genetic defects by one family, and would scarcely be noticed by another.

The distinction between individual decisions in favor of gene therapy and social programs advocated by eugenicists can also blur if gene therapy becomes commonplace. Many individual decisions can culminate in wide social effects. The social impact of gene therapy depends on how often it is used, who has access to it, which conditions are treated, and what public policies are erected to foster or inhibit it. As long as gene therapy is restricted to rare recessive disorders, it will likely have minimal social risk and large benefits to individual patients.

Application of gene therapy to enhance traits such as intelligence or physical strength cannot now be done because so little is known about the genetic influence on such traits. Most traits that some individuals might consider desirable to amplify will likely prove to be polygenic or environmentally influenced, and thus technically approachable by gene therapy only in the distant future, if ever. There is no guarantee, however, that it will always be impossible to use the techniques developed for gene therapy to improve socially esteemed mental or physical traits in at least some patients. If desirable traits can be modified by methods developed for gene therapy, then public policy for such applications may well prove analogous to those now employed for cosmetic surgery. Cosmetic surgery is not generally reimbursed as part of government or private health insurance, but is usually paid directly by individuals. Cosmetic surgery has not generated major public policy dilemmas, although controversy might arise in gene therapy if parents were attempting to secure "cosmetic" gene therapy on behalf of an unborn infant or young child, or to authorize germ line changes that would not be reversible in future generations.

Medical aspects of gene therapy

Early clinical experiments in human gene therapy will be performed on somatic cells of patients to attempt partial correction of life-threatening diseases. They will be performed to allay the signs and symptoms caused by a defect in a single gene whose normal counterpart has been cloned, and whose correction does not require careful control of expression. Gene therapy will be considered when there is no preferable alternative treatment available to the individual patient. This prediction is based on analysis of several factors described below, and underlies the analysis throughout this section. Predictions about human gene therapy are based, in part, on results of animal experiments. A short review of such animal experiments is followed by a discussion of relevant clinical considerations in humans. The medical aspects of gene therapy include reasons that genetic diseases can never be completely eliminated from the population, why certain types of genetic diseases are not good candidates for gene therapy, why germ line therapy may never be necessary or its use extremely restricted, and which disorders might be approached using gene therapy in the near future. The analysis is restricted to the early applications of human gene therapy because technical predictions beyond this time horizon are perilous, and because decisions confronting Federal policymakers in the next few years will be focused on early applications.

Genetic corrections of animals and other organisms

Gene therapy is contemplated in humans only because it has been performed in animals and lower organisms. One of the most successful attempts to genetically alter organisms involved the "cure" of a genetic defect in fruit flies (Spradling, 1983). Some fruit flies have an enzyme defect that results in their having rose colored eyes. Scientists were able to correct this abnormality by delivering the correct gene into fly cells by using DNA molecules specific to fruit flies that can carry foreign DNA into the fly's own DNA. The treated flies that took up the normal gene transmitted the

genes to their progeny, who showed normal eye color.

Gene transfer experiments have also been done in mice. Several traits have been artificially added to mouse cells early in embryonic development. In experiments involving transfer of rat growth hormone to mice, the mice that develop from the altered embryos express the foreign genes, although not in a way that is controlled like the normal gene would be. Scientists have had to use special techniques to get mammalian cells to incorporate new genes, and the genes are inserted into chromosomal or cellular locations that cannot be predicted or controlled. Examples of genes that have been transmitted to progeny in mice include the gene for rabbit hemoglobin, rat growth hormone, and a DNA fragment with both specific enzyme activity and antibiotic resistance to neomycin (Palmiter, et al., 1982; Palmiter, et al., 1983; Brinster, 1983; Wagner, et al., 1981; Williams, et al., 1984).

The growth hormone experiment was especially interesting because expression of the gene could be manipulated by the scientists, and this feature was inherited by progeny of the treated mice. Other transferred genes have also been passed to the progeny, although genetic manipulations have occasionally resulted in undesired side effects, such as sterility or induction of new mutations. These effects suggest that oversight committees will seek evidence that such side effects are highly improbable when inspecting proposals for experiments that involve human gene therapy (Working Group on Human Gene Therapy, 1984).

