOCK: Yes.

MICHAEL R. ROSE: Some of your own [Dr. Koshland's] remarks contradict themselves in that . . .

DAN KOSHLAND, JR.: I never wanted to be consistent.

MICHAEL R. ROSE: You and Winston Churchill. Why not give people the choice? It's certainly not my argument that everyone should postpone their aging. But if, with this technology, we could actually do it for some people, that would be very attractive. And if you want to die next week in that roadster, going down Highway 405, that's great. As long as no one else dies.

GREGORY STOCK: You wanted to make a comment, Andrea?

ANDREA BONNICKSEN: Yes. I don't want to defend genetic heritage and genetic patrimony, so much as to comment that it suggests an alternative to the autonomy model that is prevalent in the United States by suggesting there's a collective model too, representing a more collectivist world view. The United States is part of a number of nations. As it develops its regulations and its models, it should keep in mind that there are alternative positions throughout the world.

Because we lack a regulatory model in this country, the more we can develop incremental policy from the clinics on up, from the scientists on up—to be able to work on these questions of when it's ethical to begin, at what stage safety is assured, at what stage the effectiveness is appropriate—the more that can substitute for governmental interventions.

Those in the scientific and medical community have a responsibility to try to develop their own working rules of thumb, and that's why this conference is so important, because you are suggesting that germline interventions might be coming about. Let us begin to think

about this in concrete ways, in ways that can be publicized and published, and we will be able to develop our own regulatory models that might preempt governmental regulation or serve as a model for it, if it comes to be.

LEE M. SILVER: If we look at the fertility reproductive technologies, this country is unique in that there are no federal regulations of IVF clinics. There are hundreds of private clinics that carry out IVF and, for the most part, there have not been catastrophes because the situation is self-controlling. If you had a clinic producing deformed children, it would very quickly be run out of business, and the doctors would go to jail.

I don't see why you need extra regulations for germline engineering. The IVF-clinic model in America seems to be working quite well for the most part. You can extend this, hopefully, to the further examples we've been discussing.

GREGORY STOCK: Well, litigation and liability is certainly a strong force.

LEE M. SILVER: Yes, exactly.

GREGORY STOCK: Dr. Watson?

JAMES D. WATSON: It was correctly said that this is the first gathering where people have talked openly about germline engineering. Partly, it was in order to get somatic therapy going that it was said, "Well, we're not doing germline. That is bad. But somatic is not bad morally." It virtually implied there was a moral decision to make about germline, as if it was some great Rubicon and involved going against natural law. I've indicated, I think, that there is no basis for this view.

So, we are fighting the statement that somatic is safe, therefore, germline is unsafe; whereas, in fact, if anything is going to save us, if we need to be saved someday, it's going to be germline engineering.

GREGORY STOCK: Dr. Watson, you had a large part in creating or making successful the Human Genome Project. . . .

JAMES D. WATSON: No. No. Lee Hood. He got the machine. Without him the sequence of the human genome would be just hot air.

GREGORY STOCK: Well, Lee Hood may have made it work, . . . but you were certainly involved in some *small* way. What I wanted to ask is this: If there is no Rubicon to cross with germline engineering, and some approaches have a greater possibility of success than others, is human germline work something we then need to be thinking about trying—at least at a research level—to see whether there are possibilities worth realizing? Should there be some sort of a project toward this goal?

JAMES D. WATSON: Well, I wouldn't make it difficult to do the experiments, which is what the proposed laws against human cloning would have done. [Those laws] could make it very difficult to do the sort of experiments Mario [Capecchi] would like to do on homologous recombination, which is simply "correcting" a gene. We've got to be very careful not to admit at the outset that we're three-quarters evil and a quarter good. I just don't see the evil nature of what we're trying to do.

Genetics, in many people's eyes, has a bad connotation of the State or others determining people's lives. Which is why, again, the State should stay out of it. My feeling is, the State shouldn't tell a person either to have it or not to have it. If the procedures work people will use them, and if they don't work or if it's dangerous, it will stop.

The real enemy is a preexisting genetic inequality which makes some people unable to function well in the world. Terrible diseases—that's the enemy. Whereas some people are convinced the enemy is the people who study the genes, that we are evil people. I don't think we're any more evil than the people who run this Music Department. You know? I don't know if we're better or worse. And I suspect we're deep down trying to respond to a long-term need, and the music people are making us happy by singing hymns, which cheers us up. We should be proud of what we're doing and not worry about whether we're destroying the genetic patrimony of the world, which is awfully cruel to too many people. And I think that that's what we're all trying to fight. French, I think you know we basically agree, but it's the image. I'm sure I will be misquoted by someone who's says I'm gung ho to go ahead and do it [human germline engineering]. I would do it if it made someone's life better. We get a lot of pleasure from helping other people. That's what we're trying to do.

GREGORY STOCK: Thank you.

JOHN FLETCHER: Since we are talking about regulation, I'd like briefly to review what university-based or industry-based scientists need to know.

Somatic-cell transfer research in humans is now regulated, in all of its phases, by the Food and Drug Administration [FDA]. What about crossing the line to human germline gene transfer experiments? The NIH's Recombinant Advisory Committee's [NIH-RAC] policy on intentional germline transfer is that it "will not now entertain" protocols with this aim. Obviously, much more research in animals must occur, as well as public discussion, to cross this line. Since germline gene transfer experiments will occur in gametes or embryos, the one area to watch carefully is research with embryonically derived stem cells. In 1994 Congress prohibited federal funding of any research that

would harm human embryos. But this ban does not apply to privately funded research.

If your research is privately funded, there are no federal legal barriers to deriving stem cells from embryos. One needs to know if state law permits this research, before submitting a protocol for the research to the Institutional Review Board [IRB]. If your institution has signed a Multiple Project Assurance with the Office of Protection from Research Risks at the NIH, you promise to abide by the regulations to protect human subjects, no matter the source of funding. The "protection of human subjects" issues do not apply to embryos, but to the persons who are sources of embryos to be used experimentally. The privacy of couples in infertility treatment or donors of gametes needs to be protected. A process of informed consent for donating embryos or gametes for research needs review and approval. Finally, there are some ethical considerations about the outer limits (14 days) of permissible embryo research and prohibiting any future uses of research embryos for implantation. The report of the NIH Human Embryo Research Panel and the British guidelines for embryo research provide guidance on these points. The important message for local IRBs is that it is not illegal to do privately funded embryo research, as long as the personnel, facilities, and equipment to be involved in this research are not substantially subsidized by federal funding. Research that involves putting genes into human cells or embryos requires the approval of the NIH-RAC and would also be regulated by the FDA.

JOHN CAMPBELL: Most of the research I envisage being done in the next five or ten years would be animal work. So, even if there was a prohibition on actually putting genes in human cells, it would not be decisive in inhibiting the research that needs to be done.

GREGORY STOCK: Dr. Watson dismissed the slippery-slope argument earlier, the argument some people make that, if we once start to do these things, then gradually we will go down to who knows where. It has always seemed to me that either we're already on that slippery slope, and so might as well forget about it, or that it doesn't exist. Does anybody have any thoughts about the nature of the sort of reinforcement and self-reinforcement that occurs with these kinds of developments?

ANDREA BONNICKSEN: I would like to suggest a couple of other metaphors for the slippery slope that I've seen in the literature. One is to talk about us rapelling down the slope—that is, rather than just slipping on down without any stopping point, we can repel from the building back and forth with stopping points. Another metaphor is that of the ramshackle staircase: instead of sliding down the slope, we instead

are going down a rickety kind of staircase, and at points we stop and look back and fix it, and then we keep going. These metaphors suggest that—with these new techniques—we face not a slope but a course of action with stopping points and places to draw lines.

GREGORY STOCK: Lee, did you have a comment to make?

LEROY HOOD: I related to this idea of the sanctity of the human germline. Remember, each of our chromosomes differs by 1 letter of the DNA language in every 500. And each of our chromosomes, when it goes through the necessary manipulations to make sperm, actually undergoes recombinational events where the information is scrambled. Indeed, there are an enormous number of other events where information is altered, is rearranged, and is changed.

I would reject, utterly, the idea of a slippery slope, because it seems to be arguing that we're doing something unnatural. In fact, it is quite the contrary. We're using exactly the same kinds of techniques used by evolution, but what we're attempting to do, in a thoughtful and rational way, is to facilitate evolution, so it doesn't operate in a blind fashion—most of the changes being neutral or deleterious—but in an optimizing fashion. It's exactly the same as the analogy for antibiotics. You could argue that maybe some human would someday run into the fungus that made penicillin, but on the other hand is it unnatural? Is it a slippery slope to manipulate molecules that could kill bacteria?

The other point I would make is that there should be a fundamental distinction between basic research—learning how to do this in animal models and so forth—and the application of that research, which is where we obviously have to show a great deal more caution. What is absolutely fearful about a lot of the laws that came up in response to cloning is that they made no distinction. They went all the way back to the very core of this kind of research. Meetings like this are important because they help people gain an understanding about these distinctions and respond when laws are absolutely inappropriate.

One of the things that terrifies me about how laws get written is the realization that they're written by twenty-three-year-old staffers who are out to make a name, who studied this subject for three or four weeks. In general, those in Congress have even less idea of what this is all about, so it is a process that is not conducive to writing laws. But in spite of that, it ends up working surprisingly well.

GREGORY STOCK: Does anyone else have a comment to make about this subject? Lee?

LEE M. SILVER: There is this false notion that species try to preserve their gene pools to try to preserve themselves. That is completely false.

Species are always changing, and they even transform from one species to another. And as they change, their gene pools change naturally. This notion of a species trying to preserve itself is a false one right from the start.

GREGORY STOCK: Michael?

MICHAEL R. ROSE: I would like to address the evolutionary issue. Lee Hood has presented the technological case, and I'm very sympathetic to it. Evolution is an incredibly complex process which is not suited to platitudes. Evolution can be spectacularly creative, so much so that many of the problems in artificial intelligence are now being solved using evolutionary algorithms. When design and optimality approaches fail now, artificial intelligence designers are using evolutionary techniques—basically, natural selection and genetic recombination—on computer programs. But just as you have to acknowledge the power and creativity of evolution, you also have to acknowledge its complete indifference to us as individuals. That's not what evolution is about at all. Evolution is about the transmission of DNA sequences down through time. We're just incidental things that get in the way. We're like the foot soldier in World War I, and we're sent out of the trenches into the enemy machine guns, and we die in our millions. And that's fine with evolution as long as our DNA gets into the next generation. This is, perhaps, part of my rebelliousness to the notion of "normal." I think what is normal is a catastrophic waste, and if one were simply to accept what evolution does as normal then, hell, you can give up on most everything that medicine does. You have to reject this concept of normal. You have to take what evolution does and look at it askance, exploit what it does well, and provide what it does not provide. And, of course, for those poor individuals who are afflicted by genetic diseases—which are the products of an evolutionary process in which mutation and selection together do not guarantee that everyone of us is genetically perfect, but only that most of us are genetically pretty good—their afflictions are a concrete example of where evolution has to be firmly rejected. The fact that, to evolution, we are disposable past a certain age is another candidate for rejecting what evolution normally does and doing something completely different. I think we need to seek an appropriate balance between respect for and use of what evolution does and rejection of what evolution does.

GREGORY STOCK: Along those same lines, I would like to express the notion that evolution, as it has operated in the past, has essentially stopped for the human species. Our future evolution will be intimately connected with the technologies that are being developed today.

When you look forward, even a few centuries, it is difficult to imagine how you could separate any changes that occur to the human species from the technology that is evolving now and is now reflecting back upon ourselves. Does anyone have a comment to make about that general notion? John?

JOHN CAMPBELL: I suspect that the idea of us grabbing the reins of our own evolution is not new. Students of human evolution recognize that the major factor in the past history of humans—the past several million years in the development of humans—has been the tampering by humans with their own reproductive system, through sexual selection. Indeed, Darwin believed that sexual selection was the main factor that caused humans to evolve. He did not talk about the evolution of humans in his *Origin of the Species by Natural Selection.* He put it in a separate volume on natural selection in relation to sex and the origin of man. So, he put the origin of humans right in with sexual selection. Leakey thought the way to think about how we originated was that we autodomesticated ourselves. Other people have thought that the most important factor was the parent-offspring relationship, that the real selection pressure was the degree to which a mother protected her offspring. Undoubtedly, humans have been the main instruments in their evolution, the process which brought them to the status of being human. If we now start to tamper with our evolution, we are not doing something that is unique or unnatural or something that hasn't happened before. What I see as unique is that now we can bring our rationality to it, instead of having it based on sexual preference.

GREGORY STOCK: Dr. Koshland?

DANIEL KOSHLAND, JR.: We're doing evolution in test tubes now. In my laboratory we're using what's called combinatorial chemistry, which is what happens in evolution. You combine chemistry with the idea of selection in biology, and you make billions of mutants, of, say, little peptides. Then they are selected in your laboratory. Basically, that's what happens over evolutionary time in millions of years. This is now spreading throughout industry; the biotech industry, for instance, is using it to develop new drugs.

In some ways this comes back to germline engineering, because we've decided as a society that it's too cruel to get rid of less-effective or defective people, like those, for example, who have glasses. It really is crazy to discard a rational approach to helping our species, since we really have rejected the system that, as Dr. Campbell pointed out, has in a cruel way, over years and years, discarded the less fit. Now say we

don't want to improve the species, because that would be too mean and inappropriate to the less able.

GREGORY STOCK: Dr. Hood, you would like to make a closing comment?

LEROY HOOD: There is another way we can use evolution in absolutely incredible ways to help us decipher some of the most complicated of these "complex traits." One of the speakers mentioned—I think it was Lee Silver—that chimps and humans are 99 percent identical in their sequences. One incredibly fascinating project would be to have a Chimp Genome Project and to compare the results with those from the Human Genome Project. The genes that would be enormously fascinating to compare are those that regulate the nervous system, for therein would be a great deal of the information that separates what we can do with our minds and learning and thinking from what a chimp can do. Also, you can use evolution in a lot of ways to gain fundamental insights into the kind of things we need to be able to manipulate in the future, if we want to fundamentally change schizophrenia, manic depression, and a lot of these very, very complex multifactorial diseases.

