ARTICLE

Germ-Line Gene Modification and Disease Prevention: Some Medical and Ethical Perspectives

Nelson A. Wivel and LeRoy Walters

There has been considerable debate about the ethics of human germ-line gene modification. As a result of recent advances in the micromanipulation of embryos and the laboratory development of transgenic mice, a lively discussion has begun concerning both the technical feasibility and the ethical acceptability of human germ-line modification for the prevention of serious disease. This article summarizes some of the recent research on germ-line gene modification in animal models. Certain monogenic deficiency diseases that ultimately might be candidates for correction by germ-line intervention are identified. Several of the most frequently considered ethical issues relative to human germ-line gene modification are considered in the context of professional ethics, parental responsibility, and public policy. Finally, it is suggested that there is merit in continuing the discussion about human germ-line intervention, so that this technique can be carefully compared with alternative strategies for preventing genetic disease.

There has been considerable discussion about the merits and risks of germ-line gene modification in humans (*1*). Previous publications make it clear that this is a topic that readily provokes debate (*2*, *3*). One of our aims is to review some of the scientific advances that contribute to the development of the technology necessary for germ-line gene transfer. A second aim is to identify some life-threatening diseases that could be candidates for germ-line intervention, and a third is to consider some of the complex ethical quandaries that necessarily attend decisions about deliberate alteration of the human germ line.

Types of Potential Human Genetic Intervention

One framework for discussing human genetic intervention distinguishes four categories of procedures according to their goals and target cells (*4*). Type 1 is somatic cell gene therapy; as applied to the treatment or prevention of disease, this type of intervention involves the correction or attempted correction of genetic defects in any of the cells of the body, with the exception of the germ or reproductive cells. Given the recent developments in the field of somatic cell gene therapy, it is appropriate to enlarge the definition to include the fact that genes can be introduced into cells to provide a new function. One example of such an approach involves the insertion of cytokine genes, such as interleukin-2, tumor necrosis factor, or granulocyte-macrophage colony-stimulating factor, into a patient's malignant cells to produce an immune response (the production of cytotoxic T cells that are specifically targeted to the tumor).

Type 2 genetic intervention involves the correction or prevention of genetic deficiencies through the transfer of properly functioning genes into reproductive cells. To achieve the desired results from this approach, it will probably be necessary to replace the faulty gene rather than add a gene, the usual technique in current somatic cell gene therapy. In germ-line alteration, gene addition would be unsatisfactory because it is not possible to predict the effects of a mixture of the normal gene and the mutated gene with respect to regulatory signals necessary for normal growth and development (*5*). Thus, reliable, predictable gene replacement is a needed advance before germ-line intervention can be seriously considered.

Type 3 and type 4 genetic interventions would involve the use of somatic cell or germ-line gene modifications, respectively, to affect selected physical and mental characteristics, with the aim of influencing such features as physical appearance or physical abilities. A principal difference in these uses of genetic modification is that they could be directed toward healthy people who have no evidence of genetic deficiency diseases. Further, type 4 genetic intervention, if successful, could assure that the enhancement would be passed on to succeeding generations.

Our main focus here is on the use of type 2 genetic intervention for disease prevention in individuals and their descendants. Whether or not germ-line genetic modification for this purpose constitutes eugenics is beyond the purview of this discussion. As the following sections will indicate, our analysis concentrates on serious or life-threatening somatic disorders in which the aim of germ-line modification would closely parallel the traditional goals of health care and public health. For selected readings on the definition and history of eugenics, one can consult the following references (*6*).

Germ-line genetic modification could be effected either before fertilization or in the early postfertilization stages of embryonic development. Here, we make no attempt to distinguish between germ-line gene transfer into preimplantation embryos and gene transfer into gametes or the cells that produce gametes. Obviously, these two approaches involve different developmental stages. Although many of the ethical questions surrounding the two approaches are identical, interventions at the pre- and postfertilization stages also raise distinct issues. Given our limited state of knowledge, it is not possible to predict whether one approach will turn out to be more advantageous than the others. It must be acknowledged, however, that at present most of the experimental work involves DNA transfer into one of the pronuclei of the zygote, the delivery of DNA into a four- or eight-cell embryo by a vector, or the use of embryonic stem cells.

Scientific Considerations

Much of the scientific infrastructure for germ-line genetic intervention is being developed as a result of a variety of approaches. In 1980, it was demonstrated that direct injection of foreign genes into the pronucleus of the fertilized mouse egg, followed by oviductal implantation of the surviving zygotes, resulted in the integration and apparent retention of exogenous genes in all cells of the newborn animal; the foreign genes were transmitted to the offspring (*7*). Since that time, transgenic animals (*8*) have become a major tool in the study of genetic disease, developmental genetics, immunology, oncology, and neurobiology. Although microinjection has been a very useful technique, retroviral vectors have also been used to insert foreign genes into the mouse embryo (*9*).