Most of the animal experiments noted above resulted in germ line changes of the treated mouse lines, The experiments were done to investigate animal development, rather than to pave the way for human application of gene therapy. More recent experiments have been done on somatic cells of animals, and are more directly analogous to what would be done in early human trials. Several groups of investigators have successfully inserted genes into the bone marrow cells of mice, and have shown production of proteins from the inserted genes in cells that derive from bone marrow cells (Kolata, 1984c; **A.** D. Miller, 1984; Williams, 1984; Anderson, 1984). These experiments used modified viruses as the gene transfer agents in ways quite similar to those that might be used in humans, although treatment of the recipient mice was more drastic than may be acceptable for humans, and data on long-term risks (e. g., reversion to infectious virus type, induction of new mutations, predisposition to cancer, and integration into the germ line) were not reported. The new studies show great promise, and demonstration of technical feasibility should encourage animal experiments to ascertain the magnitude of the risks.

Other recent experiments demonstrate that proper regulation of gene expression in the cells of humans and other higher animals is more complex than in fruit flies and bacteria. Early attempts at gene therapy in humans will probably, therefore, be conducted on diseases for which there is reason to believe that precise regulation is unnecessary for therapeutic benefit, such as ADA and PNP deficiencies. Early plans to apply gene therapy to diseases in which regulation would be important have been thwarted by the complexity of regulation, although such obstacles may eventually be overcome. Hemoglobin disorders, for example, will not be the first candidates for human gene therapy because of the need for regulation of globin expression (Anderson, 1984).

Reasons genetic diseases cannot be eliminated

There will always be patients who suffer from genetic diseases. It will never be possible to eliminate even single gene defects, although the prevalence of some disorders, especially some dominant ones, could be significantly reduced. New mutations causing genetic defects will always occur, and so people will be born carrying such mutations. Neither would it be possible to stop the expression of recessive diseases by preventing those who carry one copy of any abnormal gene from mating, because humans carry an estimated 5 to 10 recessive defects in their genome on average, and so no one would be permitted to mate.

It is already possible to prevent the birth of children with some genetic disorders through

genetic counseling, prenatal diagnosis, and family planning. The number of diseases for which this is possible will grow as we learn more about human genetics. It is unlikely, however, that current methods for preventing genetic disease will prove practical for all, or even a large fraction of couples in the near future. Most genetic disorders still cannot be detected prenatally, and tests for carriers are available for even fewer diseases. Yet effective prevention requires such tests. Furthermore, such tests must not only be available; they must also be used. Barriers to use include cost, complexity, and lack of public awareness. Given the large number of potential genetic diseases, it is unlikely that any one screening test will screen for all, or even most genetic diseases. This means that for many disorders, couples will only know that they are at risk after an affected child has already been born. Thus, until the entire child-bearing population is screened for a given defect, or prospective parents know of special risks, even those diseases for which all the relevant tests are available will persist.

It maybe useful to screen some populations for some defects. Screening programs for Tay-Sachs carriers among Jews of Eastern European descent, and for thalassemia among Mediterranean populations have been successful in some instances. These successes cannot be generalized to all genetic diseases, however, and are probably relevant only to a few relatively common disorders.

Effective use of genetic screening and selective testing presumes public awareness that such tests are available and acceptable. Families must wish to use the technologies and expect to benefit from the information provided. This requires that there be no stigma attached to carrying a potential genetic defect and trust that genetic patient data will be properly used. (Issues relating to control of and proper access to genetic patient data are discussed below, and in app. B.)

There are a few genetic diseases whose prevalence could be dramatically reduced. Huntington disease is a dominant trait encoded in chromosome 4 that causes a debilitating brain disease that usually becomes evident only in a patient's 40s or 50s (after reproductive decisions have been made). All those who carry the gene for Huntington disease will develop the disease if they live long enough. If carriers could be told whether or not they had the gene before deciding to have children, and if all those who carry the gene decided not to have children, then the gene could be eliminated in a single generation. This is true of Huntington disease because it is almost always inherited and only rarely due to a new mutation (this is not true for many dominant disorders).