GREGORY STOCK: Does anyone else have a closing comment they feel burning within them?

LEE M. SILVER: This is not something that is going to happen overnight or even within the next thirty or fifty or a hundred years. But for the first time we understand that as a species we have the ability to self-evolve. That's what the difference is with this new technology versus the sexual selection which occurred subconsciously in previous years. I mean, this is an incredible concept: that our species has the ability to self-evolve. I wanted to make that point.

GREGORY STOCK: This has been an incredibly rich day, and a long one. I would like to thank our speakers. It's wonderful to have a discussion that is as open and frank as the one that occurred today, and I hope it moves out beyond this room.

DANIEL KOSHLAND, JR.: And I'd really like to thank you [Gregory Stock] and Dr. Campbell, because I think you stuck your necks out and did a great job.

GREGORY STOCK: Thank you. And with that, the "Engineering the Human Germline" symposium is closed.

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PART III

OTHER VOICES

This final part offers additional perspectives on human germline engineering through short essays from ethicists, lawyers, theologians, public-policy makers, and scientists from both the United States and abroad who have thought deeply about the issue. To emphasize the breadth of opinion about this genetic technology, each contributor has written an essay based on one of only three question sets about key issues concerning human germline engineering. Each question has thus been answered by several contributors. But their answers are neither commentary on previous portions of the book nor on each other's essays. Rather, this is a collection of independent snapshots of opinion.

The first set of questions confronts the issue of human germline engineering head-on by circumventing the matter of safety, which has often muddied discussions about the technology. Safety is a distinct issue of its own. Opinions differ about what level of safety would be adequate, but no one argues that we should apply the technology to humans before it is medically "safe." To imagine how we would view the technology if it were truly safe brings our different attitudes about human germline engineering into sharp relief.

> If germline engineering procedures were demonstrated to be no more risky in humans than natural conception, what limits would you place on the types of interventions allowed? Would your opinion be altered if the technology allowed the blockage of transmission of these alterations to future generations?

The second set of questions seeks commentary about some of the more commonly expressed worries about germline engineering and attempts to gauge concern about the technology.

> Some have asserted that altering the genetics of human germinal cells would be an assault to human dignity, others that it would lead down a slippery slope with dire consequences. What is your assessment of the eventual possibilities and dangers of human germline engineering, and what are your biggest fears about its implementation? Would humanity be better off in a distant future where no direct modification of the genetics of human germline cells were allowed, or in one where significant modification were available?

The third set of questions is straightforward. Given the powerful dynamics bringing technologies like germline engineering into the realm of possibility, should we try to erect international measures to control them?

> Some have advocated the development of an international policy on germline engineering and cloning. Do you think this would be preferable to a patchwork of national policies and, thus, worth pursuing?

Each contributor has been identified by a short biographical blurb, but to give readers a context in which to read the essays, we've also included his or her answer to a hypothetical personal question that may offer readers even better insights into the thinking of these individuals. Perhaps their views on this will help us prepare for that day when we or our children are confronted with a similar question.

> Imagine you were conceiving a child by in vitro fertilization, and your obstetrician convinced you that the embryo of your child-to-be could, without additional risk or cost, be given an artificial chromosome to increase his or her life expectancy by a decade. Would you use the procedure?

Beyond the Issue of Safety

If germline engineering procedures were demonstrated to be no more risky in humans than natural conception, what limits would you place on the types of interventions allowed? Would your opinion be altered if the technology allowed the blockage of transmission of these alterations to future generations?

Glenn McGee: "Parental Choices"

The human germline is not sacrosanct. For the sake of argument, we will assume that alteration of the genes of the yet-to-be born, yet-to-be conceived, or their progeny poses no special health risks to anyone involved or yet to be involved. Why ought we be fearful, then, of altering our inheritance through direct physical changes to germline cells? The principal objection to germline alteration has been that it crosses a bright line between the bucolic operations of nature and the engineering of humans by humans. It is supposed to be dangerous to cross this line—dangerous to the children involved and dangerous for our species.

If we eliminate the danger of overt physical toxicity for the offspring involved, what dangers remain for these individuals? I would argue that human germline modifications are, under these assumptions, no more dangerous than other kinds of parental choices. More specifically, I would argue that the means we use to secure our desired procreative outcome are strictly linked to the ends in view. The means alone are not the issue. The question is how well the means suit our ends, and how well our ends

square with what is ethically acceptable for parents to desire. If germline alterations can be used responsibly, within the context of parental common sense and as part of institutions designed to carefully monitor the outcomes of those alterations, then it is hard to see how they will harm children or future generations. There is no reason to be opposed in principle, either, to the improvement of human beings or to the direct actions aimed at that goal. Of course, the devil is in the details. Which human parental goals are intelligent, and which pose profound dangers? In an article in *Hastings Center Report*, "Parenting in an Era of Genetics [March 1997]," I argue that there are several clear "sins" that we encounter in parenthood, whether our means of "engineering" is high- or low-tech. These dangers of parenthood, and the ethnographic means of assessing them, should be the focus of bioethics in an era of germline therapy. We have to distinguish between the uses of parental wisdom that are to be allowed, and those that should be disallowed by the institutions involved: medicine, family courts, churches. Beyond the obvious question of which uses of genetic technology should be banned or regulated, moreover, is the issue of the rhetorical role for bioethics: should bioethics be in the business of recommending to parents that they choose or forego particular kinds of germline modifications? Arguably, bioethics in this area has focused too much on what should be allowed and too little on what should be recommended.

Dangers to the human species are more intractable. Virtually every author of a recent tome on genetics has suggested that we are moving into a new evolutionary period, in which human beings describe and promulgate the kinds of creatures that will be born. The observation is profound, and it points to a fundamental truth. People can observe, classify, and control more of human embodiment than ever before in recorded history. The development of molecular biology and biophysics, as well as their clinical corollaries, portends more such control. But, again, where is the bright line that divides nature's machination from human engineering? Elsewhere I argue[1] that theories of "genetic progress" and dystopian analyses of genetic downfall are almost always predicated on a Luddite refusal to analyze the distinctions between technology and nature with rigor and care. Technological innovations aimed at improving human health are age-old, and, indeed, we have taken many steps toward improving our ability to conceive children whose lives will be improved by virtue of our actions. Fears of eugenics are not without meaning. We could, indeed, make mistakes with our species that would cost the lives of many, and genetic policy could indeed cheapen the lives of those yet to be born or yet to procreate. But the lesson of eugenics is a special and historically-situated one. Today, our fears about germline genetic engineering should center on the

danger to our species of thoughtless, libertine progress into the breach. We proceed headlong into genetic engineering without even a casual glance in the direction of reforming family law, research restrictions, or our educational institutions. Families taken off guard by genetic technology thus rebuke it as "playing God." The greatest threat to our species is the ignorance within our social institutions whose role it is to provide support for good decision making. Genetic counselors cannot replace town hall meetings, church discussion, and good educational institutions.

> If you could do so safely, would you use an artificial chromosome to extend the lifespan of your child?

I would probably be among the thoughtless, casting my own love of life into a bid for my child's immortality. When I was a boy, I wondered about when and how my parents would die. I hoped that I would never see that day, and that I would somehow be forever young. Deep in us is a fear of death, a fear of loss of meaning. The danger of technologies that promise a longer life is that they commodify what should be a spiritual conversation about what it means to want to live, and what it means to want to live longer. In principle, I see no reason to object to having a longer life. I'd like to see people in space. I would like my child to have more time to grow and love and learn. But the plain question is, at what cost?

The danger of genetic choices such as this is that they cast parents in a more perilous role. How will I relate to my child? Parents already come to resent their children as they age. My child's promise—which liberates me at one level by relieving my burden and offering solace in my aging—is also a yoke I must bear. I feel myself dying, even as my child grows and grows out of the society and needs that, for me, are most important. Will my choice to give a child more years come to haunt me and our relationship? Moreover, what will I have wrought on the world? Would a collective choice to live longer in the American style cost so much money for so many as to implicate my child in the exploitation of the poor? I'm not sure. Finally, I would be among those paying for extra years. But I am not so sure that such a choice should be mine in the first place.

Sandy Thomas: "Thoughts on the Ethics of Germline Engineering"

A major objection to germline engineering is the notion that a person's genetic makeup should not be directly determined by the deliberate choice of another. It can be argued that preimplantation screening, prenatal

screening, and even abortion allow manipulation of an individual's genome. However, the potential impact of germline gene therapy on the next and future generations raises additional concerns. Here, the parents are not merely considering the best interests of their unborn child, but those of their child's unborn descendents. Concern has focused largely on the irreversibility of genetic changes effected by germline gene therapy and the denial of decision making by future generations. There is anxiety that if therapeutic interventions were permissible, genetic enhancement would soon follow.

We are currently at an interesting stage of knowledge in the field of human genetics. Our understanding of diseases caused by single genes has grown rapidly, and nearly all diagnostic genetic tests are for these diseases. At the same time, we are beginning to see that the role of susceptibility genes in many common diseases is complex, that such genes may have multiple effects, and that interaction between genetic and environmental influences may be difficult to unravel. Our knowledge about genes for personality traits, for intelligence and behavior, is by contrast very limited.

If germline gene therapy were no more risky for humans than natural conception, would there be ethical objections to eliminating disease genes? For example, the replacement of recessive cystic fibrosis alleles by dominant normal genes through homologous recombination in fertilized eggs could be viewed as a positive intervention which justified the deliberate determination of the genetic makeup of future generations.

In reality, few situations are likely to be as straightforward. Where a disease gene is dominant, as in the case of Huntington's disease, homologous recombination at both gene loci would require very high levels of efficiency. If a couple at risk of carrying a single-gene disease had gone to the trouble and expense of in vitro fertilization, preimplantation screening of embryos would provide a much simpler way of offering the family reproductive choice. Moreover, engineering for complex diseases is unlikely to be viable, and "success" will be impossible to measure. Even if germline gene therapy allowed for blockage of transmission of these alterations to future generations, the same limitations would apply. Under what kind of circumstances should we be considering germline gene therapy for a single generation? Would we be doing so for that small group of patients who object to abortion following an adverse result from prenatal testing? I would argue that this is an unrealistic scenario except, perhaps, for the most serious genetic diseases. In any event, unless gene transfer in embryos was 100 percent efficient, the procedure of selecting some embryos and rejecting others might be unacceptable to these patients

The costs of allowing clearly defined medical interventions, as in the case of cystic fibrosis, might be the opening of the door to enhancement.

The idea of "designer babies" raises a whole range of serious ethical questions. The view of some scientists that because something is technically possible, it will invariably be done, is misplaced. Scientific possibilities should not, in and of themselves, determine policies that need to reflect ethical, legal, social, and economic considerations. The application of germline gene therapy to effect novel and beneficial therapies is one thing. It is quite another to think in terms of use of the technology to allow parents to improve their chances of having an above-average child.

Even with our limited knowledge about the heritability of, for example, intelligence, musical ability, and sporting prowess, it is clear that we are not simply the "sum of our genes." For many traits (and most common diseases), both genetic and environmental factors are likely to be important. Even if the genetic influences affecting a trait are well understood, there is likely to be variation in the symptoms and outcomes observed. To encourage the idea that we should manipulate the genome to "make better human beings" raises major ethical and scientific problems. From the viewpoint of ethics, the notion of enhancement ignores the fundamental principle of respect for persons which is expressed in action and procedures that give due weight to personal autonomy and integrity. By introducing selected specific traits of this kind into an embryo, a parent imposes his values of what is "better." How could the teenager or young adult rebel against his or her selected genes? Parental choice would extend into the child's life in a way that could compromise his rights as an individual to pursue his *own* path.

Raising potentially unrealized expectations of parents in the abilities of their unborn child is unlikely to be in the child's best interests. Ambitious parents who have invested in gene therapy to secure a bright future for their child may not be well placed to cope with failure. The child who has been unsuccessfully enhanced for intelligence may suffer low self-esteem and be denied the right of being valued for himself, regardless of his abilities. If enhanced intelligence is seen as a means of "bettering" one's children, there is a real danger of an increased stigma being attached to people who are less intelligent. The stigma associated with mental disorders should serve as a warning to us.

In conclusion, advances in human genetics will bring benefits to a wide range of people through the development of more effective drugs and prenatal genetic testing for a wide range of common diseases. In contrast, germline gene therapy is unlikely to make a significant contribution to public health within the next thirty years. Our limited understanding of how human genes behave and interact should restrict, delay, and, if appropriate, prevent some applications, including those in germline engineering.

If you could do so safely, would you use an artificial chromosome to extend the lifespan of your child?

I would not use the procedure involving the addition of an artificial chromosome to increase the life expectancy of a child. The development of new medicines and medical procedures should be focused on improving the *quality* of people's lives. As new therapies are developed to treat common and debilitating diseases of old age, longevity will be enhanced. The notion that medical research might be directed at increasing life expectancy per se is, in my view, misguided and ignores the right of *future* generations to their own autonomy. Germline gene therapy to eliminate heart disease or cancer would be less controversial, in that they could be seen as being in the child's best interest. There is doubt, moreover, that the introduction of artificial chromosomes into the germline could be designated as risk free, since the effects in future generations could not be thoroughly evaluated.

Sheldon Krimsky: "The Psychosocial Limits on Human Germline Modification"

Our thought exercise assumes that the health risks of human germline genetic alteration have been reduced to rates that fall below genetic abnormalities of natural reproduction. This means that the genetic modification of germ cells (GMGC), including deletion, addition, duplication, rearrangement, immobilization, or expression of gene sequences, coding or noncoding, would produce only the desired ("positive") outcome. Or, in the case that a genetic modification produces multiple genomic or phenotypic effects, it also assumes that those effects would not add any risks to the health and well-being of the individual (over his or her lifetime) beyond the background risks we attribute to natural conception. It shall also be assumed that any decision to undertake GMGC in procreation is strictly voluntary, has an economic cost, and has perceived benefits to the parents.