Another successful approach takes ad-

N. A. Wivel is director of the Office of Recombinant DNA Activities, National Institutes of Health, Bethesda, MD 20892. L. Walters is professor of philosophy and Joseph P. Kennedy, Sr. Professor of Christian Ethics, Kennedy Institute of Ethics, Georgetown University, Washington, DC 20057. This article was written by the authors in their private capacity. No official support or endorsement by NIH or Georgetown University is intended or should be inferred.

vantage of homologous recombination between a desired DNA sequence and a chosen target gene (*10*). In the creation of animal models for human genetic diseases, inactivation of the target gene or so-called "gene knockout" has been proven to be a successful methodology. With the design of a targeting construct to introduce a terminator codon into a critical coding exon of the gene, premature translation termination occurs or critical coding sequences are deleted from the target gene (*11*). After positive or negative selection procedures and the identification of cells that show the desired homologous recombinational event, the embryonic stem cells are injected into blastocysts; the blastocysts are then transferred into the uterus of a foster mouse. After delivery and maturation, the resulting chimeras can be mated with appropriate inbred strains of mice. Thus far, human diseases that have been modeled in the mouse by means of this technique include β-thalassemia, Lesch-Nyhan syndrome, Duchenne's muscular dystrophy, sickle cell anemia, Gaucher's disease, and cystic fibrosis (*12*). Although the embryonic stem cell has been of crucial importance for the development of the mouse models, it remains to be determined if there is an equivalent counterpart in the human system.

Several characteristics of foreign DNA integration in transgenic mice illustrate the complexities associated with manipulation of the embryonic genome. The frequency of integration is highly variable but may be increased by linearization of the DNA (*13*) and by increasing the number of copies inserted into the pronucleus (*14*). Integration has been associated with deletions, duplications, and translocations of the DNA (*15*). Many studies suggest that integration occurs randomly in the host genome, which is a problem in terms of accurate gene targeting. In the absence of site-specific integration, there is always the potential for insertional mutagenesis. The function of a normal gene could be impaired, conversion of a proto-oncogene into an oncogene could occur, or inactivation of a tumor suppressor gene could take place.

Although some research focuses on gene inactivation to create mouse models of disease, there is also a growing literature that indicates that the transfer of genes into the mouse germ line can result in the correction of specific genetic defects. Shiverer mice that had a deletion in the gene coding for myelin basic protein and a phenotype of tremors and convulsions were successfully treated by the introduction of the wild-type gene into the germ line (*16*). The offspring of dwarf mice, deficient in the production of growth hormone, showed a restoration of normal growth pattern when treated with a fusion gene of metallothionein and rat growth hormone (*17*). Hypogonadal mice that lacked a complete gonadotropin-releasing hormone gene and were therefore sterile exhibited reproductive capability when treated with the wild-type gene (*18*). When administered cloned human β-globin genes, the offspring of mice with β-thalassemia showed a loss of the red blood cell abnormalities and correction of the anemia (*19*).

During the past 5 years, researchers have used the germ-line approach to prevent several additional human diseases in laboratory animal models. There is now a mouse model for the human X-linked hereditary disorder ornithine transcarbamoylase deficiency; the affected mice have sparse fur, abnormal hair, and abnormal skin. Treatment with the wild-type gene restores the normal phenotype and restores normal orotic acid excretion (*20*). Insulin-dependent diabetes mellitus, present in the nonobese diabetic (NOD) strain of mice, is probably of autoimmune origin; there are defects in genes related to the major histocompatibility complex. Transgenic mice expressing normal gene constructs fail to develop inflammatory changes in the pancreatic islet, and diabetes does not occur (*21*). Mucopolysaccharidosis type VII, a lysosomal storage disease that results from deficiencies in the stepwise degradation of glycosaminoglycans, has also been produced in a mouse model; the introduction of a normal human β-glucuronidase gene into the mice corrected both the phenotype and the biochemical disorder underlying it (*22*). In a demonstration of the thesis that gene addition can also be effective in the treatment of cancer, lymphomas were induced in mice with a retrovirus containing a herpes simplex virus thymidine kinase (HSV-TK) gene. This HSV-TK transgene was selectively expressed in lymphoid cells; when the mice were treated with ganciclovir, almost all of the animals showed complete tumor regression (*23*).