Elimination of the gene would, however, entail large numbers of coordinated personal decisions. Marjorie Guthrie, wife of the famous folk singer Woody Guthrie who was afflicted with Huntington disease, posed a difficult question that bears on any program to prevent the birth of those with Huntington disease, "Does anyone really think it would have been better for Woody not to have come into the world-in spite of everything?" (Cited in Rosenfeld, 1984). Is the disease so awful that the birth of potential Huntington patients should be prevented when they would have several decades of relatively normal life? This is just one of several difficult dilemmas that emerge from advances in genetics related to particular diseases. New genetic technologies for determining the genetic makeup of humans may provide the information about whether one is susceptible to Huntington disease[8] and other disorders, but cannot determine a moral choice that involves social, religious, and personal values. In the absence of compelling social justifications, decisions are and should be left to individuals, families, and health professionals in a particular situation.

Even if all diagnostic tests are available, there are families for whom the prospect of selective abortion is unacceptable, or who choose not to avail themselves of genetic testing technologies for other ethical, religious, legal, social, or medical reasons. Such couples, while not at increased risk of having children with genetic diseases, will nevertheless inevitably bear some children with genetic defects. The only way to avoid this would

[8]A method of detecting Huntington disease before symptoms emerge, and even before birth may he available within a decade—a technique is already available for certain families (see app A; Wexler, 1984; Gusella, 1%43: Rosenfeld, 198.$).

be to circumscribe their liberty, making the judgment that the potential social benefit overrides their autonomous right to choose what is best for themselves and their families. The generally high regard for personal autonomy in our society implies that such couples' right to make reproductive decisions will be protected.[9]

Existence of new mutations, absence or unavailability of genetics tests, and freedom of choice all suggest that genetic diseases will continue to exist, and therapies for them in infants, children, and adults will continue to be needed.

Types of Genetic Disease That Are Poor Candidates for Gene Therapy Now

CHROMOSOMAL DISORDERS

In addition to genetic diseases that are caused by mutation of single genes or small numbers of genes, there are others caused by abnormal chromosomes. One group of genetic disorders is defined by a surfeit or deficit of chromosomes in cells of the affected individual: patients have an abnormal number of chromosomes or parts of chromosomes. The most common such disorder is Down syndrome, which affects one in 600 live-born infants. Chromosomal disorders overall affect one in 200 newborns, and account for half of all spontaneous abortions (Burrow and Ferris, 1982).

Gene therapy for chromosomal disorders is not scientifically possible now, even in experimental animals. Chromosomal abnormalities involve the improper placement, absence, or duplication of fragments of chromosomes or entire chromosomes. Chromosomes typically contain hundreds or thousands of genes, and there are no techniques presently available for inserting enough DNA to correct such large defects in either somatic or germ cells.

COMPLEX AND DOMINANT TRAITS

At present, there is a large technological gap between those diseases for which gene therapy is promising in the near term and those about which so little is known that gene therapy cannot even be rationally contemplated,

Complex traits such as intelligence and physical stamina, are not sufficiently understood to merit serious contemplation of any genetic intervention, and gene therapy could certainly not be justified, both because such intervention might not be considered '(therapy, " and because there is no gene whose insertion would likely be effective. Even if gene insertion could reliably alter physical and mental abilities, many question whether it would ever be used, because it would have to be cheaper and more effective than other techniques for altering human characteristics. Genetic techniques would have to prove more effective or less costly than education, indoctrination, physical and mental training, and drugs.