The most serious moral problem that I see in permitting the voluntary use of GMGC in human reproduction for any purpose whatsoever is that it will establish a role for genetic technology in raising aspirations of prospective parents for attaining a culturally defined but morally impoverished ideal of the genotype/phenotype of their progeny.

Among the most problematic cases are those involving the uses of GMGC for procreating children of a particular sex, body size, shape, or skin color. Offering people the opportunity to choose the phenotype of a child

will result in psychosocial pathologies, including deeper class and racial divisions within society.

The use of GMGC or other techniques to determine the sex of a child can, in a patriarchal society, lead to the superabundance of males with unanticipated consequences to traditional courtship patterns and gender equity. In many parts of the world where racial prejudice based on skin color is pervasive, some blacks may feel pressured to avail themselves of GMGC to insure light-skinned offspring. If this genetic modification were possible, it would reinforce social prejudices by connecting "medical procedures" with racist stereotypes that imply "whiter is better."

The same may be said of body types. Young adolescent girls, responding to media messages of "perfect body image," are prone to anorexia nervosa. Abnormal dieting and obsession with caloric intake are pervasive among normal preteens and adolescents. Women who recall their own pained adolescent years struggling with body image might be inclined, if offered, to choose a body type for their offspring that more closely resembles contemporary media images. While people may aspire to have children resembling our contemporary media "gods" and "goddesses," it would be a grave human error to use GMGC to narrow the genotype/phenotype of the population. The public identification of genetics for this purpose reinforces the dangerous notion that there are universal standards of beauty and that science supports such standards. Even if there were but a few wealthy individuals who could afford to use such methods (assuming they were effective and safe), the symbolism that science has developed a reproductive technology that offers parents choices of body types for their offspring has profound psychosocial implications. And while cosmetic surgery responds to similar social cues and prejudices, it cannot affect the genotype and therefore will not narrow genetic diversity and serve a eugenics purpose. The psychosocial arguments against modifying germ cells for "enhancement" apply whether or not the alterations are transmitted to future generations. The availability of eugenic techniques in reproduction to a minority of affluent people will support the "geneticization" of a society, enabling an aristocracy with so-called proper genes to use it to their class advantage.

What about the selective use of GMGC for deleting or repairing life-depriving genetic defects? Can we establish a reasonable and sustainable moral boundary that prohibits modifying clinically normal germ cells yet accepts the repair of abnormal ones? Theoretically, we might be able to justify a boundary that permits the use of GMGC in conjunction with in vitro fertilization exclusively for extreme genomic abnormalities. Realistically, our decentralized institutions providing reproductive services, including infertility clinics, sperm banks, and prenatal care, would make it virtually

impossible to maintain a boundary between the use of GMGC for life-threatening genetic diseases, "enhancements," and the vast grey area in the middle. Just as surgeons have great latitude in the use of cosmetic surgery, and physicians can prescribe drugs for uses other than those approved in drug trials, if GMGC were approved for some uses of human reproduction, there would be no centralized system of control to prevent slippage.

Assume a best-case scenario: two heterozygotes, carrying single copies of a gene that is life-threatening for homozygotes, who do not wish to pass the gene to their offspring, seek relief through GMGC. We must ask if there are reasonable alternatives to germline modification, such as egg selection or sperm donation. If germline modification is the procedure of last resort for producing a healthy offspring, then we must balance the interests of parents with the broader social concerns that this first step will be the starting point for less agreeable (more morally ambiguous) forms of germline changes. With no assurance that our institutions and laws can prevent slippage in applying GMGC, any decision should weigh heavily on the side of "no first use." An international convention on proscribing the use of GMGC can set the framework for civil laws against eugenics on the part of signatory nations.

> If you could do so safely, would you use an artificial chromosome to extend the lifespan of your child?

If I am given a hypothetical choice that allows me to endow my offspring with excellent health and longevity without compromising the child's personhood in any way, which does not compromise the health of my wife, which does not have any adverse implications on race, class, gender oppression, which is universally available, and for which there are no trade-offs (the procedure is just an add on), I would accept it. Of course, in vitro fertilization implies extracting eggs from a woman, which can have adverse effects. Perhaps we can add the proviso that the method adds no risk to the egg donor. I would do lots of things I don't ordinarily do (such as pray or live on a macrobiotic diet) if I had certainty it would create a better world or healthier children. Of course, I have to assume that if this were such a perfect and cost-free method to insure the health and longevity of my progeny, one that is universally available, many others would avail themselves of it and there would be no stigma associated with its use. It would be like a smallpox vaccination. Some people may be opposed on some principled grounds to vaccinations, but by and large having the availability to vaccinate against diseases has been a positive contribution to human civilization.

Perhaps some day there may be "genetic vaccinations" for men and women. The purpose of these "vaccinations" would be to repair mutations of germ cells in vivo before conception. If that ever were possible, it would make me rethink the "no germ line intervention" stand. Presumably, if the State were responsible for such "vaccinations," then a centralized guidance system could prevent its use for "enhancement" purposes that tend toward the medicalization of social or cultural ideals.

Kevin T. FitzGerald: "Do We Know Ourselves Well Enough To Be Engineering Humans?"[2]

Germline genetic technology could significantly change our understanding of human nature as well as radically alter procedures for treating human disease. Since ethical decisions concerning the proper uses of new medical technologies are grounded in concepts about human nature, it follows that we need to scrutinize these concepts as to their completeness in describing and explaining what it means to be human.

Presently several concepts of human nature can be found within the ethical frameworks used to address the issues raised by germline interventions. Most of these concepts have a particular field of academic inquiry (e.g., science, philosophy, or theology) as their primary source, though that source may not be explicit.

Some concepts commonly employed are based on philosophical and/or theological tenets about human characteristics. Since these tenets generally were formulated hundreds or thousands of years ago, the science which informed them is quite dated and results in somewhat rigid or "static" concepts of human nature. Overreliance on these concepts creates heuristic frameworks often at odds with contemporary scientific knowledge. Hence, even though those who apply this type of ethical framework may intend to protect and to value human nature, the discontinuity of their concepts of human nature with contemporary science weakens their arguments.

In what may be an overreaction to static concepts of human nature, other concepts are used which too readily embrace contemporary scientific knowledge. These concepts are bereft of religious, moral, and other humanistic knowledge about human nature and rely solely or predominantly on scientific information. This lack of nonscientific sources of knowledge leaves these concepts of human nature with an impoverished description of humanity by reducing the human to the merely biological or physicochemical. How can such concepts be employed in a heuristic

framework to assess the total impact that genetic research and its applications will have on human nature and society?

Still another option often suggested is to focus almost exclusively on individual choice and allow the marketplace to decide the issue. For example, let parents decide how to apply germline genetic interventions for their own children. This option has two major problems. First, the vast majority of those who promote such an approach also want to prevent blatant misuse by limiting interventions to "responsible" ones made by "responsible" parents, so it still must be determined who and what is "responsible."

The second problem arises from the first. If the marketplace is to be the arena wherein the choices of what constitutes good germline intervention are to be decided, then what about those "responsible" parents who cannot afford any of the selections? The bottom line for this approach isn't morality or science, but economics. By default, those who are considered "responsible" parents will be determined by their financial status. Hence, this option faces the same difficulty as those previously mentioned—an incomplete consideration of the total human situation.

Is there a better alternative to the three approaches mentioned above? In my judgment, such an alternative would include concepts of human nature derived from all the relevant fields of academic inquiry and practical experience. The advantage of this approach is that it can provide an integrated ethical framework which takes into account the common good as well as the good of the individual. Human diversity is valued not only from a scientific perspective, but also as a societal good resulting in the enrichment of all.

It is sometimes argued that this integrative approach is too complex, inefficient, and slow for evaluating the potential uses of germline technology. It is much easier to contend with the concerns of only science, or religion, or economics, and not with the entire rich tapestry of the human condition. Moreover, it is argued that this more complex and complete ethical approach is unnecessary, since all the ethical approaches above might agree to applying safe and predictable germline interventions to assist individuals with lethal diseases not treatable by other means.

This argument is shortsighted. The fact that different ethical approaches reach the same conclusion at some point does not make them equally valid over time. Most predict that, once applied successfully to lethal illnesses, attempts will be made to extend the application of germline genetic interventions to other diseases or use them for enhancement purposes. At that point, the limitations of the first three ethical approaches will become all too evident. No one academic discipline or field of practical experience alone can direct us toward the best use of this powerful new technology.

I strongly argue for the development of concepts of human nature based on knowledge gathered from all the pertinent areas of human inquiry and experience. Such concepts will help us to understand more fully who we are as human beings. From this knowledge, we can conceive of who we want to become and how genetic engineering might be applied to assist us in reaching that goal.

> If you could do so safely, would you use an artificial chromosome to extend the lifespan of your child?

The mere addition of years is, in itself, not meaningful. Without knowing how those ten years would be lived, I would be inclined not to make such a choice. When we choose to invest our energies and resources in activities that require a great deal of effort and commitment, we do so because of the promise of long-term benefits for ourselves and others. Marriage, raising a family, and education are examples of such human activities. The addition of ten years to an eighty-year life span does not intrinsically hold the promise of such benefits; therefore I would not invest in it until the hope for a return on the investment was sound.

Ruth Hubbard: "Germline Manipulation"

I would oppose germline interventions even if it were possible to show they are safe. The need is, at best, marginal and does not warrant the investment of time, money, or expertise necessary to perfect the technology and test it sufficiently to determine its efficacy and safety. It represents a distortion of priorities at a time when babies are sickening and dying, not because their genes are "defective," but because their families cannot muster the resources to enable them to be born, and grow up, healthy. One of the most serious problems with many of the current reproductive technologies is that they escalate the emphasis our society places on our personal "blood lines." Yet, DNA *über alles* is a most unfortunate ideology to propagate. Among other problems, it focuses our attention too exclusively on individual health, while public health is deteriorating.

The usual reasons given for trying to modify human germ cells or embryos are either specific health benefits or "enhancement." But, there is *no* way to accurately predict the effects of germline genetic engineering for a future person, much less for her or his descendants, because genes always function in concert with other factors. There is also no justification for germline engineering, because there are other ways to achieve the desired results.

With regard to health benefits, germline engineering requires in vitro fertilization (IVF), and that always produces several embryos. Each of these can be biopsied, and couples can avoid having a child with the mutation they wish to avoid by not allowing gestation of those embryos. The only situation in which this would be impossible would arise if both partners were homozygous for the identical alteration in the same gene, surely a very unusual circumstance. Such couples could use someone else's sperm, eggs, or embryos, or adopt a child. Therefore, we are not talking about condemning people to remain childless, perhaps only not to perpetuate their own DNA.

As for the notion that we need germline interventions to "enhance" the abilities we can expect to pass on to our children, I believe that people who cannot deal with the uncertainties implicit in having a child even before that child is gestated are in for trouble. Successful parenting surely requires that we be flexible enough to accept our children, whoever they are.

Germline engineering is a societal issue that involves far more than technical questions about DNA. Realistic discussions about it, therefore, need to move beyond disembodied DNA, genes, and embryos. Even just at the biological level, germline manipulations involve: hyperstimulating women's ovaries, removing their eggs, putting embryos into their womb, and conditioning that womb to accept and gestate at least one embryo and bear one baby, and often more than one baby because of the increased likelihood of a multiple pregnancy. Such risks are implicit in IVF, but it is one thing to accept them when IVF is the only way a woman can have a child that is hers biologically. It is foolhardy to accept them in the hope of germline "improvements."

Take a much simpler example. No one could have predicted that giving pregnant women diethylstilbestrol (DES) would years later produce cancers in the children they were gestating at the time. Also, it would have taken much longer to recognize this effect had the children developed more usual types of cancer.

In germline engineering, each step involves its own health and psychosocial risks, the extent and variety of which are largely unknown. A study has just been initiated in England to examine the records, collected over up to three decades, of more than 3,000 women to try to establish whether the drugs used in connection with IVF pose a cancer risk and how great the risk is likely to be. When even that is not known, surely we must face up to our ignorance about the physical, psychological, and social impacts of every step involved in germline manipulations.

Discussions about the advisability and safety of germline engineering must go beyond the technical details of how to get the right bit of DNA in-

serted at the right place and how to control the way it functions. To this end, they must include people familiar with the health and psychosocial aspects of ovulation, conception, gestation, birth, and raising children. Indeed, any attempts to genetically alter germ cells, embryos, or fetuses should be preceded by impact statements that consider the potential effects on health as well as the entire range of economic and psychosocial impacts on children, parents, and society.

> If you could do so safely, would you use an artificial chromosome to extend the lifespan of your child?

I tend to avoid all "elective" medical procedures. I would, therefore, never try to "improve" the future health or extend the life span of a "person" who hasn't even been gestated. When I think about what it takes to help a child become a responsible, contented, socially useful adult, genes are only a minor consideration. Human beings have been around for a long time. Our genes and environments have, therefore, had a chance to coadapt so that most people do just fine. A few people are born with serious disabilities, but then the job is for society to provide the support they and their families need so they can live the best and most productive lives possible. I constantly encounter people with disabilities who live good lives, and nondisabled people who don't. I would have to be mad to imagine that I am sufficiently clairvoyant to try to extend the life span of a future human being when it is just an embryo.

Gregory E. Pence: "Maximize Parental Choice"

Almost everything that Americans believe about genetic engineering and cloning of humans is false, due to decades of titillating science fiction, sensationalistic reporting in the media, and unthinking opposition. Hence, most people's thoughts and feelings on these topics need education.

Indeed, I personally would like to ban the phrases "test tube baby," "genetic engineering," and "cloning." For the latter, I would substitute the less emotional phrase, "somatic cell genetic transfer," or SCGT.

To assume that germ cells could be modified in a human embryo and have no more risk of harm to the child than natural conception is to remove the only real, moral objection to such procedures. All the other objections to such procedures are either unjustified or surreptitiously assume the resulting child will be harmed in some way, e.g., psychologically by the prejudiced attitudes of others.