Even though rapid advances in the study of germ-line gene transfer in animal models are a legitimate cause for optimism, several important technical problems would need to be resolved before this technology could be considered for human trials. (i) Any inserted gene, along with its necessary promoters and regulatory sites, will have to function normally, with regulated expression if that is required. (ii) The gene insertion must not cause insertional mutagenesis so that normal gene function is impaired. (iii) There must be no lingering effects from the original gene deficiency. (iv) Finally, the gene insertion procedure must not induce genetic side effects (*24*). Other criteria should also be satisfied before germ-line gene modification of human disease is attempted. In research that focuses on the postfertilization stage, there must be sufficient assurance that the manipulation will not be lethal to the preimplantation embryo (a mortality rate of consistently less than 5% in animal systems would be necessary as a preliminary goal); there needs to be a high efficiency of gene transfer; and the integration site of the new DNA must be controlled (*25*). There is no question that the aforementioned requirements are stringent, but they pose largely technical problems that may be accessible to approaches that are inherently a part of basic research.

Possible Scenarios for Germ-Line Intervention

The following two scenarios are intended to illustrate some of the types of clinical situations that, in the future, might justify consideration of germ-line gene modification.

1) Both parents are homozygotes who are afflicted with a recessive genetic disorder—that is, both have two copies of the same gene mutation at a particular locus in their chromosomes. Therefore, all of their offspring are likely to be affected with the same genetic disorder.

This kind of situation is likely to arise as medical care succeeds in prolonging the lives of people with genetic disorders such as sickle cell disease or cystic fibrosis. If somatic cell gene therapy is used with large numbers of people afflicted with recessive genetic diseases, some of the somatic cells of such people will be able to function normally, but their reproductive cells will remain unchanged, thus assuring that they will transmit their genetic disease to the next generation. If two such phenotypically cured people have children, all or almost all of their children will be afflicted with the disease that their parents had. Each succeeding generation of these children will need somatic cell gene therapy for the treatment of their disease. One strategy for dealing with this situation obviously would be to perform somatic cell gene therapy in each new generation, preferably early in life before the disease has caused serious damage. An alternative strategy would be to perform germ-line modification for disease prevention in a single generation for each family line.

2) Both parents are heterozygotes for a recessive genetic disorder. Each has one copy of a normal gene and one copy of a mutated gene at a particular locus in their chromosomes. If the inheritance is Mendelian, 25% of the parent's offspring are likely to be normal, 50% are likely to be carriers like their parents, and 25% are likely to be afflicted with the genetic disorder. An example of a disease in this category is β-thalassemia. (Similar examples could be developed for dominant or sex-linked dis-

orders, but the ratios of phenotypic expression would vary.)

Because these parents have a 75% chance of having a phenotypically normal child, one could question the need for even considering germ-line gene modification in such cases. Actually, there would be three options for approaching this situation. First, screening could be carried out during the first or second trimester of pregnancy with chorionic villus sampling or amniocentesis, followed by selective abortion. Second, the use of preimplantation embryo diagnosis after in vitro fertilization could provide the necessary information for identification of a homozygote that presumably would be discarded. Third, germ-line genetic intervention could be viewed as an alternative to the first two approaches if the parents wish to avoid selective abortion or to avoid producing children who are carriers of genetic defects, even if the children are not themselves afflicted with genetic disease. The parents would know that children who are carriers might one day face precisely the kind of difficult reproductive decisions that they as parents are facing.

Candidate Diseases for Intervention

Although specific genes have been cloned and characterized in several genetic deficiency diseases, this achievement alone does not constitute a qualifying indication for germ-line gene modification. If somatic cell gene therapy is effective and seems less likely to introduce new mutations than germ-line modification, there may be less justification for the germ-line approach.

Most of the current somatic cell gene therapy proposals for the treatment of cancer involve the transduction of cytokine or histocompatibility genes into autologous tumor cells for the purpose of creating antigenic recognition by the patient's T cells. However, there is one type of malignancy that potentially could be treated by germ-line intervention. Retinoblastoma is a cancer that affects the retinal germ cells; it accounts for about 2% of all childhood malignancies. Approximately 40% of retinoblastoma patients have bilateral disease and pass the trait to their children as an autosomal dominant disorder (*26*). It was hypothesized originally that two mutational events are necessary for the development of the tumor. The first mutation is inherited as dominant trait, and the second mutation is acquired somatically (*27*). About 25% of patients with bilateral disease have visible deletions involving chromosome 13q14, and those with a normal karyotype have deletions at the *RB1* locus that are detectable by Southern (DNA) blot analysis (*28*). Patients with mutations at the *RB1* locus also have a higher-than-average susceptibility to other types of cancers, especially osteogenic sarcoma (*29*). Thus, for the 40% of patients with retinoblastoma who have a germ-line mutation, germ-line gene modification would have the potential of preventing multiple malignancies.