Dominant traits, and ***poorly understood recessive diseases*** are also poor candidates for gene therapy in the near future. Therapy of such disorders will depend on the specific cause and biochemical or metabolic manifestations of the disorder. To date, no dominant disorder is sufficiently well understood to warrant an attempt at gene therapy.[10] **There are,** however, a few dominant traits that could potentially be treated using gene therapy. Gene therapy might eventually be contemplated for those enzyme defects inherited as dominant traits, and for diseases caused by deletions of small amounts of DNA that could be replaced (there is some evidence for such deletions in retinoblastoma and Wilm's tumor—cancers usually developed in childhood that are inherited as dominant traits). In such cases, the decision to undertake somatic cell gene therapy for the dominant disorder will not significantly differ from consideration of recessive traits. Nevertheless, few dominant disorders have been characterized biochemically, and simple gene insertion may not correct many dominant disorders. Correction of dominant diseases may require insertion of extensive amounts of DNA, gene surgery to remove the defective gene, or both; techniques for these more complex manipulations have not been demonstrated in mammals. Prospects for gene therapy of dominant disorders are therefore, in general, poorer than for recessive enzyme defects, although a few dominant diseases might be addressed.

[9]L. Andrews, 1984d, citing ***Carey*** v. ***Population Services International,*** 431 U.S. 678, 685 (1977).

[10]This generalization does not apply to traits that are dominant in males and recessive in females (X-linked traits).

Reasons Germ Line Therapy May Be Unnecessary

Germ line gene therapy may never be widely practiced because treatment of abnormal embryos and gametes offers little advantage over selection of normal ones.

Germ line therapy, as currently practiced in animals, involves taking embryos in vitro, genetically altering them, and returning them to a female for further development. In early embryonic stages, only a few cells are present. To determine whether the embryo is normal or abnormal would require that one have a test that provided a diagnosis without disrupting the few cells. No such tests exist at present.[11] There are prenatal diagnostic tests, but these are useful only later in pregnancy, when many more cells can be sampled to make a diagnosis without harming the fetus, 12

In order to practice gene therapy on an early embryo, one would have to treat either all embryos or only ones known to have a treatable genetic defect (Harsanyi, 1982; Pembrey, 1984). Treatment of just those embryos carrying genes for a particular disorder would require a way to identify them. If methods to identify embryos carrying the abnormal gene were available, though, it would be easier and safer to merely select a normal embryo rather than treat an abnormal one (Harsanyi, 1982). If all embryos are treated, then a significant fraction of normal embryos would be unnecessarily subjected to the added risks of gene therapy manipulations, The ratio of normal to abnormal embryos depends on the type of genetic defect being treated. In the most common scenario, involving two parents who are known carriers of a recessive gene, only one in 4 embryos would develop the disease, and so one unaffected and two asymptomatic carrier embryos would be treated for every one in which the disease was prevented. If parents have dominant or X-linked traits, at most half those treated would develop the disease. The situations described are those that would yield the highest fractions of abnormal embryos; most other types of traits would have even less favorable ratios of affected to normal embryos.

Gene therapy on embryos is also made less likely because of the need to ensure that it has been successful. Unless gene therapy were almost certain to work, parents might seek to determine that the defect had been corrected, much as they can now ask for prenatal diagnosis. Checking the success of gene therapy would require either a test for the embryo before it were reimplanted, none of which exists, or availability of a test later in pregnancy and before delivery. If such a test were available, it could be used for conventional prenatal diagnosis. Gene therapy of embryos would thus not avoid the ethical dilemmas already associated with conventional prenatal diagnosis, and would offer little advantage over selection of normal embryos or fetuses, while significantly increasing risks. For cases in which parents did not wish to check on the success of gene therapy, because of religious convictions or because they would not change their actions based on prenatal tests, this argument would not apply.

There are certain situations in which germ line gene therapy might be contemplated. For example, if a man and a woman both had PKU or sickle cell disease and wished to have their own children, then the parents and physician would know in advance that all embryos would acquire the disease because of the parents' genetic constitution. This situation would eliminate the risk of unnecessarily treating unaffected embryos, but might still require a method for ensuring that the gene therapy had been successful (although parents might choose not to test this because of personal or religious beliefs).