There can be no reasonable objection to parents choosing to remove a gene or cluster of genes, or to modify genes, that cause something normally regarded as bad, such as a disease or handicap. Although some disability advocates insist that there is nothing wrong with being deaf, a dwarf, or having Down's syndrome, no reasonable parent would choose to have a child with such a condition when he or she could have a normal child. Indeed, in my opinion, it might be *immoral* to choose to have such a child if one could otherwise have a normal child.

Most people object to letting parents attempt to enhance a child's genotype through germ-cell modification. Usually the hidden assumption is that it really wouldn't work—that something would go wrong—and that the child would be harmed. That takes back the assumption of this essay.

The most-repeated objection is that if society let parents make such choices, they would only want "perfect children." Such an objection assumes that ordinary people can't be trusted in creating children. It also implies that wanting the best possible genetic base for a child is a bad motive.

People have not thought this objection through. Men and women exercise choice in selecting mates and in having children. We are quite comfortable with the fact that most of the present six billion earthlings choose the mate they think is the best possible for them and their children. If exercising choice is so bad, why isn't choice about reproductive mates also a dangerous thing? (If we "allow" such a practice, will people want only "perfect" mates?)

Obviously, what you want and what you get are not the same. As for gene enhancement, it is likely that, for the next decades, we will only have the knowledge to create one trait, especially when its base requires several genes and multifactorial environmental support. As such, parents will have to choose the kind of direction they want to go and decline other directions, e.g., to their child, literary talent but not football talent.

Here is one argument for allowing children to be produced by somatic cell genetic transfer. At least here, we know the cluster of traits that the ancestor had, and many of them may have been genetically based. We may be more likely to get the desired phenotype by reproducing an existing genotype than my fiddling with germline techniques one trait at a time.

Many other objections to attempting human SCGT are based on possible psychological harm to the resulting child from prejudiced reactions of others or from misplaced expectations of parents. We should not ban a reproductive option because some people are prejudiced or misguided. Education is the correct response to prejudice or incorrect expectations, not federal bans.

I do believe that the first attempt at human SCGT should be regulated, in America by a committee such as the Recombinant Advisory Committee

(RAC) at NIH, because the first case is very important to the acceptance of a new option. Louise Brown, the first baby created by in vitro fertilization, fortunately came out healthy, but problems developed in the Baby M case where a surrogate mother was used (and hence, commercial surrogacy was criminalized in some states). So we must be as certain as possible that the first attempt to create a baby by human SCGT will come out well, both for the sake of the child and for the sake of future attempts.

All of this assumes that reproductive science could know one day that germline interventions or somatic cell genetic transfer would cause no physical harm to the resulting child. That is a big assumption. I welcome the day when it is true.

> If you could do so safely, would you use an artificial chromosome to extend the lifespan of your child?

Some day soon, when the opportunities arise, we will see the wisdom of allowing parents maximal choice about their future children. This is not state-controlled eugenics (which attempted to take away such choices from parents), but its opposite. If a child can be given an extra decade of life by an artificial chromosome, or 50 percent more memory through a therapy in utero, then I personally would feel *obligated* to give my future child such benefits. I believe that my child would be grateful to have been deliberately given such a benefit.

Others might disagree and choose not to do so for their children—a decision I would respect. What I fail to understand is how other people—or the federal government—could think it just to prevent me from benefiting my future children in this way, e.g., by a ban on such enhancements (perhaps from a misplaced concern for equality and social justice). I see no difference between such a ban and a similar ban on parents sending their children to computer camps in the summer: both are intended to better children, both will be done most by people with money, and both are not the business of government.

Stefan F. Winter: "Our Societal Obligation for Keeping Human Nature Untouched"

Tucholsky's words, "The essence of the sea cannot be judged upon by the nature of its drops," came to mind in 1996 as my colleagues and I at the forty-nation Council of Europe were discussing possible attempts to alter the human genome. Decades earlier, Tucholsky had reflected on the dangers

of oversimplification of natural phenomena. In my view, the present global debate on germline engineering is in danger of doing just this. Europeans did, however, manage to avoid such oversimplification when, in 1997, they wrote Article 13 of the European Convention on Human Rights and Biomedicine—the first legally binding European document of its kind. It states: "An intervention seeking to modify the human genome may only be undertaken for preventive, diagnostic or therapeutic purposes and only if its aim is not to introduce any modification into the genome of any descendents."

The reason Europe created such a clear provision on this biomedical subject is that it is so much more than just a medical issue. The question posed to me for this essay implicitly considers only risks that are medical in nature, but that wrongly ignores the enormous ethical and social dimensions of this topic. And it is precisely these larger dimensions that are paramount because, with germline engineering, the scientific community would be moving away from issues of health and towards an attempt to design a "new mankind."

If germline engineering procedures were made "safe," as the question posits, more and more couples would be tempted to use them instead of natural conception. What I fear is that most such couples would be interested in *nonmedical* indications and follow a eugenic approach concerned with extending the human life span, increasing intelligence, or enhancing physical abilities.

Even ignoring that social behavior would dramatically shift from natural toward in vitro conception, a guarantee not to cross the line from medicine towards eugenics can be imagined only for preimplantation genetic diagnostic techniques (PGD) because, unlike germline interventions, they involve no alteration of the human genome, no direct intervention into human nature, and no possibility of enhancing physical or mental abilities. Moreover, even with PGD, severe ethical problems remain about the questions of what constitutes a *severe* disease and who controls the use of the technology.

Besides well-known social and ethical considerations and medical risks, the European approach to the protection of the human genome and our prohibition of germline interventions was driven by the argument that there is almost no medical need for germline gene "therapy." Admittedly, there are rare homozygous lethal conditions not amenable to PGD, and there are the arguments put forward by some authors that therapeutic enhancements such as interventions to delay the onset of age-related diseases, susceptibility to viruses such as HIV, and even cancer preventatives could be done only by germline engineering. But the question remains: do we really want artificially constructed human beings? And who is entitled to make such fundamental decisions?

Germline gene therapy requires in vitro fertilization, but IVF generally involves the fertilization of many eggs, so in most situations the likelihood of acquiring at least one healthy embryo by PGD would be high. And if there are parents opposed to PGD on ethical grounds, they remain free to use normal conception or to forego having children. From the medical point of view, despite being at high risk for bearing children with serious monogenic diseases, affected couples generally have a 50–75 percent chance of bearing healthy offspring. Only in very rare cases are they faced with a lower chance of having healthy children so, with a medical indication of a severe genetic disorder, it makes sense to focus on the reimplantation of healthy embryos instead of the insupportable risks of attempting to cure affected embryos. In those few rare cases of severe genetic disorders not amenable to PGD, for the time being medicine will be unable to provide a genetic treatment.

Other, more profound, ethical problems have been attributed to preimplantation diagnosis, however, so I believe even PGD must be judged on a case-by-case basis to insure that embryos are adequately protected and that the procedure is ethically acceptable. In each case, the appropriateness of using PGD should be judged by an ethical committee that can evaluate whether the procedure is intended for a purely medical indication.

I see no compelling arguments for the introduction of germline interventions on human beings under any circumstances. And even if the technique were "improved" so that transmission of genetic alterations to future generations could be blocked, my position on this would not soften. It is interesting that the main focus of the germline debate tends to be on the nonmedical uses, not the few rare diseases only treatable by this technique.

These general societal applications are what raise my personal fears about the future of my children. On the one hand, success in somatic gene therapy, the discovery of new genetic diseases, and the arrival of new knowledge from molecular biology will make nonmedical requests for germline interventions increasingly likely. But, on the other hand, failures in somatic gene therapy will drive researchers to think about germline intervention as an alternative. With the growing burden of increasing health care costs, it would be a dangerous temptation if germline gene interventions—although difficult and expensive at first—were some day seen as a way of controlling medical costs, because we should not forget that nonmedical possibilities are what has opened today's germline debate.

> If you could do so safely, would you use an artificial chromosome to extend the lifespan of your child?

My answer starts with a question: Where would we go from here? Fighting disease is one thing, playing God another. Imagine the ensuing race for

immortality; imagine a world with predetermined human life spans under societal control. Such scenarios far exceed our capacity to manage the process. What if the question had been about prolonging life not for a few decades, but for one hundred or two hundred years? Is that a world in which we would want to live? I think not, so my response to the offer of germline intervention to extend the life spans of my own three children is an emphatic "No!"

I believe that my children will want to have their own children and grandchildren normally and to enjoy a natural, not an artificially determined, lifespan. But this is not an easy choice for me. As a medical doctor, I know that it seems natural to consider added longevity as a good. But notwithstanding this "dogma," I'm convinced that once germline manipulation in humans begins, there will be "no way back to paradise." I have no doubt that germline gene interventions are theoretically possible and can likely be achieved technically. But we should never apply them to human beings. The breeding of mankind would be a social nightmare in which no one could escape.

To avoid the future risks associated with the development and use of germline gene manipulations, health policy should totally ban these interventions. This has been successfully done in the Council of Europe's Convention on Human Rights and Biomedicine, and it is very encouraging that the UNESCO Declaration on the Human Genome endorsed by the United Nations in 1998 points in this same direction. But in any event, who—according to the Hippocratic Oath—could ever be certified to offer what, for the vast majority of cases, is a technique that cannot be justified medically? Do we really want a "brave new world"?

Long-Term Possibilities and Dangers

Some have asserted that altering the genetics of human germinal cells would be an assault to human dignity, others that it would lead down a slippery slope with dire consequences. What is your assessment of the eventual possibilities and dangers of human germline engineering, and what are your biggest fears about its implementation? Would humanity be better off in a distant future where no direct modification of the genetics of human germline cells were allowed, or in one where significant modification were available?

Alex Mauron: "The Question of Purpose"

A frightening new technological gimmick has been terrorizing people for quite some time. It provides a method for manipulating individuals by actually changing the connections between their brain cells! Furthermore, people whose brain structure has been altered in this way go on to produce similar neuronal changes in other people, so that these alterations resonate through successive generations and infect ever-increasing numbers of hapless humans. People promoting this dreadful technological monstrosity claim that, in the long run, people will be "better off" with engineered brains. Now there you see the typical hubris of the scientist-technocrat. He is blind to the long-term effects of this irreversible interference with the natural order. Society is held hostage to his technological utopia. Future generations as much as present-day society are the nonconsenting victims

of his supposedly benevolent intrusions. Therefore: hands off from our neurons!

This awful technology is called neuronal phenotype manipulation, a.k.a. education.

At this point, maybe you think that I am taking a cheap shot at the opponents of human germline engineering. Comparing the willful modification of genomes with the time-honored process of developing minds by teaching them may seem preposterous. And yet shouldn't we ask whether the slogan "hands off from our genome" is any different from "hands off from our brains"? Actually, I believe it is, but the difference is subtler and less obvious that many opponents of germline engineering allow.

"Playing God," eugenics, the revolutionary character of bringing human evolution under human control: Those are the core features of many arguments against germline interventions. They have in common a central assumption, namely, the special standing of the human genome. It is claimed that our genome is important in a way that everything else isn't. The genome is construed as the ontological hard core of our being, the main determinant of our individual and species characteristics, the necessary and sufficient cause that makes us us. The genome has practically become the secular equivalent of the soul.

Now that scientists and medics have replaced priests, I guess that's fair. Still, this assumption is both ironic and ill-directed. Ironic, because the same people who tirelessly warn us of the perils of genetic reductionism suddenly make the human genome the inner sanctum of humanness. Ill-directed, because it focuses attention away from what really matters, namely phenotypes. Medicine, including medical genetics, is about human illness and suffering, whose links to phenotypic characteristics are direct, while they relate to genes only in a roundabout way. This is why, in Eric Juengst's terminology,[3] phenotypic care and prevention have a moral priority over genotypic prevention. All of them are ethically legitimate if they respect patient and familial autonomy, as well as the reproductive rights of individuals and couples. However, this may be more difficult for genotypic prevention, where the rationale of a particular genetic intervention can (but need not) shift to a largely populational goal of genome cleansing. To substitute genomes for people as the legitimate receiver of medical care would go against the grain of a liberal medical ethos, because "(The) traditional emphasis on personal rather than public interests and values is central both to the intrinsic moral merit of genetic medicine and to its societal acceptance in free societies."[4] This, in effect, provides an ethical test for germline interventions: Are they primarily person centered or gene-pool centered? To the extent that germline interventions become a realistic proposition (I still need to be convinced), some will pass the test;

some, perhaps many, will not. In the end, there appears to be little basis for a wholesale rejection or acceptance of germline interventions.

This is not exactly an exciting statement. But then, to go back to neuronal phenotype manipulation, a similar conclusion would apply. This "technology" isn't exactly innocuous either. Education is fine, everybody is for it. But let us not forget that we are reaching the end of a century which, more than any other, has seen explosions of global violence in the name of nationalism, racial hatred, and ideological and religious fanaticism. In other words, propaganda, brainwashing, and groupthink are the dark doppelgängers of the very same "technology" whose bright side is called education. At the end of the day, it all depends on the purpose. If we leave aside specific techniques but consider technologies in the broadest sense, i.e., wide-ranging ensembles of theoretical knowledge, insight, practical know-how and specific tools, then the conclusion is clear. Technologies do not come with an ethical label *good* or *bad* affixed to them on a priori considerations. It all depends on the ethical evaluation of their various purposes and the ethical implications of their use. This is an extremely banal conclusion. But then, banal conclusions are sometimes true.

> If you could do so safely, would you use an artificial chromosome to extend the lifespan of your child?

If there were no additional risk or cost, of course I would. Can anyone seriously say No? Much of modern health care in the broadest sense has been about prolonging life, perhaps not as an explicit central goal, but certainly as a most welcome collateral benefit. I cannot see how increasing longevity could in itself be wrong. Of course, many additional questions (for instance about the quality of added life) immediately come to mind, but I presume that one talks here of prolonging life per se.

But there is a catch: "Without additional risk or cost!" Is there anything in medicine that is both risk- and cost-free? I cannot quite take the question seriously. It is like asking someone who doesn't believe in free lunches whether he is worried that a free lunch might cause him indigestion.