One can also identify monogenic deficiency diseases that would be candidates for prevention by germ-line gene modification. Lesch-Nyhan syndrome, Tay-Sachs disease, and metachromatic leukodystrophy share certain characteristics: the genes have been cloned; the mutations have been characterized; the central nervous system (CNS) is the target organ of the pathology; the CNS lesions are widespread; and the clinical outcomes are marked by profound disability and premature death. Somatic cell gene therapy, if applicable, would almost certainly require surgical intervention, and it would be difficult to postulate postpartum treatment of newborns affected with these disorders.

1) Lesch-Nyhan syndrome affects about 1 in 10,000 males and has an incidence of about 200 new cases in the United States per year. The disease is caused by a deficiency in the purine metabolic enzyme hypoxanthine-guanosine phosphoribosyltransferase (HPRT), which is necessary for the conversion of inosine and guanosine to their respective ribonucleotides. Complete deficiency of HPRT causes hyperuricemia, hyperuricaciduria, and severe neurological dysfunction, including choreoathetosis, self-mutilation, and varying degrees of mental retardation (*30*). Findings of dopamine deficiency in the brains of patients with Lesch-Nyhan syndrome (*31*) and animal model evidence suggest that the loss of central dopaminergic neurons may account for some of the CNS symptoms (*32*). The gene for HPRT is located on the long arm of the X chromosome and consists of nine exons and eight introns spanning 44 kb (*33*); 17 independent mutations have been identified (*34*).

2) Tay-Sachs disease occurs as an autosomal recessive disorder in about 1 in 3600 infants of Ashkenazi Jewish parents, although cases have been reported in French-Canadians, Pennsylvania Dutch, and French-Acadian populations (*35*). This disease is caused by the absence of β-hexosaminidase activity, resulting in the accumulation of gangliosides or complex sphingolipids in lysosomes, principally in neurons. In the classical infantile form of the disease, the symptoms begin to appear at 3 to 5 months of age. These include developmental arrest, blindness, intractable seizures, and progressive neurological deterioration leading to death. The responsible gene, *HEXA*, is located on chromosome 15, and 30 allelic mutations have been reported to date. There are several clinical variants of this disease, but two common mutations occur with the infantile form, a 4–base pair insertion in exon 11 (*36*) and a splice junction mutation in intron 12 (*37*).

3) Metachromatic leukodystrophy is a lysosomal storage disease that is transmitted as an autosomal recessive disorder. The overall incidence and frequency have not been determined. The disorder is caused by the deficiency of arylsulfatase A, and the substrate of this enzyme is the glycolipid cerebroside sulfate, which is a component of myelin. As cerebroside sulfate accumulates in the lysosomes, it causes progressive demyelination. Symptoms most commonly appear around the age of 2, and affected individuals do not usually survive beyond the first decade of life. The major symptoms include ataxia, spastic quadriplegia, optic atrophy, and dementia (*38*). The gene is located on chromosome 22, and there is a correlation between genotype and phenotype. There are two alleles, allele A and allele I; patients homozygous for allele I have the early-onset form of the disease. Three mutations have been described in allele I, two in the coding sequence where there is a substitution of tryptophone 193 by serine and threonine 391 by serine and a third that destroys the splice donor site at the exon-intron border of exon 2 (*39*).

In the case of all three of these diseases, it probably will be necessary to replace the mutated gene with a normal gene at a specific insertion site. There may be requirements for gene regulation that are not yet apparent, simply because our knowledge of developmental genetics is still quite incomplete. In these devastating CNS disorders, the technique of germ-line gene modification represents a potential strategy for the prevention of irreversible pathology.

Ethical Issues

Even if the technical obstacles to carefully targeted germ-line gene modification can be overcome, there remains the question of whether this powerful new approach to prevention should be used in humans. Active discussion of the ethical dimensions of germ-line gene modification has already begun, well in advance of essential technical capabilities. Despite recent warnings against premature consideration of still-distant technologies, it seems useful for public discussion to continue; such discussion should include individuals from science, medicine, ethics, law, and the general public to provide maximum opportunity for consideration of the many facets of the problem. Broad participation in the discussion is recommended because the decision about whether or not to proceed with

germ-line gene modification will be a major public policy decision. As several commentators have noted, the human gene pool is a joint possession belonging to all members of the human species.

There are numerous ethical arguments for and against germ-line gene modification, and the following discussion is meant to be representative of the types of issues raised by various observers. Although it would be unrealistic to expect a consensus with regard to the most compelling arguments of either persuasion, it seems apparent that most arguments have been influenced by the underlying culture, in this case, a pluralistic Western democratic society with a strong interest in individual rights.