The strength of the arguments against germ line gene therapy would also diminish if gene transfer techniques became extremely reliable. How-

[11] Techniques for separating animal embryos and growing identical twins from them have, however, been developed (Maranto, 1984b). These same techniqes, if applicable to humans, might eventually be used to do diagnostic tests on cells separated from the embryo early in development. This would permit preimplantation and later prenatal genetic screening, and might also allow monitoring of the efficacy of gene therapy without harming the embryo or fetus. This might, however, be ethically unacceptable.

[12] There are economic and technical reasons, however, to intensify the search for techniques to detect genetic defects in single or small groups of cells in early embryonic development. Techniques of *invitro* fertilization involve great economic cost and failures cause severe emotional distress; in this setting, a premium is placed on ensuring the normal status of embryos before they are implanted.

ever, this would require dramatic technical improvements in gene transfer and would not eliminate the ethical dilemmas.

The medical complications of gene therapy suggest that germ line therapy on early embryos may never be ethically acceptable, even if it becomes technically feasible, except in extremely rare matings between parents whose genotype for a genetic disease is known. Uncertainty about possible effects of such therapy in future generations may preclude application of germ line gene therapy for even these instances.

Criteria for Beginning Human Gene Therapy

The decision to approve the application of gene therapy to humans should depend on satisfaction of several requirements. The requirements will be based on analysis of risks and benefits for the individual patient and consideration of the wider implications of approving gene therapy for any given patient. The factors considered in analyzing which applications of human gene therapy might be approved will include potential effectiveness, safety, reliability, presence or absence of alternative treatments, severity of symptoms, and prognosis. Each of these will be considered in relation to a particular genetic disease in an individual patient. Some generalizations about these factors, however, apply to the technique of gene therapy as a whole.

SAFETY

Judgments of the safety of gene therapy will be based on animal data and comparison to similar human interventions. For those few genetic disorders, such as thalassemia, that have counterparts in animals, short term safety can be assessed by experiments that measure clinical improvements in animals. For other diseases, it will be necessary to base judgments of safety on animal data obtained in experiments that involve gene transfer, although clinical benefit in the animals cannot be measured. Experiments might be performed, for example, using the same gene and delivery system as would be used in humans, and the animals observed to see if they express the gene or develop side effects.

Questions of safety include not only short term effects, but also long term consequences that may require years to ascertain even in animals (if such long-term risks can be assessed at all). Intergenerational effects would be especially difficult to assess, but would be of concern only if germ line cells were affected. Long-term studies of multiple generations of animals may also be required when and if germ line therapy is ever anticipated.

Defects that could affect a patient's progeny would be a concern if germ cells were affected by gene therapy. Protocols for human gene therapy of somatic cells will therefore be reviewed for evidence that ensures that germ cells are not affected (Working Group on Human Gene Therapy, 1984). The risk of germ line effects has precedent in cancer chemotherapy, radiation therapy, and some types of vaccination. Each of these technologies has a risk of inducing new mutations in the patient that could be passed onto the patient's progeny. If somatic cell gene therapy is done outside of the body, the risk of germ line effects is likely to be extremely remote. If, however, experiments involve administration of gene therapy to the whole patient, then germ line side effects will be a concern, and such risks must be outweighed by the severity of the disease or the magnitude of potential benefit in the individual patient. In the case of ADA or PNP deficiency, for example, the length of the patient's life would be less than 2 years and would be of low quality without gene therapy. For such a patient, the risk of germ line effects might be acceptable, particularly if such effects could be detected and the patient's reproductive decisions informed by this knowledge.

There are some special risks of using viruses to transfer DNA, and assurances of the safety of such transfer viruses will be prominent in approval of human experiments (Working Group on Human Gene Therapy, 1984). The special risks of viruses include the possibility of rearrangement of genetic material in the host that would lead to formation of an infectious agent. It is quite probable that scientists will be able to design DNA

derived from viruses that cannot revert to its more infectious form (Rawls, 1984; Anderson, 1984).