Rabbi Barry Freundel: "Gene Modification Technology"

Gene modification technology is not fundamentally different from any other technology mankind has developed. It carries with it great potential for good and great potential for evil. Anything with the capacity to impact on nature will, of necessity, present both possibilities as it becomes part of

human reality. As a matter of both principle and practicality, Jewish law has never sought to ban any technology. In a philosophical sense, Judaism sees the statement to Adam and Eve, "To procreate, to fill the world and to subdue it" as a positivist view of human progress. To call someone a "partner in creation with G-d" is to grant that individual one of the finest compliments Jewish thought has to offer. That which exists in this world is raw material to do G-d's work and the discovery of a new technology is simply an uncovering of another method built into creation by G-d for mankind to use in positive ways.

Further, as a matter of practicality, banning new technologies will not work. Someone, somewhere, will proceed with the technology and, precisely because he or she will be a renegade if the technology is banned, he or she is likely to use the technology in ways that are entirely unsatisfactory from a moral standpoint. Far better, then, to regulate rather than to prohibit.

There are clearly positive possibilities for genetic manipulation technology such as removal of Tay-Sachs disease or hemophilia as a threat to mankind. These uses would be seen by Judaism as fulfilling a positive meritorious imperative of Jewish law. Aesthetic considerations such as removing an inherited, disfiguring mole would also be sanctioned by Jewish law. Anything which improves the individual or the species will ultimately be viewed favorably from a Jewish law perspective.

Certainly, there are potentials for abuse in this technology. Eugenics, abusive and selfish construction of children to meet particular standards and personal fantasies, and "brave new world" scenarios are all possibilities and must be protected against. However, Judaism approaches such questions with a fundamental optimism. It believes that mankind will find ways to produce far more that is positive than is negative from its technological advances. In addition, if human beings were given free will by their Divine Creator, limiting their ability to make choices that have moral content would in itself be a denial and denigration of the special place that human beings hold in creation.

For Judaism, there is no doubt of either a practical or philosophical nature that a world that possesses this technology would be far better than a world that does not. I believe, therefore, that the traditional segments of our community would advocate for more research and more development of technological possibilities. This should be done with appropriate regulation to ensure that uses of the technology are positive and not abusive.

Even if the question is phrased to focus on human beings gaining control of their own evolution, I do not find that to be any more troubling than discussing any other human capacity to alter the natural world. I take this

position as a result of Judaism's teaching that human beings are the most important part of G-d's created universe. In mystical literature, human beings come from a higher place in G-d's economy than the angels. G-d has entrusted this world to humankind's hands, and the destiny of this world has always been our responsibility and challenge. Whether or not we live up to that challenge is our calling and essential mission. If G-d has built the capacity for gene redesign into nature, then He chose for it to be available to us, and our test remains whether we will use that power wisely or poorly.

> If you could do so safely, would you use an artificial chromosome to extend the lifespan of your child?

I would without any doubt have the procedure done and allow the child to live for a longer period of time. In Judaism, life is a positive value. In fact, one could argue that it is an infinite value. A longer life gives a person more time to be involved in good deeds and in the tasks presented by G-d to this world as His challenge to us. Increasing life expectancy through genetic manipulation is not different than increasing life expectancy by better management of disease or by developing new surgical procedures. Any type of increase in length of life is a positive for which the provider is deemed meritorious to the highest degree. Sanctity of life for us means increasing that life to the fullest extent possible.

I am often asked to cite one Jewish teaching that impresses me above all others. In response, I point to two sentences in a work known as Ethics of the Fathers. Ethics of the Fathers is a collection of the Talmudic rabbis' favorite and most important statements about Judaism and Jewish life. In that collection there is a teaching to the effect that one hour of bliss and happiness in the World to Come is better than all of life in this world. That is a sentiment shared by many religious belief systems.

In the same context, Ethics of the Fathers states that one hour of repentance and good deeds in this world is greater than all the life in the World to Come. To my knowledge, Judaism is the only belief system that sees some type of greater value to this world than to the World to Come. For this reason the question requires little thought in order to provide an answer from a Jewish law perspective. Every hour added to someone's life comes with the possibility of doing good deeds and repentance and is, therefore, more valuable in this way than all of life in the world to come. Given that belief, one cannot answer this question except in the affirmative. I would assume that my child will share my Jewish values and would also not hesitate to affirm that this was the right decision.

Erik Parens: "Justice and the Germline"

If we aspired to create a more just society, would germline interventions be publicly supported and esteemed?

Champions of germline interventions usually point to helping couples have healthy children. But the number of people who could not have a healthy child by some other means is minuscule. Therefore, if biotechnology companies are going to give stockholders a return on their investment, there will be pressure to sell non-health-related interventions—which, for lack of a better term, we can call "enhancements." But so what? Parents have always sought "enhancements" for their children. Why should the prospect of germline enhancements move anyone to hand wringing?

In one scenario for the future, whether one gains access to germline enhancements will be a function of one's resources. This scenario raises the question, would such limited access widen the gap between the haves and have nots? To begin thinking about that question, it is helpful to consider a crude distinction between purchasing *new tools* and purchasing *new capacities.* The privileged have always had access to new technological tools that have enabled them to increase their productivity and thus their resources. The printing press, for example, no doubt conferred a competitive advantage on those who could afford access to it. The privileged also have always had access to opportunities, such as better schools, that have enabled them to cultivate their native capacities and increase their productivity and resources. But how much one could benefit from a new tool, and how much one could benefit from the cultivation of one's capacities, was to some extent limited by one's native capacities—by one's draw in the genetic lottery.

So one of the things that might be *new* about germline enhancement would be that one's draw in the genetic lottery would not pose the same sort of limitation; to some extent, the lottery could be "rigged." The ability to buy not only tools and opportunities to cultivate one's native capacities, but also to buy new or enhanced capacities themselves, would make some individuals doubly-strong competitors for many of life's goods. Thus, there seems reason to at least think about the possibility that germline enhancements might widen the already obscene gap between those who have and those who don't.

In a different scenario for the future, everyone would have access to germline enhancements. This scenario raises the question: with respect to *which* understandings of "better" would such enhancements be undertaken? What conceptions of normality and perfection will prospective

parents have in mind when they attempt to genetically "improve" their children? In a liberal society, we not only recognize but honor the right of parents to shape their children in many ways, from giving them orthodontia to giving them violin lessons. We notice, however, that giving a child straighter teeth is an intervention different in magnitude than, say, giving her lighter skin. Giving a child the opportunity to learn the violin is different in magnitude than, say, hoping to give her the capacity to be more aggressive and competitive. The magnitudes of these interventions are different enough so that it would be a mistake to rest easy in the view that there's nothing here new enough to deserve our reflection. Moreover, to the extent that such interventions will be influenced by dominant conceptions of normality, and to the extent that those conceptions are arbitrary creations of advertisers whose job is to make consumers feel that they lack something, the prospect of selling these interventions should be an occasion for reflection.

As we think about using germline interventions to shape our children, we must remember that such shaping could be used to spare some children from the suffering associated with not fitting dominant conceptions. Nobody I know thinks suffering per se is good. Children shouldn't suffer in order to be taught, or to teach anybody else, a lesson. But we should not allow our desire to ameliorate suffering in the short run to allow us to inadvertently produce more suffering in the long run.

In the short run, we might be able to reduce the suffering associated with being different by making people more the same. There is another, probably more difficult—though perhaps ultimately more humane—way of attempting to reduce such suffering. Instead of using biotechnology to change the bodies of individuals to make them better conform to dominant conceptions, we could use education to change how we think about those who are different. It would be tragic if, as we increasingly are able to change the bodies of individuals to avoid the suffering associated with being different, we are increasingly disinclined to change the complex social attitudes and conditions that produce that suffering in the first place.

I am not saying that those who aspire to create a just society should refuse to consider germline interventions. I am saying that before we embark on that project, we should try to think much harder about the long-term consequences. The question is not, do germline enhancements raise brand new ethical problems? There are no new ethical problems under the sun. The question should be, will these techniques exacerbate injustices that already plague us? Will supporting these techniques tend toward more justice or less?

If you could do so safely, would you use an artificial chromosome to extend the lifespan of your child?

The prospect of life extension raises difficult questions for those concerned about justice and the germline. If my wife and I were thinking only about our child, we probably would be delighted to increase her or his life expectancy by a decade. But we are committed to thinking about not only our own children, but about their children, and about all the others with whom they will share the world.

It does not require a vivid imagination to see the probable ecological consequences of widespread extension of the human life span beyond what many biologists have discerned to be the "natural limit." If one considers galloping human population growth, dwindling forests, dying fisheries, and global warming, one sees no pressing ecological need for humans to live longer. If our moral concern extends beyond an exceedingly narrow conception of what is good for us and our children, then life extension looks like a lamentable use of extraordinary human intelligence. Many of us in the "developed" nations may be tempted to say, "Well, the *real* environmental problem is the result of those folks in the 'developing' nations having so many children. *We* only have one or two children per couple." The birth rate in the developing world is a huge problem, but equally huge is the problem that we in the developed nations are consuming limited resources at an unconscionable rate. The idea of now trying to extend our lives—and thus our opportunities to consume still more—strikes me as woefully shortsighted at best. Thus, to the kind offer of life extension for our prospective children, my wife and I would say, "Thanks, but no."

Burke K. Zimmerman: "Human Germline Intervention: What's the Fuss About?"

The targeted, fully controlled modification of the human genome in a fertilized embryo is technically feasible. I shall thus begin by assuming, first, that we have a detailed knowledge of the human genome, the functions encoded by each set of genes, and the variations that make us different from one another, and second, that we are able both to correct obvious genetic pathology and to select—without introducing unwanted errors or genetic artifacts—the alleles that confer a variety of known traits to our children.

Let us examine the potential uses of such methods in light of the prevailing ethical standards governing the practice of medicine, the auton-

omy of parents trying to provide the best possible lives for their children, and distributive justice. It is difficult to see how adding germline modification to all of the other things one now can do for one's children, and in fact that one is expected to do to bring them health, quality education, and opportunities for developing their talents, poses anything inconsistent with the ethical norms that prevail, at least in western society.

The physician has an acknowledged ethical responsibility to use whatever methods are available to treat and prevent illness or pathology in his patients. If safe and reliable germline genetic surgery on a newly fertilized embryo is available to correct a known inherited genetic pathology, then, unless other means exist to avert that pathology, the physician has a moral obligation to use this technique to try to ensure the health of the baby. Physicians have no such moral imperative, however, at least according to today's norms, to assist prospective parents in attempts to give their children added genetically determined talents or more desirable physical attributes. But neither, of course, do physicians have an ethical proscription to help people enhance themselves through cosmetic surgery, which is routinely done.

Parents are expected to give their children the best possible opportunities in life. Thus, we promote their health and education and optimize their environments to give them greater opportunities. Why, then, should this responsibility not also extend to genetic factors that may determine a child's physical and psychological attributes, including even cognitive ability? While people can slightly improve their children's odds by carefully selecting a mate, only germline intervention will permit full control of their genetic endowments. Is there some unwritten social truism that people must forever be bound to play a genetic lottery when they procreate? Would not the well-accepted principle of autonomy leave such a choice solely to the prospective parents?

Autonomy, however, is often at odds with the principle of distributive justice. Since such germline techniques are not likely to be cheap, at least in the beginning, nor to be covered by national health programs or, in the United States, by private insurance, these techniques would remain a privilege of the wealthy. It is feared that their use would only widen the gulf between existing social and economic classes. *The Bell Curve*, Herrnstein and Murray's widely attacked work,[5] contends that, for generations, significant selection has been skewing the gene pool between the upper and lower classes. Their arguments may be flawed, but germline methods for the privileged would guarantee such a dichotomy.

Nonetheless, to demand justice in this province when it is not applied elsewhere is inconsistent. In the United States, even minimal healthcare is not available to everyone. The distribution of wealth, privilege, and

opportunity, particularly the kind that provides children with a rich environment rather than a culturally and educationally impoverished one, is grossly skewed in most of the world. In the absence of broad and serious commitments to improve distributive justice with respect to the many *existing* elements that contribute to the quality of people's lives, arguments about the inequities of germline intervention ring hollow.

Of course, the techniques of germline intervention, as with computers and other new technologies, will be steadily improved in their reliability, scope, and cost. But if this is the slippery slope, then its effect will be to make this privilege of the wealthy generally available.

I do have some worries, however. The deliberate reassortment or correction of genes that are part of us does not really enter the realm of the unknown. But, one day, someone may be tempted to try to leapfrog human evolution by attempting to design a new gene from supposed first principles. Given our dismal record in predicting the consequences of new technologies, and our perennial smugness in believing we understand far more about nature than we do, I would have grave doubts about the wisdom of such intervention, even with extensive data from animal models. While we may eventually understand how this marvelous creation, including our brain and other components, actually works, we must keep in mind that the human system is the metastable result of a long evolutionary process, and that the pieces all work together in optimized harmony. Adding new or altered components, however good our knowledge of the system, could have unpredictable consequences. This represents a risk that no one should ask an unborn child to assume.

> If you could do so safely, would you use an artificial chromosome to extend the lifespan of your child?

Of course I would want my child to have an additional ten years of quality life. Who wouldn't?

I am assuming that, in being offered the opportunity to extend the lifespan of my child-to-be by adding an extra chromosome pair, there were already extensive human data to show that the procedure was safe and actually slowed the aging process. Naturally, I would wish to review personally all of the data and experimental protocols used to establish both the efficacy and the outcome of the procedure. In any case, my decision would be very conservative.

But, while being convinced that the safety and reliability of the procedure would be simply a matter of stringent scientific validation, the question of how an additional chromosome would assort when it comes my offspring's turn to procreate is another matter. My decision would clearly

have an important effect, not only on my son's or daughter's life but on his or her children and on all subsequent generations. Therefore, while there may not yet be human data on the next generation, I shall further assume that there are extensive animal data on the fate of such an additional chromosome throughout many generations and on its interaction with the existing set of chromosomes. If my child wishes to have children someday by someone who did not happen to get an extra chromosome, we had better be sure that a dangling unpaired chromosome is not going to cause trouble.