There are several arguments in favor of developing the capabilities for human germ-line genetic intervention (Table 1):

1) The health professions have a moral obligation to use the best available methods in preventing or treating genetic disease, and certain types of genetic disorders may require germ-line alterations. If the current strides in the study of molecular genetics continue and sometime in the future it is appropriate to consider germ-line gene modification, it should be done in the context of extending a therapeutic continuum; chemicals have already been given to activate dormant genes, such as the attempted use of 5-azacytidine to increase fetal hemoglobin production in patients with sickle cell anemia, and lung transplantation has been used to treat cystic fibrosis (*40*). When it is determined that germ-line intervention is the best application of molecular medicine for a given disease, and if it is acceptably safe and efficacious, then it will be in the best interests of patients to have the health care system offer this technology. To rule out this option in advance and in principle would mean breaking with a long-standing tradition of medicine to either treat or prevent all types of diseases (*24*).

2) The principle of respect for parental autonomy should permit parents to use this technology to increase the likelihood of having a healthy child. With the burgeoning growth of in vitro fertilization and the increasing ability to make compensatory maneuvers for various types of infertility, there has been a strong declaration of parental autonomy, ultimately directed toward optimizing the chances for the birth of a healthy child. Notwithstanding certain court decisions regarding abortion or the request to terminate life support, it would be ethically problematic for legislators or judges to interfere with procreative liberty when parents are acting on the basis of their deeply held moral convictions and are attempting to prevent disease in their offspring through germ-line modification (*41*).

3) Germ-line gene modification is more efficient than the repeated use of somatic cell gene therapy over successive generations. At least in the case of highly prevalent genetic disorders, disease prevention through germ-line modification may be the most efficient approach to reducing the incidence of disease. For example, although five protocols have been approved by the NIH Recombinant DNA Advisory Committee for somatic cell gene therapy of cystic fibrosis, none of these interventions would affect more than the patients selected for the particular studies. Because cystic fibrosis is the most common genetic deficiency disease among U.S. Caucasians, occurring in approximately 1 in 2500 births, one could easily make the case that it would be more efficient and cost-effective to use germ-line gene modification to eliminate the problem both for the patient and for future generations (*42*).

4) The prevailing ethic of science and medicine operates on the assumption that knowledge has intrinsic value and should be pursued in the vast majority of cases (*23*). The acquisition of knowledge is of fundamental importance to science and medicine. The mere fact that advances in gene targeting or preimplantation diagnosis could lead in the future to proposals for germ-line modification in humans should not deter researchers from pursuing these lines of inquiries. Similarly, if germ-line modification becomes a reliable technique for preventing disease in laboratory animal models, the fear of possible misuse of the technique in humans should not interfere with the conduct of well-controlled clinical trials with human subjects. It would be both inhumane and tragic if special interest groups or those who set public policy attempted to block potentially promising lines of scientific inquiry on the basis of political viewpoints or speculative fears. Reasonable public policies will attempt to prevent the misuse of new technologies while also having the goal of promoting the development of novel approaches to the prevention and cure of serious disease.

Any balanced perspective on germ-line intervention must acknowledge that numerous arguments against the use of this technology in humans have also been advanced. Some of the more important counterarguments (Table 1) are the following:

1) Germ-line gene modification is an expensive intervention that would affect relatively few patients. The incidence of classical Mendelian genetic diseases is quite low; the sum total of known genetic diseases affects approximately 2% of all live births. To invoke the need for a very expensive technology for the attempted remediation of extremely uncommon situations is a difficult matter at a time when there is public discussion of rationing medical resources. Although the expense of pre-embryo diagnosis is considerable, there is no reason to assume that germ-line gene modification would be less expensive, particularly because the latter process could require large numbers of oocytes and embryos to assure the safety and efficacy of the germ-line approach.

2) Alternative strategies exist for avoiding genetic disease. The need for germ-line gene modification may be avoided by improved strategies of preimplantation and prenatal genetic diagnosis. Embryo freezing has been successfully demonstrated in animal models and in humans (*43*). Blastomeres can be removed from the embryo and retain their viability (*44*). With the aid of polymerase chain reaction analysis, the DNA from one or two cells can be amplified and subjected to diagnostic tests for multiple genetic and chromosomal disorders (*45*). Such techniques have made possible the genetic testing of embryos before implantation. Preimplantation diagnosis represents an advance over the methods of amniocentesis and chorionic villus biopsy, which require a pregnancy to be in place and for which the only currently available intervention is selective abortion. Selection processes such as these can achieve many of the goals of germ-line intervention with procedures that may have a lower order of risk. However, whether to transfer or discard embryos that are heterozygous

Table 1. Some ethical arguments for and against germ-line gene modification.