One special concern relates to the potential mutagenicity and carcinogenicity of gene therapy using techniques now available (Rawls, 1984; Anderson, 1984). It is not yet possible to control how and where inserted DNA integrates into that of the host cell. Insertion of genetic material may thus lead to new genetic mutations in the cells so treated (Gordon, 1981). It has also raised the prospect that inopportune insertion of new DNA may rarely cause or predispose a patient to develop cancer. Recent evidence about cancer genes suggests that certain cancers may be associated with abnormal expression of genes that are present in normal cells. Abnormal expression has been induced by viruses similar to those that are being developed to facilitate gene transfer, and cancer-like characteristics have been induced by techniques that closely parallel other methods that might be used for gene therapy (Hayward, 1981). The frequency with which gene transfer results in deleterious mutation or predisposition to cancer appears quite low, perhaps one in ten thousand to one in a million, suggesting that risks may well be less than for cancer therapy, immune suppression, or radiation (Working Group on Human Gene Therapy, 1984). Nevertheless, evidence for low risk of carcinogenesis will be explicitly sought in the approval process preceding early clinical trials (Working Group on Human Gene Therapy, 1984).

The short- and long-term risks of gene therapy are not known. It is thus inappropriate to attempt gene therapy except in the face of otherwise extremely poor prognosis until more is known about the risks. Determination of safety will likely derive from observations of animal experiments and the early instances of human gene therapy undertaken in patients with severe diseases—such as ADA deficiency, PNP deficiency, urea cycle defects, or Lesch-Nyhan syndrome–that lack a preferable alternative therapy in a given patient; for such patients, even a low probability of benefit may outweigh the uncertainties and risks of treatment. If animal experiments and early human applications prove safe, diseases with somewhat better prognoses might then be treated by gene therapy.

EFFICACY

Human gene therapy should not be approved until there is evidence that it might work; codes of research ethics require this. Commencement of experimental human gene therapy will require evidence from tissue culture and animal experiments. in the small number of diseases for which there is an animal model, judgments of efficacy can be based directly on clinical correction of animal diseases. In other diseases, constituting the majority of genetic disorders, it will be necessary to base judgments on studies in tissue culture, related human diseases, and relevant animal studies. Experiments might produce evidence, for example, that the human gene were expressed in treated animals or could be expressed in the patients' cells in vitro. The disorders in which gene therapy might soon be attempted do not have exact animal models, and so the earliest experimental human treatments may well be based on tissue culture studies and indirect animal experiments.

Demonstration of efficacy will require evidence that a gene can be delivered to a tissue where it can be effective, that it will remain in cells long enough to have an effect, and that the product of the gene is sufficiently expressed. In some future cases, these factors may require that the transferred gene serve as a direct replacement for the abnormal host gene, occupying the same location in the same tissue. In other cases, including those for which gene therapy is being seriously considered now, it may not be necessary to correct the defect so precisely.

In the case of ADA or PNP deficiency, for example, it may require only a little enzyme produced in bone marrow cells to sufficiently compensate for the biochemical defect. The absence of animal models indicates that the only way to test this is to do a human experiment. This is seriously considered for ADA or PNP deficiencies only because the diseases are rapidly fatal and there is, for most patients, no alternative therapy. Evidence for potential patient benefit for these

diseases may thus require only that the ADA or PNP enzyme be detected in bone marrow cells of the patient following gene transfer.

Genetic diseases that affect the brain constitute a particularly large group of disorders for which the question of organ specificity is crucial. There are several dozen genetic diseases whose most prominent symptoms are neurological, including Tay-Sachs disease, metachromatic leukodystrophy Lesch-Nyhan disease, and phenylketonuria (PKU). The brain differs from other organs in two important respects. First, the nerve cells, whose impaired function gives rise to symptoms, do not proliferate like bone marrow cells after they mature. This implies that genetic material introduced into one nerve cell cannot be amplified by allowing that cell to reproduce for many generations. Second, the brain has highly selective mechanisms for transporting substances from the bloodstream to brain tissues. Correction of biochemical defects elsewhere in the body may therefore not correct the defect in the brain, and may not eliminate neurological or behavioral symptoms.