And if, as I was about to allow the procedure to proceed, a last-minute finding indicated a long-term downside of any sort, I would surely change my mind and, no doubt, chastise myself for not having considered such a possibiliy in the first place. But what if the news comes after his birth?

If I have acted with proper respect for the limitations of the scientific method, then my child should at least understand the basis for my decision. But if I were too conservative, and he found himself aging sooner than his contemporaries who had undergone the procedure, would he resent me one day as being an ultraconservative old fuddy-duddy unwilling to take risks? Unless of course his peers were experiencing an unexpected consequence, for example a much higher than usual cancer rate—would he then be thankful for my wisdom? On the other hand, if I chose to extend his lifespan, he would surely thank me, unless he were one of the excess cancers.

Thus, while I would use my best judgment to do right thing for my child, nothing is certain. As in all the other decisions we make in bringing up our kids, every choice is something of a crapshoot. There is, therefore, no guarantee whatsoever that the next generation would appreciate my decision, whatever it may be, as every parent of grown children knows all too well.

Paul R. Billings: "Germline Culture—The Genetics of Hubris"

One view of the twentieth century, when so many of the developments in human genetics have occurred, is that it has been humanity's most bestial—we have fought amongst ourselves more viciously and killed each other more copiously than ever before. Few wise individuals predicted that outcome, fewer still claim to understand it today; control of the forces which produced the recurrent tragedies certainly eludes us.

Another formulation of our recent past might instead emphasize changes in relationships. For instance, our relations with others have been altered by the telephone, video, E-mail, and the psychological constructs

of Freud and others. Our position vis-à-vis the natural world has been reformed by travel in space, on airplanes, and in cars, by sanitation and new foods, by antibiotics, and by the investigations of science that have demonstrated human life's identity with other life forms on earth.

Some see promise in these changes, while others sense threats. Some look optimistically for new information and synergies, while others feel ever more alienated and helpless to maintain value in their lives. Change has always occurred; for some it is welcome, while for others it only bodes loss, pain, and the end of life.

When *HMS Titanic* sailed from England in 1912, the ship embodied one narrow view of humanity's relationship to the natural world. Bigger, better, more powerful than any previous boat, this vessel was unsinkable, impervious to the furies which had ravaged the lives of seafarers for all of time. *Titanic* was the quintessential product of human endeavor and the industrial revolution that had transformed many late nineteenth-century cultures. With its many decks crammed with a cross-section of the society it left landbound, *Titanic* represented the wrestling of control of ocean navigation and travel from the gods and nature, and the placing of that control firmly, safely, and forever under humans. But the intricate interaction between nature, with its complex systems, and humans, with their essential limitations, was misunderstood. The high aspirations embodied by the *Titanic* ended in still repose on the ocean floor along with the lives of over 1,500 passengers.

Though we have far more scientific information relevant to genes and genetic manipulation than ever before, our ignorance is still overwhelming. Simple concepts such as what a gene is, or how a gene's biochemical variation correlates with measurable phenotypic phenomena, turn out not to be simple. Continuing human creativity and efforts to *understand* will fill in some gaps in our knowledge, but much may remain obscure. We can hope for more useful information, for special cases that will allow our knowledge to be applied, and for serendipity that will lead to unexpected good. Moreover, by attempting to understand human genetics and gene manipulation, we may gather information useful in other pursuits or develop models that illuminate their inherent limitations.

The anthropologist Gregory Bateson once noted, "The map is not the territory." Yet a few biotechnologists armed with powerful new "weapons" against human diseases are using a new and primitive "map" to direct an assault that will affect themselves, their neighbors, and—if the germline is modified—generations to come. To suggest that even this highly-trained and specialized group can assimilate a diverse variety of inputs and viewpoints, temper their hubris to appreciate the role of fashion and biological and nonbiological complexity, appreciate the social construction of many

human conditions and characteristics, and balance human needs against our wish to help and to control the unknown is more than is reasonable to expect. To implement so powerful a technology when there is no true need, so much ignorance and such diversity of opinion, and a clear forewarning that it will create more inequality and suffering for both those changed and those left out, is intervention without consent, mandate, or justification.

Are we scientists undeterred by the wisdom of the sociologist Thorstein Veblen who, when commenting on whether men and women differed in their ability to learn, suggested deferring that assessment until both had been treated equally for several generations? Will we lobby groups that can barely appreciate the implications of applying genetic "fixes" prematurely or inappropriately? Is the schism of science and other cultures, noted by C.P. Snow, about to yield a fissile energy that will humble us? What are the risks, and what are the possible gains?

I challenge myself nearly every day to know when to act despite my own failings and ignorance, and to not act as if I know things that I don't. Each day I temper myself with the Hippocratic wisdom, *primun est non nocere* (first, do no harm). I am not sure what level of assuredness would be required for the implementation of human control over the evolution and design of its DNA. Even to ask such a question, in my view, reflects both a reckless temerity and a blindness to the many ways human culture has already modified forces at work in the natural world. I do know that we are *not* at that point and that medicine's moral guide is still derived from caring for those who are sick. Genetics, like the other sciences, exists as a challenge to ignorance. Its tools are limited by rationality and generate not truth but questions, the answers to most of which are not known.

> If you could do so safely, would you use an artificial chromosome to extend the lifespan of your child?

The extension of life expectancy is not an unfettered "good." Otherwise, the aphorism, "Life is hell and then you die," might simply be, "The more, the merrier."

Another decade of pain, loss, frustration, poverty, torture, violence, victimization, fear, abuse, and indignation would not be relished or desired by most people. Even with today's seeming progress and relative prosperity, some choose suicide to end a life which might otherwise continue for some time. The point is that longevity is a *conditional* good, dependent on a complex array of factors. The biomedical literature on how health care consumers differentially value "life years" is one reflection of this issue's complexity.

As a physician, I have sworn to lessen individual suffering and to take measures to maintain the public's health. Even this limited responsibility is hard to satisfy, so I am grateful for its limits. As a father, I rail against the presumption that I should know best about matters pertaining to the life of my child. I would prefer not to overreach my paternal role and, instead, try simply to protect my child's life and provide what is needed for her growth.

I trust that my child would understand my wish not to presumptuously interfere with lives other than my own. Since, in the physical universe in which we shall forever live, the posed conundrum is implausible without risk or cost, it is equally unlikely that such an intervention could be reversed without impact. If a technology were actually available on such impossible terms, I might be forced to reconsider my views both on this issue and on the role of scientists as deities. But more likely, I would wonder if I next were to be sold a bridge in Brooklyn.

James Hughes: "Liberty, Equality, and Solidarity in Our Genetically Engineered Future"

If we respect people's right to bodily autonomy, we need to permit people to choose germline and enhancement genetic therapies. Most of the arguments against gene therapy are either based on uncontestable matters of faith or describe risks insufficient to justify abrogating this fundamental liberal democratic right.

Bio-Luddites reject germline therapy and insist that we preserve the genetic "patrimony" for future generations. But our grandchildren will not thank us for passing along genetic diseases for them to fix through far less effective somatic therapies. Descendants generally prefer to inherit property that has been well maintained and improved, not maintained as a historical landmark. Our grandchildren will likely appreciate being made a little smarter, stronger, and healthier before birth.

A second argument used to stall the genetic revolution is that the genome is too complex to predict the certain catastrophic consequences of our modifications. This is Luddite mysticism, a warning against hubris. The genome is undoubtedly complex, and before we allow potential parents to apply germline therapies we should understand their consequences reasonably well. But we already have certain knowledge that genetic disease and disability is a bad thing (despite the arguments of disability advocates to the contrary) and that the potential benefits of genetic enhancement are enormous. The burden of proof for the product safety of

genetic therapy needs to be finite, achievable, and balanced against these known benefits. Alleged risks to descendants ten generations from now are irrelevant. Our ability to fix any mistakes will rapidly advance in every decade.

What is really at stake in this debate is whether we will find the liberal democratic road to the genetically engineered society. The late twenty-first century will be made up of humans and human-animal hybrids, augmented by genetic engineering, nanotechnology, and information technology. Some societies will delay this transition to posthuman diversity as long as possible, adhering to a rigid biofundamentalist notion of what humans and citizens are supposed to be. But the individual and collective advantages to be had from the extension of human ability will make the transition very likely. Nations that refuse to embrace genetic enhancement will find themselves at a serious disadvantage. To block this transition will require an unlikely global regime of authoritarian surveillance, since the technologies will eventually be cheap and easily hidden in small labs.

The question about genetic engineering is not whether it will occur, but whether democracies will embrace the transition and shape it with the values of liberty, equality, and solidarity. A basic principle of liberty is respect for bodily autonomy. If we allow individuals and parents to choose their own genetic course, and avoid government prohibitions of or mandates about gene therapy, the results will be diverse, dynamic, and progressive. People will choose all kinds of body types for themselves and their kids, but most will choose to be healthier, longer lived, and more able. What better guarantee and reflection of liberty than a society embracing a growing diversity of healthy, able bodies?

As to equality, a universal, publicly financed package of health services is a prerequisite for the equitable provision of genetic therapies, whether the therapies are included in the plan or purchased on the market. After we establish equitable access to basic genetic therapies, we also have a responsibility to encourage parents to provide their children all reasonable opportunities for health or abilities. Today we agonize about how strenuously to coerce parents to give their kids an education and provide them with vaccinations and necessary medicine. In the future, we will agonize about parents who deny their children routine, safe, and effective genetic enhancements for health, intelligence, and ability. Liberal democracies may avoid an absolute mandate on genetic enhancement, the way we currently permit home schooling and religious exemptions to vaccinations. But even if legal, it will still be unethical for parents to refuse to provide their child cheap, effective genetic therapy or enhancement. If the therapy involves no great cost and no risk, this act of omission will be ethically equivalent to actively robbing them of life, health, or ability.

To preserve solidarity, we need a new model of collective identity, of "transhuman" citizenship. Rights and citizenship must be redefined around the abilities to think and communicate, not around human, version 1.0, DNA. As humanity subspeciates through germline therapy, it will be best if we can remain part of the same polity, a common society of mutual obligation and tolerance, for as long as possible.

In the end, genetic therapies raise no new questions, only old political ones. Do we have a strong enough scientific and regulatory apparatus to understand the consequences of our actions? Do we have the courage to tolerate free choices and extend the boundaries of our polity? Do we have the fellow feeling to ensure the general good and secure the rights of our fellow citizens? Genetic engineering just raises the stakes on these old challenges.

> If you could do so safely, would you use an artificial chromosome to extend the lifespan of your child?

Yes, I would use cheap, safe, and effective therapies to enhance my children' s abilities. In fact, I believe it is a moral obligation of parents to act in their children's best interests, and by definition I think greater intelligence, health, and longevity is in their interest. We frown at the mother who drinks and smokes heavily during pregnancy, and we smile on those who take their vitamins and then work hard to stimulate their newborns physically and mentally. Why is genetic therapy morally different? This holds equally true for whether the choice is to fix a genetic disease or to enhance abilities beyond the human norm. We don't condemn parents who work to give their kids better diets or educational environments above the national average, we praise them.

I am incredulous at disability advocates who argue that correcting genetic disabilities is a form of discrimination against the disabled. Are we to deny parents the option of correct their children's retardation or infirmities? Perhaps we should then also refuse to allow parents of PKU (phenyl ketohuria) kids to put their kids on the diets that would prevent their retardation, or refuse therapy to kids with any disease since, "That's the way they were meant to be," and therapy implies we don't love them for who they are.

Many skeptics also fall back on the potential unforeseen consequences of the therapies. The standard of evidence of safety needs to be specific to the therapy, however. In fixing serious genetic disabilities in my kids, I would accept much weaker evidence of the safety and efficacy of the therapy. For cosmetic enhancements, such as for our family's obesity, I would require a much higher standard of evidence, especially if there were effective nongenetic therapies.

George Ennenga: "Would Humanity Be Better Off . . . or, What Would It Be Better For?"

We consider our historical tracts, monuments, parks, and, by extension, the global ecosystem as our common heritage. Their conservation is imperative to the common good, and their availability is held as a right. Including the human genome in this legacy and conserving it against change might seem indisputable.

However, the processes and actualities of biology are different from those of politics, society, or architecture. *Nature* and *genome* are useful as abstractions in discussion but have no biological foundation. In biology, there are only individuals that can be considered collectively as a species. The ecosystem is compounded from individuals of manifold species in complex, changing, adaptive zones. A genome is generalized from the genetic character of individuals. Changes in adaptive zones are accommodated by a concomitant response in genetic combinations of those individuals. So, while a social contract or building exists in stasis, environments and genomes evolve in dynamic mobility. The principles are change and adaptation, not conservation and stasis.

Questions of modifying our genetic character lead to considerations of our common good and our highest purpose as a species. When we appraise the common good, we must refer to John Stuart Mill. He defined the *common good* as the highest inclination for individuals in an educated society, and *right action* as that which promotes the most happiness for all. These terms differ in biology, as opposed to politics and sociology. Happiness for every species must be construed as its greatest suitability to and survivability in its adaptive zone. Insuring that suitability must be the greatest common good, for our species as well as for all others. Collectively, our suitability must be a major priority.

Yet, we live not only in a natural habitat, but mostly in our created cultural environment. Although we have evolved little genetically in the past 40,000 years, our cultural evolution has been extraordinary, indeed, earth shattering. While organic evolution changes steadily, but without clear patterns, our cultural evolution grows exponentially. The accumulated technological developments of the past 200 years only indicate how vast our cultural evolution will be in future centuries. Increasingly, we humans will slip inside our cultural environments to become their authors and their subjects. These future environments will change and, no doubt, be varied, and so we will need to be equally mobile. Assuring our suitability and harmony in these various zones must be our greatest common good, otherwise we will not be at all happy.

"Artificial Evolution" is the controlled manipulation of genetic information from one generation to the next, where the first variational step is engineered and the second selection step is insured by humankind. It is qualitatively different from natural evolution. The biotechnologies of in vitro fertilization (IVF), gene transplantation, and germline engineering are the methods of developing this loop out of evolutionary time.