Arguments in favor
Moral obligation of health professions to use best available treatment methods.
Parental autonomy and access to available technologies for purposes of having a healthy child.
Germ-line gene modification more efficient and cost-effective than somatic cell gene therapy.
Freedom of scientific inquiry and intrinsic value of knowledge.
Arguments against
Expensive intervention with limited applicability.
Availability of alternative strategies for preventing genetic diseases.
Unavoidable risks, irreversible mistakes.
Inevitable pressures to use germ-line gene modification for enhancement.

carriers of a genetic trait remains an important issue for the selection strategy.

3) The risks of the technique will never be eliminated, and mistakes would be irreversible. Germ-line gene modification will always be associated with the risk of unpredictable genetic side effects, and for this reason it never should be approved for use in humans. Whatever the mechanisms of review and approval, they are not likely to be fail-safe because it is not possible to guarantee safety and reproducibility in biological systems. Further, there is the ever-present potential for the delayed appearance of unpredicted side effects that could be passed onto future generations; for example, subtle adverse effects on the brain could appear many years after genetic intervention, and such effects might not be detected in animal models that were used to develop the preclinical data. In summary, the risks are much greater than those associated with somatic cell gene therapy, where the side effects are most likely to be confined to one patient.

4) Germ-line gene modification for serious disease will inevitably lead to the next step, genetic enhancement (*1, 3, 24, 46*). Germ-line gene modification is a dangerous step onto a "slippery slope." Although the initial emphasis of this type of genetic alteration may be on the prevention of disease, it seems likely that there would follow a gradual shift to include efforts at enhancement (*47*). It is true that there are both clinical researchers and bioethicists who have asserted that therapy can be differentiated from enhancement in a definitive way (*48*). Indeed, on the surface it would appear reasonably straightforward to set up a rather well-defined dichotomy between the use of germ-line intervention for prevention of disease and use for enhancement. However, maintaining this dichotomy could prove to be a difficult task. There are already existing precedents for treating conditions that would not meet any consensus definition of disease. For example, the treatment by means of recombinant human growth hormone (HGH) of dwarfism secondary to human growth hormone deficiency has not been a provocative step, but a recent decision to administer recombinant HGH to children of short stature, who have no evidence of HGH deficiency, has been highly criticized. The criticism has centered around the thesis that short stature, per se, is not a disease (*49*) and that this intervention therefore is an enhancement rather than a medically indicated treatment.

Future Developments

It has been noted that ethical issues evolve through four stages: threshold, open conflict, extended debate, and adaptation (*50*). All four stages have been visited in the emergence of somatic cell gene therapy. In 1967, the promises and dangers of gene transfer were first enunciated (*51*), and in the 1970s there were frequent criticisms of the dangers inherent in genetic manipulation (*52*). In the period from 1980 to 1988 there was extended debate that led to a stronger ethical consensus, and acceptance arrived in 1990 with the approval of the first somatic cell gene therapy protocol.

Because the readily identifiable technical problems necessarily consign germ-line gene modification to the relatively distant future, a discussion of the ethical issues might be viewed as an exercise in the abstract. There probably would be some agreement that this is a threshold period, although strongly differing opinions have already been expressed. Open conflict and extended debate will probably be natural steps in the public discussion of these issues. It is impossible to predict the outcome of this conversation. Germ-line modification could ultimately be regarded as a technology too dangerous to undertake or it could be viewed as a justifiable approach to preventing certain forms of genetic disease. It would, in our view, be a useful investment of time and energy to continue and in fact to intensify the public discussion of germ-line gene modification for disease prevention, even though the application of this new technology to humans is not likely to be proposed in the near future.