Artificial Evolution will provide the way for our species to change and grow in accord with environments of the future and in accord with nature, especially including human nature. Freeman Dyson holds that, "In the next hundred years . . . we will see genetically engineered plants and animals adapted to the colonization of various asteroids and planets. . . . As humanity expands its living space away from the earth, our one species will become many, . . . some adapted to heat, others to cold, some to zero gravity, others to strong gravity, some to high pressure, others to living in the vacuum of space."

From this vantage point, it becomes critical to identify the principles of change and mobility as central to our future. If our greatest happiness and common good is to be served, our species must keep genetically apace with our cultural evolution and in harmony with future adaptive zones. Far from conserving the genome in stasis, we must activate our genetic character diligently, conscientiously, and responsibly to guarantee our suitability to expanding environments of the near and far future. Our dignity, and even our security, will be enhanced by modifying our species to fit new environments. Failing to act upon the opportunities of germline engineering would condemn our species to a static role in an otherwise dynamic universe and would greatly delimit our futures. Artificial Evolution will be our method, truly our vehicle, into those futures. It will be our way of recognizing, of honoring, and of turning to our wider universe. What higher purpose, what greater dignity for humanity might there be?

> If you could do so safely, would you use an artificial chromosome to extend the lifespan of your child?

It is rather like extending the party for an hour. . . . No hesitation whatsoever, given the procedural safety. My main concern would be that others, like my young daughter, did not have the same opportunity. She would no doubt feel jealousy, but hopefully appreciation and wonder as well. By extension, the ethical issues are ones of fair distribution and availability of this or any other specific procedure in our Artificial Evolution. Natural Darwinian evolution is nonprogressive, discontinuous, and without value. Our species is not part of a progressive sequence; it is no more or less important than another. But, by creating *longevity* as a human value in

our offspring, or any other human value such as *useful drugs*, we are bringing value and progress to the evolutionary process. A life is more valuable to us as *longer*, but, more than that, the whole process becomes progressive and continuous to us. This added chromosome, then, would create continuity in evolutionary time and, thus, if not for extending the party for one child, but simply for itself, would be a marvel.

Jan C. Heller: "Why Human Dignity Should Not Keep Us from Genetically Engineering Our Children"

Within certain natural and cultural constraints, the ability to shape our individual and collective futures in deliberate and self-conscious ways is a distinguishing characteristic of the human species. Human germline engineering holds the potential to remove some formidable natural constraints on this ability. Would it be permissible to remove some of the cultural constraints as well?

One of these cultural constraints is the belief that there is something in the nature of being human that utterly prohibits us from engineering the human germline. That "something" is often discussed as being dignity, a quality that humans are said to enjoy because, from the Western religious view, we were created in the image of a personal deity, or, in its secular derivative, because we have the capacity to become persons. This constraint leads to a prohibition on human genetic engineering based not on the uniqueness of our genome, but on what this genome makes possible—our personhood.

Dignity, I believe, ought to be regarded as a genuine moral constraint, and thus it ought to limit what we can do in the effort to shape our futures. But it is a constraint that rationally can be applied only to certain classes of humans. It makes obvious sense to discuss the dignity of living humans. We would not think it right to kill some innocent humans so that others would enjoy a better future. It also makes sense to discuss the dignity of humans who will live in the future. We would not think it right deliberately to leave, say in a former war zone, landmines that might harm future people simply because they do not yet exist. And we even grant limited dignity to dead humans, such as when we respect their Last Wills and Testaments. However, it makes no sense to discuss the dignity of a class of humans that I call "contingent future persons." These are *people who may or may not live in the future, depending on our choices.* Future children who might have their germlines engineered are in this class of persons, assuming, of course, a sufficiently advanced technology.

The dignity of contingent future persons cannot be violated by *any* choice that brings them into existence. Indeed, they cannot be said to have dignity. This claim is based on the fact that the identity of any person is time dependent, that is, contingent on the time of its conception. Thus, if agents can control the timing of the conception of a future child, any sufficient alteration of that timing will result in a *different* child actually being born—different, that is, than the child who would have been born had the timing of conception not been altered. The same claim can be made about embryos whose genomes are altered after conception: A child with a different identity will actually be born as a result of the alteration. Could the dignity of the child who is *actually* born be violated by such technologies?

However regrettable, the answer to this question is No. Any reference to the dignity of such a child leads to an argument that becomes hopelessly circular and self-defeating. Before the child who is actually born has been conceived, it (obviously) does not yet exist as a person to whom dignity can be ascribed. All reference to its dignity must await (at least) its conception as the person it will finally be, and by that time its dignity is not in question. Said differently, because the choice we are evaluating is the very choice that will make it possible for a contingent future person to come into existence with dignity, we cannot refer to the dignity of that future person when trying to decide whether to bring it into existence.

Ethically, this means that human dignity cannot be violated by bringing a child into existence with its germline engineered. If this is true, then we can determine the permissibility of the proposed technologies only by considering their likely consequences. My hunch is that they will not be sufficiently bad to warrant a prohibition on all human germline engineering. Moreover, if there is a market for such technologies, it might be better to put incentives in place to nudge their development in certain directions and to do so in a highly-regulated environment.

> If you could do so safely, would you use an artificial chromosome to extend the lifespan of your child?

This question is somewhat like asking whether I would be willing, without risk or obligation, to accept, say, a large amount of money for my future child. I suspect most of us would accept this gift, just as most—assured that no additional risk or cost would be incurred—would probably agree to increase their future child's life expectancy by a decade. A more difficult question is whether I would agree to such a procedure *knowing that my spouse and I do not need the IVF (in vitro fertilization) technology to conceive a child.* That is, when such procedures become widespread, would we forego natural conception and incur the moral, emotional, and economic costs of

IVF in order to give our future child the *chance* to live an extra decade (for the artificial chromosome cannot guarantee the extra time)? Since most prospective parents will not require IVF to conceive a child, this question is the more likely one to be asked as such options become widespread.

I would first try to weigh the risk of not having *any* child using IVF against the likely statistical prospect of having a normal child conceived naturally. If I opted for IVF, I would then try to weigh the likely benefits and burdens of an extra decade. For this, I need to make a prediction about the *conditions* under which the child's extra life would be lived, say, ninety to one hundred years from its birth. Would the child be likely to enjoy good physical and mental health? If *many* people were living an extra decade of life or if the population were very large, would there be enough resources for my child? If *few* people were living an extra decade, would my child become a target of discrimination or envy? In the end, if I were using IVF in any case, I might opt to insert the artificial chromosome. However, in view of the uncertainties of IVF and of future conditions, I would not forego natural conception for a chance to give my child an extra decade of life.

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Regulation and Jurisdiction

Some have advocated the development of an international policy on germline engineering and cloning. Do you think this would be preferable to a patchwork of national policies and thus worth pursuing?

Darryl Macer: "Universal Bioethics for the Human Germline"

Germline engineering and cloning technologies present a challenge to the tolerance of individual and cultural reproductive autonomy enshrined in the human right for reproductive choice. While the creation of a child by the assistance of any technology cannot be made a crime, I believe there is a need for international regulation and education to promote responsible parenting. This is based on the shared biological heritage and destiny of human beings in all "nations"; on the transitory nature of "nations" and the precedents for international law to protect humanity's common interests; and on the common perceptions and bioethical reasoning of peoples around the world—universal bioethics.

One of the arguments behind international approaches to regulate germline gene therapy is that the genome is shared by all people who have diversified from a common African ancestor over the past 100,000 years.

The germline is common property under the international conventions on human rights, and the common heritage concept is enshrined in the UNESCO Declaration on the Human Genome and Human Rights unanimously accepted by all 186 countries of UNESCO in November 1997, and by the United Nations General Assembly in 1998. Another argument based on common future interest is that because people migrate and those born as clones or with altered germlines will move across national borders, the whole world is potentially at risk.

International guidelines provide some minimum standard. Many nations will not develop their own regulations, so an international umbrella guideline is needed to protect the present and future peoples of these countries. Who has ethical interest in protecting the germline? National governments may pay health costs, but regional blocks such as the European Union may also take on this role. Human rights laws are already based in international law. All people have a common interest in the germline, so transnational guidelines are desirable, unless we want racial hygiene laws designed to protect the citizens of one country that outlaws germline therapy from the reproductive cells of people from the free-market genetic engineering state.

There are already successful transnational agreements to protect common interests and the interests of innocent parties from future technological advances. Such agreements include the law of the sea, laws against ocean dumping, conventions against biological and chemical weapons, laws against the militarization of space, declarations of human rights including those on reproductive freedom, conventions aimed at halting ozone depletion, and treaties to slow the loss of biodiversity. If we protect the commons of the sea, it is not surprising that we want to protect the commons of the human genome.

The UNESCO Declaration bans human reproductive cloning in Article 11, which generally has been supported by countries that have debated it. But this prohibition raises serious questions about reproductive autonomy by claiming that the technique is against human dignity. A similar argument also was used in the European Bioethics Convention against germline genetic engineering, but given the range of techniques that are legally supported at this time, one can certainly question whether an individual couple's reproductive choice in these matters really would be contrary to human dignity.

While it is important to adopt standards that are suitable to each society, such standards should be based on the views of the individuals in each society. At present, some countries have standards based on false assumptions of cultural uniqueness. Within even a single community, opinions

differ about bioethics issues such as preimplantation diagnosis, gene therapy, and risk. But data shows that people may use the same universal principles or ideals, even if they sometimes balance them differently to arrive at different decisions. Universal bioethics does not mean identical decisions; it means that the range of decisions in any one society is similar to those found across the whole world. It is also not the same as absolute ethics, saying that there is one correct ethical decision for a given set of circumstances; rather it would say that because of our love of life and human rights, people in any society should be given some choice over decisions of their lives. If people are the same everywhere, then the same standards of bioethics may be applied everywhere, while respecting the freedom of informed choice and responsibilities to society. This is universal bioethics.

The need for discussion of the consequences of germline gene therapy and enhancement is international, but many developing countries do not possess resources to have national education programs. The success of cosmetic surgery suggests that, once it is possible, the 20–30 percent in developed countries who accept genetic engineering to improve intelligence, physique, or personality, may do so in practice, as will the majority of people in developing countries.[6]

The purpose of regulation is to avoid doing harm. At the same time, loving good also demands us to do good. To cure disease using genetic therapy is a good, and those who want to ban it should prove otherwise. Above all, we need to educate people how to exercise informed choices in medical therapy, restricting choice only if this will harm others or society in general. Regulations should postpone the general use of germline genetic therapy, reproductive cloning, or enhancement until people can make such difficult decisions more wisely, but their decisions will transcend artificial boundaries of culture or nation.

> If you could do so safely, would you use an artificial chromosome to extend the lifespan of your child?

No, I would not use the procedure, because I would want to see the results in reality. If the technique existed, then at least in the lifetime of the child, the technical ability would come to allow the change during his or her life time. It would be better to let children decide their own fate, because informed choice would respect their autonomy. If 99 percent of society was performing the change, however, and it was shown to be safe, then I might allow it from the beginning, in the same way I support vaccination.

Lloyd Cohen: "Multi-Jurisdiction Regulation of Germline Intervention—A Policy with Neither Virtue Nor Prospect of Success"

Leaving aside its virtues and vices for a moment, is a unified international system of regulations of germline engineering even possible? The lessons from other areas of human activity are that only some shared gains from mutual cooperation and some means of retaliation for defection permit any multinational system of regulation and restraint to succeed. The partial success stories I am aware of all involve regulation of international trade, either agreements to abstain from imposing tariffs such as the General Agreement of Tariffs and Trade and NAFTA or, alternatively, agreements to restrict sales and raise prices such as OPEC. The character of these successes is that each of the participating parties sees it as in its interest that the collective enterprise succeed, and that each is subject to sanctions from the other participants if it cheats on the agreement. Unless multinational regulation of germline engineering offers some substantial gain to the participating nations and entails some prospect of retaliation, its "success" even in the limited sense that it would result in adherence, to say nothing of whether it would serve a good end, appears highly doubtful.

The jurisdictional breadth of any regulation should correspond to the breadth of substantial interest. So, for example, Moscow, Idaho, and Moscow, Russia do not share a common set of parking regulations, because the residents of each locale are largely unaffected by the parking rules in the other. On the other hand, mercury-laced wastes from mining operations in Montana that leach into the upper reaches of the Missouri River create potential health hazards for people in Louisiana. So, as a threshold issue, we must ask what dangers are posed by germline manipulation and whether those dangers have significant cross-border manifestations.

I have heard mention of three sorts of dangers. The first is a moral objection to making decisions that affect the genetic inheritance of unknown (and unborn) others; the second is some concern with inequalities (and therefore inequities?) in access to genetic advantages; and the third is a general concern with the integrity of "the gene pool." Leaving aside, for the moment, whether there is any substance to any of these objections, there is the ancillary issue of their jurisdictional and geographical character. That is, to what extent does the weight of concern diminish with political and geographical distance?

The first two objections are of a moral/political character with which the educated layman is well familiar and have little to do with genetics

per se. People in other countries may engage in practices that we find odious. Whether it be slavery, abortion, the prohibition of abortion, capitalism, or communism, our knowledge that these vile practices take place anywhere in the world distresses us, and so we seek to eliminate them. That said, offensive abortion laws in Lagos, Nigeria, distress Americans less than those in Windsor, Ontario, and both far less than those in Detroit, Michigan. So, too, with these claims of an ethical harm to others resulting from germline engineering. If Brazilians place too much emphasis on the genes that lead to success at soccer, it will trouble Americans decidedly less than if New Yorkers do so.

Beyond that, however, the presumed immorality of genetic manipulation remains largely a mystery to me. The evil done to one's issue by manipulating their genes, or alternatively the evil done to others by giving an advantage to one's own issue not available to all, seems petty indeed. As for the first, who better than the parents and grandparents to make the decision for their prospective issue? They are clearly the most reliable agents of that future person's interest. As a general matter, we trust parents to make decisions that affect the future health, character, and personality of their children. I can see nothing substantially different in the case of germline engineering that warrants a different policy.