REFERENCES AND NOTES

1. H. J. Muller, *Perspect. Biol. Med.* **3**, 1 (1959); G. Wolstenholme, Ed., *Man and His Future* (Churchill, London, 1963); Council of Europe, Parliamentary Assembly, 33rd Ordinary Session, "Recommendation 934 (1982) on Genetic Engineering" (Strasbourg); President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research, *Splicing Life* (Government Printing Office, Washington, DC, 1982); J. C. Fletcher, *Va. Law Rev.* **69**, 515 (1983); U.S. Office of Technology Assessment, *Human Gene Therapy: Background Paper* (Government Printing Office, Washington, DC, 1984); G. Fowler, E. T. Juengst, B. K. Zimmerman, *Theor. Med.* **10**, 151 (1989); E. T. Juengst, *J. Med. Philos.* **16**, 587 (1991); M. Lappé, *ibid.*, p. 621; K. Nolan, *ibid.*, p. 613; Canada Law Reform Commission (B. M. Knoppers), *Human Dignity and Genetic Heritage: Study Paper* (Law Reform Commission, Ottawa, 1992); S. Elias and G. J. Annas, in *Gene Mapping: Using Law and Ethics as Guides*, G. J. Annas and S. Elias, Eds. (Oxford Univ. Press, New York, 1992), pp. 142–154; R. Munson and L. H. Davis, *Kenn. Inst. Ethics J.* **2**, 137 (1992).
2. J. D. Howell, *J. Clin. Ethics* **2**, 274 (1991); R. Moseley, *J. Med. Philos.* **16**, 641 (1991); A. L. Caplan, in *Gene Mapping: Using Law and Ethics as Guides*, G. J. Annas and S. Elias, Eds. (Oxford Univ. Press, New York, 1992), pp. 128–141; B. D. Davis, *Hum. Gene Ther.* **3**, 361 (1992); J. C. Fletcher and W. F. Anderson, *Law Med. Health Care* **20**, 26 (1992); J. V. Neel, *Hum. Gene Ther.* **4**, 127 (1993).
3. A. Lippman *et al.*, *Hum. Gene Ther.* **4**, 135 (1993).
4. L. Walters, *J. Clin. Ethics* **2**, 267 (1991).
5. W. F. Anderson, *J. Med. Philos.* **10**, 275 (1985).
6. C. B. Davenport, *Heredity in Relation to Eugenics* (Holt, New York, 1911); M. H. Haller, *Eugenics: Hereditarian Attitudes in American Thought* (Rutgers Univ. Press, New Brunswick, NJ, 1963); K. M. Ludmerer, *Genetics and American Society: A Historical Appraisal* (Johns Hopkins Univ. Press, Baltimore, MD, 1972); D. J. Kevles, *In the Name of Eugenics: Genetics and the Uses of Human Heredity* (Knopf, New York, 1985); R. J. Lifton, *The Nazi Doctors* (Basic Books, New York, 1986), chap. 1; R. N. Proctor, *Racial Hygiene: Medicine Under the Nazis* (Harvard Univ. Press, Cambridge, MA, 1988); P. Weindling, *Health, Race, and German Politics between National Unification and Nazism* (Cambridge Univ. Press, Cambridge, 1989); T. Duster, *Backdoor to Eugenics* (Routledge, New York, 1990); P. R. Reilly, *The Surgical Solution: A History of Involuntary Sterilization in the United States* (Johns Hopkins Univ. Press, Baltimore, MD, 1991).
7. J. W. Gordon, G. A. Scangos, D. J. Plotkin, J. A. Barbosa, F. H. Ruddle, *Proc. Natl. Acad. Sci. U.S.A.* **77**, 7380 (1980).
8. J. W. Gordon and F. H. Ruddle, *Methods Enzymol.* **101**, 411 (1983).
9. H. van der Putten *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **82**, 6148 (1985); P. Soriano, R. D. Cone, R. C. Mulligan, R. Jaenisch, *Science* **234**, 1409 (1986).
10. O. Smithies, R. G. Gregg, S. S. Boggs, M. A. Koralewski, R. S. Kucherlapati, *Nature* **317**, 230 (1985).
11. O. Smithies, *Trends Genet.* **9**, 112 (1993).
12. L. C. Skow *et al.*, *Cell* **34**, 1043 (1983); M. Hooper, K. Hardy, A. Handyside, S. Hunter, M. Monk, *Nature* **326**, 292 (1987); M. R. Kuehn, A. Bradley, E. J. Robertson, M. J. Evans, *ibid.*, p. 295; P. Sicinski *et al.*, *Science* **244**, 1578 (1989); D. R. Greaves *et al.*, *Nature* **343**, 183 (1990); V. L. J. Tybulewicz *et al.*, *ibid.* **357**, 407 (1992); J. R. Dorin *et al.*, *ibid.* **359**, 211 (1992); J. N. Snouwaert *et al.*, *Science* **257**, 1083 (1992).
13. R. D. Palmiter *et al.*, *Nature* **300**, 611 (1982).
14. R. L. Brinster, H. Y. Chen, M. W. Trumbauer, M. K. Yagle, R. D. Palmiter, *Proc. Natl. Acad. Sci. U.S.A.* **82**, 4438 (1985).
15. L. Covarrubias, Y. Hishida, B. Mintz, *ibid.* **83**, 6020 (1986); R. D. Palmiter and R. L. Brinster, *Annu. Rev. Genet.* **20**, 465 (1986); P. A. Overbeek, S. P. Lai, K. R. Van Quill, H. Westphal, *Science* **231**, 1574 (1986); G. A. Scangos and C. Bieberich, *Adv. Genet.* **24**, 285 (1987); K. A. Mahon, P. A. Overbeek, H. Westphal, *Proc. Natl. Acad. Sci. U.S.A.* **85**, 1165 (1988).
16. C. Readhead *et al.*, *Cell* **48**, 703 (1987).
17. R. E. Hammer, R. D. Palmiter, R. L. Brinster, *Nature* **311**, 65 (1984).
18. A. J. Mason *et al.*, *Science* **234**, 1372 (1986).
19. F. Costantini, K. Chada, J. Magram, *ibid.* **233**, 1192 (1986).
20. C. Cavard *et al.*, *Nucleic Acids Res.* **16**, 2099 (1988).
21. T. Lund *et al.*, *Nature* **345**, 727 (1990).
22. J. W. Kyle *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **87**, 3914 (1990).
23. F. L. Moolten, J. M. Wells, R. A. Heyman, R. M. Evans, *Hum. Gene Ther.* **1**, 125 (1990).
24. B. K. Zimmerman, *J. Med. Philos.* **16**, 593 (1991).
25. J. W. Gordon, *Am. J. Med. Genet.* **35**, 206 (1990).
26. F. Vogel, *Hum. Genet.* **52**, 1 (1979).
27. A. G. Knudsen, *Proc. Natl. Acad. Sci. U.S.A.* **68**, 820 (1971).
28. K. Kloss *et al.*, *Am. J. Med. Genet.* **39**, 196 (1991).
29. E. Matsunaga, *J. Natl. Cancer Inst.* **65**, 47 (1980).
30. M. Lesch and W. L. Nyhan, *Am. J. Med.* **36**, 561 (1964); J. E. Seegmiller, F. M. Rosenbloom, W. N. Kelley, *Science* **155**, 1682 (1967).
31. K. G. Lloyd *et al.*, *N. Engl. J. Med.* **305**, 1106 (1981).
32. G. R. Breese, H. E. Criswell, G. E. Duncan, R. A. Mueller, *Brain Res. Bull.* **25**, 477 (1990).
33. P. I. Palel *et al.*, *Somatic Cell Mol. Genet.* **10**, 483 (1984).
34. B. L. Davidson *et al.*, *Am. J. Hum. Genet.* **48**, 951 (1991).