In some sense, the opposite concern is that the parents will do too good a job, that is, that they will provide their own offspring an advantage that others with fewer financial resources will not have available. To those morbidly concerned with absolute equality of result, this may seem a substantial problem; it does not seem so to me. Far more substantial environmental and genetic advantages—through assortive mating—are already available to those with financial and other advantages. Germline manipulation would be a trivial addition to this inequality. Indeed, given the likely rapidly declining cost of genetic engineering over time, the ability to enhance the genetic virtues of one's offspring will become widely and cheaply available and thus serve to equalize the genetic endowment of human beings.

The final, and most substantial, external effect on others of genetic engineering is some transformation of the human "gene pool." Here, too, the danger seems illusory. Imagine the thoroughly implausible possibility that Brazil, for example, were to engage in germline engineering that created changes in the genotypes and phenotypes of Brazilians that the rest of us found unappealing. How different is that from what already exists? The nations of the world already differ in their gene pools to a far more substantial degree than could (in the foreseeable future) be brought about by genetic engineering. In response to this difference, in order to prevent or at least minimize the entrance of those undesirable phenotypes and

genotypes into another nation's population and gene pool, the obvious policy is to restrict immigration. Why is that policy not sufficient to handle germline engineering?

But, more realistically, how likely is it that the Brazilians or anyone will transform their own gene pool in a way that we find so unattractive? Does anyone have a serious objection to eliminating Huntington's? or Tay-Sachs? or breast cancer? or to increasing intelligence?

So, in conclusion, I can see neither the prospect nor the virtue in multi-jurisdictional regulation of germline engineering. Further, while I await some more powerful argument from the other side, for the moment I see the need for precious little additional national regulation beyond that which is already applicable to medical procedures on human beings.

> If you could do so safely, would you use an artificial chromosome to extend the lifespan of your child?

Which part of life is being extended? If it is ten years of healthy maturity, the answer is a clear Yes. If it is ten years of senile decrepitude, the answer is a clear No. If it is ten years of childhood, the answer is less clear. If it adds to each of these periods of life proportionally, simply slowing down the growth and aging processes, the answer is a qualified Yes. I would wonder whether it slows down life in any other internal sense.

On some deeper level you are asking about preferences with respect to a *sui generis* class of genetic manipulation. All other sorts of manipulation would be directed to affect some characteristic of life, such as intelligence, health, or size. The question you pose is more fundamental dealing with life itself, not its constituent parts or character. Is life per se worth living? And, if so, is more better than less? This is a deeper question than I care to address in this forum and subject to these space limitations.

Appendix

Select Questions from the Public to Participants in the "Engineering the Human Germline" Symposium

QUESTION: Am I correct, Dr. Anderson, that you're saying that the risk/reward ratio is the driving force? If so, the line you drew between enhancement and treatment is somewhat inaccurate. For instance, you might view blocking aging as an enhancement, but there's obviously considerable reward to that.

FRENCH ANDERSON: I would not consider the normal aging process a disease. The consequences of aging—namely, cancer, heart disease, stroke, and so forth—are degenerative processes that take place; those are diseases.

LEE SILVER: I think one of the ways of getting over the problem that French mentions is also a question of what you mean by *enhancement*. When parents want to give something to their children which already exists in other individuals and society, you already know how that will operate. You're talking about an alternative allele that other parents give to their children naturally, but that you can't give to your children because you don't have it. And no one wants to have an average child, of course. I don't know anybody here who would. So, is it enhancement to give your child something that other children get naturally? I would think it's very difficult to stop parents from doing that particular kind of treatment.

MICHAEL ROSE: I'd like to make a somewhat different point. I think you're tieing yourself up into all kinds of knots that arise from the medical model, which is basically inherited from Hippocrates. It's a model that's 2,500 years old. I would suggest that if you reconsider your basic biology, in terms of concepts like quantitative genetics and fitness,

selection, genetic variance, and environmental variance, you would find your way out of a lot of these problems.

FRENCH ANDERSON: Is breast cancer normal?

MICHAEL ROSE: Aging is totally normal. Breast cancer is dramatically age dependent, so if you're alive over age 100 you're way overdue for mortality in terms of the normal aging pattern, to which I say: If we find something that enables us to live to be age 200, even if I'm an M.D., I'm not going to say No to it, even if it's abnormal. I mean, what can be abnormal can be fantastic.

FRENCH ANDERSON: Is breast cancer normal?

MICHAEL ROSE: In terms of the age-dependent profile, to get cancer is very normal. It's difficult to find a person over age ninety who, on autopsy, does not show some signs of cancer, some signs of tumor.

FRENCH ANDERSON: So you would say that breast cancer is normal?

MICHAEL ROSE: So are all the cancers. The older you get, the greater your chance of getting Alzheimer's; the older you get, the greater your chance of cardiovascular disease. All of these things reflect the failure of natural selection to operate at those ages. The functions we have when we are young do not betoken normality, which is a meaningless concept in biology; they instead betoken the action of natural selection to make our bodies work well.

FRENCH ANDERSON: I would say that if you think that Alzheimer's, breast cancer, and so on are normal, then you are tied up in philosophical knots that you need release from.

QUESTION: My question is about the idea of medical ethics. Informed consent is usually required for a patient. We can't even agree about whether an embryo is an individual. How in the world can we address the idea of informed consent when we make changes to the germline?

JOHN CAMPBELL: Informed consent sounds like something you could not have unless it was in advance; but I think you can.

In my examples, a change is made that is genetic but of absolutely no consequence until it is activated. The only thing that would happen would be a particular transcription factor produced in a particular cell type. The recipient has to choose whether to activate this particular gene cassette.

If people are really concerned about this issue, we could take an artificial chromosome or a segment of it and put a lock on it so that none of the genes would have any effect until a person took an artifi-

cial hormone pill to unlock the cassettes, and then the person would be able to have a new engineered phenotype. He could decide.

I don't see that there's anything that says germline engineering means that the person can't have choice. If that's important, it's a technical issue we can give to our genetic engineers and say, "That's a constraint you have to work under. A person must have a choice before he has any change made to his physical body."

LEROY HOOD: But the other point one can make is that, as Mario [Capecchi] pointed out in his talk, there has been a lot of genetic engineering practiced—therapeutic selective abortions and things like that—where there isn't any prior choice. It's something that's been done for a long time in society. So these are complicated issues, and I don't think you can categorically say we should always require informed consent. The other thing I would say is that, although you can design these reversible kinds of things, it's quite clear that if we start engineering more complicated traits, it isn't going to be possible to make all of them so easily reversible. And we are going to have to face up to this important question.

DANIEL KOSHLAND: I'm not sure informed consent is always necessary. When I was a kid I didn't have an option about whether I would go to school or not. My parents told me to go. And I told my children. My children didn't have a vote on who their mother was when I decided to have children. So I think, sometimes, to extend informed consent to the embryo is really sort of a theoretical construct.

QUESTION: We've heard a lot about safe and careful manipulation of genes and have been cautioned about the interaction of different genes. I understand that, within a given period of gene activity, certain effects could be observed and then the artificial gene might be terminated, but the interaction that took place certainly would have repercussions, and I'd like to hear more about them.

MARIO CAPECCHI: I think what you're asking is whether we will ever know what we're doing. Are the interactions so complex that we can't anticipate what's going to happen? I think we have a few of things going for us based on experience with different kinds of animal models.

That's why I promote research—you can do increasingly complex research in animals. You can start with the mouse and go to a sheep and then go to nonhuman primates and thereby test the procedures in increasingly complex animals. In terms of physiology, this is a very reasonable approach. Those kinds of measurements can be done long term, to gather the needed information.

But when we get into treatment of mental deficiencies, it may become much more difficult to predict the outcome. It's going to be a long time before we actually understand how the mind works. We have no idea. How do we get information? Where do we store it? How can we retrieve it?

All of those parameters may have to be understood before we contemplate cures for mental deficiencies. So it's a long road, and we won't have guides. We won't have animal models to rely on. Drosophila (a fruit fly) does fairly complicated manipulations, but it doesn't think. It's fairly hardwired. Mice can learn. For example, we can teach them all sorts of smells, and we can reinforce their behavior and put them through learning paradigms. But it's still a long way from cognitive recognition and identity. My guess is that we're not going to be ready for quite a while.

I want to point out one thing, however: Scientists always overestimate what they can accomplish in five years. And they always underestimate what they can do in twenty-five years, because you don't know what new developments are going to completely change the rules. Right now it may be difficult for us to think about these things. But ten years, twenty years from now, it may be a very different story.

QUESTION: My question is about somatic gene therapy. I know there are problems with diseases in the brain because you can't access the brain physically. There are blood-brain barriers. Dr. Anderson, have you found any ways of solving somatic gene therapy problems in spite of these barriers?

FRENCH ANDERSON: The question is a very astute one: How well is somatic gene therapy working? The unfortunate fact is that, with the exception of a few anecdotal cases, there is no evidence at present that there is a gene therapy protocol that helps in any disease situation.

Our bodies have spent tens of thousands of years learning how to protect themselves from having exogenous DNA get into their genomes. And so, we were all a little naive to think that if we just made a viral vector and put it into the human body, it would work. The body's done a very good job of recognizing viral sequences and, basically, inactivating them.

So the answer to your question is—not just the more obvious questions like the blood-brain barrier and so on—but the straightforward question: "Does gene therapy work?" The answer is, at this point in time, it does not work. Now, does that mean it's never going to work? Well, no. It will. And there are now some very hopeful signs in a few clinical protocols. But the fact is we have a long way to go. And to look

at germline gene therapy in twenty years is probably too early. To think of artificial chromosomes being used for gene therapy in twenty years I think is definitely too early. But I agree with Mario [Capecchi], who said, "We all have a tendency to overestimate what we can do in five years and underestimate what we can do in twenty-five years." And maybe exciting things will happen fifteen, eighteen years from now, so that in twenty years these things will be possible.

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Notes

Introduction

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Part II

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Part III

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Glossary

Allele. One of several alternative structural forms of a gene.

Chromosome. The organelle which contains the genes.

Clone. Multiple genetically identical individuals or copies of a gene; also, the act of making clones of organisms or genes.

CRE. A recombinase enzyme that causes recombination at pairs of *loxP* sites in DNA molecules. It splits the DNA molecule in the center of the *loxP* sites and rejoins the pieces. CRE can fuse two circular molecules of DNA into one or can splice out the segment of DNA between the two *loxP* sites in one DNA molecule.

DNA. Deoxyribonucleic acid. A long double-stranded polymer which is the gene molecule of all life, except for certain viruses.

Ecdysone. A steroid hormone of insects, but not of humans, that activates a certain set of insect genes by binding to and activating an ecdysone-dependent transcription factor.

E. coli. The colon bacterium *Escherichia coli* widely used in the study of microbial physiology and genetics.

Enzyme. A protein that catalyzes a specific biochemical reaction.

Exon. A coding portion of a split gene that is separated from the rest of the gene by a noncoding intron DNA sequence.

Gene. A segment of DNA coding for a single polypeptide molecule. The term is sometimes used more loosely as a particular region of the chromosome responsible for a discernible phenotypic trait.

Genetic code. The correspondence between the nucleotide sequences of gene molecules and the amino acid sequences of the protein gene product.

Genetic recombination. The exchange of segments between two chromosomes, usually a key part of the reassortment of genes during the sexual process.

Genome. The total genetic material of a cell or organism.

Genotype. The total genetic information of an organism (see Phenotype).

Heredity. Transmission of genetic traits across generations.

Heritable. A genetic trait that is passed on to descendants.

Homology. Phenotypic characters derived from a common ancestral origin.

Human Genome Project. An ongoing program to determine the nucleotide sequence of the entire human genome, expected to be completed around the year 2003.

In vitro. A biological process taking place in artificial conditions; in contrast, *in vivo* pertains to processes in a living cell or organism.

Inducible. Produced or activated in response to an external condition.

Intron. A noncoding segment of DNA located within a gene.

loxP. The DNA target site for CRE recombinase enzyme (*see* CRE).

Menopause. The cessation of ovarian and menstrual cycles at the and of a woman's fertility, usually between the ages of forty-five and fifty-five years.

Messenger RNA. An RNA molecule that is translated into a polypeptide in the process of gene expression.

Mutation. A heritable change in the structure of a gene.

Nematode. A primitive roundworm extensively studied by developmental geneticists.

Nucleic acid. A polymer of ribonucleotides (RNA) or deoxynucleotides (DNA). The sequence of its nucleotide subunits encodes genetic information.

Nucleotide. The subunits of a nucleic acid, consisting of a sugar, a phosphate, and one of four types of bases: adenine (A), guanine (G), cytosine (C), or thymine (T) (or uracil [U] in the case of RNA).

Oligonucleotide. A short DNA or RNA molecule.

Ovulation. Release of an egg from the ovary.

Phenotype. The observable biochemical, anatomical, and behavioral traits of an organism determined by its genotype in its environment.

Protein. A macromolecule comprised of one or more polymeric chains of amino acids.

Recombinant DNA. A composite molecule made by artificially joining DNA molecules from two different sources.

RNA. Ribonucleic acid. A nucleic acid with a ribose sugar backbone instead of deoxyribose as in the case of DNA and generally existing as a single chain instead of a double helix.

Superallele. An uncommon gene allele that extends a beneficial trait in a person who carries it.

Transcription. Synthesis of an RNA molecule with the corresponding base sequence of a DNA molecule, as the first step in gene expression.

Translation. Synthesis of a polypeptide with an amino acid sequence dictated by the base sequence of a messenger RNA.

Virus. Ultra-microscopic, obligatory, intracellular parasites; incapable of autonomous replication or metabolism.

Wild-type sequences. The unmutated sequence of nucleotides in a particular gene or of amino acids in a protein of a species.

X chromosome. A sex chromosome. Female mammals have two X chromosomes. Males have an X and a Y chromosome.

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