35. L. Drucher, R. L. Proia, R. Navon, *ibid.* **51**, 371 (1992).
36. A. Tanaka, H. H. Pannett, K. Suzuki, *ibid.* **47**, 567 (1990).
37. R. Meyerowitz, *Proc. Natl. Acad. Sci. U.S.A.* **85**, 3955 (1988).
38. J. B. Stanbury, J. B. Wyngaarden, D. S. Fredrickson, J. L. Goldstein, M. S. Brown, in *Metabolic Basis of Inherited Disease* (McGraw-Hill, New York, ed. 6, 1989), pp. 881–905.
39. V. Gieselmann *et al.*, *Dev. Neurosci.* **13**, 222 (1991).
40. H. I. Miller, *Hum. Gene Ther.* **1**, 3 (1990).
41. R. M. Cook-Deegan, *ibid.*, p. 163.
42. L. Walters, *Nature* **320**, 225 (1986).
43. A. Trounson and L. Mohr, *ibid.* **305**, 707 (1983).
44. R. S. Prather and N. L. First, *J. Exp. Zool.* **237**, 347 (1986).
45. M. W. Bradbury, L. M. Isola, J. W. Gordon, *Proc. Natl. Acad. Sci. U.S.A.* **86**, 3709 (1989).
46. D. J. Weatherall, *Nature* **331**, 13 (1988); *ibid.* **349**, 275 (1991).
47. E. M. Berger and B. M. Gert, *J. Med. Philos.* **16**, 667 (1991); A. Mauron and J.-M. Thevoz, *ibid.*, p. 648.
48. W. F. Anderson and J. C. Fletcher, *N. Engl. J. Med.* **303**, 1293 (1980); W. F. Anderson, *J. Med. Philos.* **14**, 681 (1989); *Hastings Cent. Rep.* **20** (no. 1), 21 (1990); L. Walters, *Hum. Gene Ther.* **2**, 115 (1991).
49. A. Toufexis, *Time* **142**, 49 (1993).
50. J. C. Fletcher, *Hum. Gene Ther.* **1**, 55 (1990).
51. M. W. Nirenberg, *Science* **157**, 633 (1967).
52. P. Ramsey, *Fabricated Man: The Ethics of Genetic Control* (Yale Univ. Press, New Haven, CT, 1970); M. Hamilton, Ed., *The New Genetics and the Future of Man* (Eerdmans, Grand Rapids, MI, 1972).
53. The authors wish to thank the following people for helpful discussions of the issues considered in this article: R. M. Cook-Deegan, K. Fitzgerald, S. J., E. Juengst, J. G. Palmer, and O. Smithies.