Doctors and scientists do not know which brain defects can be corrected only in brain cells and which might be treated by modifying other tissues. Lesch-Nyhan disease is due to the absence of HPRT enzyme in all cells. Its worst symptoms are due to disruption of brain functions. There is uncertainty about whether or not the disease can be treated by correcting the biochemical abnormality in cells other than brain cells (e.g., bone marrow cells) (Anderson, 1984; Merz, 1984). Further, there is no way to test whether treatment of bone marrow cells would cure the brain dysfunction except through human experiments. If the disease could be treated by alteration of bone marrow, then patients who already have this severely debilitating disease could be treated. Otherwise, the only currently conceivable alternatives are treatment of cells early in development (that might also entail germ line changes), or prevention of the disorder by prenatal diagnosis and selective termination of pregnancy.[13]

[13]Other alternatives, such as implantation of genetically altered nerve cells or insertion of genetic material using engineered viruses specific for nerve cells, are theoretically possible, but have never been successfully demonstrated, even in animals.

Many questions about efficacy will be addressed by future genetic and clinical research. Determinations about which diseases can be treated and which methods are most successful must be made before human gene therapy becomes routine medical practice.

RELIABILITY

Experimental or medical therapy should be undertaken only if the procedures are sufficiently reliable to suggest that the potential scientific and clinical benefits outweigh the risks of ill effects or failure.

Animal experiments involving gene transfer, with the exception of those done in lower organisms, until recently had a relatively low probability of success in any one organism. This was tolerable to the investigators because their interest was in gene expression and animal development, and they could select the most scientifically interesting result from a large population of therapeutic failures. Such techniques are ***not*** acceptable for correction of genetic diseases in humans, where there must be of potential benefit to the individual treated.

Application of gene therapy in humans is now seriously considered only because of advances in the methods of delivering genes into cells and stable expression of genes so delivered (Anderson, 1984).

ALTERNATIVE TREATMENTS

Gene therapy will be acceptable only if it offers the best prospect of success among all potential treatments for a given patient. Factors that might be considered in comparing gene therapy to alternatives will include educated judgments about:

expected efficacy,
anticipated costs (to the patient or overall), and
magnitude and type of risks.

Such judgments will vary from physician to physician and patient to patient, as for any medical technology.

The genetic basis of a disorder does not imply that its treatment must also be genetic. There are several treatments that have proven effective in

some genetic diseases. The clinical manifestations of hemochromatosis can be prevented by periodic blood donation. Dietary treatments of PKU, galactosemia, urea cycle defects, and several other disorders considerably improve patient prognosis, although they are only partially effective and impose substantial limitations on patients and their families. Vitamin supplementation of those with Wernicke-Korsakoff encephalopathy and several other disorders can be quite effective.

Drug treatments can compensate for some genetic defects. Clinical investigators have already discovered two drugs that lead to partial correction of sickle cell disease by inducing expression of a type of hemoglobin, normally only expressed during fetal development, that can compensate for the errant sickle cell protein (see Technical Note 4). Clotting factors can be given to hemophiliac patients, and biotechnology may greatly increase the availability and reduce the cost of such factors.

Clinicians have also pursued the possibility of directly administering enzymes that are missing due to genetic defects (Desnick, 1981). Such enzyme therapy has not been clinically successful, but advances in drug administration could render such therapy practical. Development of drug pumps that reside in the body and deliver hormones, enzymes, or other chemicals for long periods of time may reduce the need for gene therapy. A new insulin pump developed by NASA, for example, promises to work for years without need for battery replacement (Langone, 1984).

Gene therapy is not the only way to restore normal genetic information to some organs of a patient with a genetic disease; some genetic defects may be remedied by transplantation of whole organs or tissues. Bone marrow transplantation has been successful, for example, in treating thalassemia, sickle cell disease, and immune deficiencies; liver transplants have been performed for Wilson disease (Desnick, 1981; Friedrich, 1984). Transplantation is a serious prospect for only a small minority of potential patients, however. This is because current methods require tissue compatibility between the donor and the recipient, a rare event, and because the methods require highly risky treatments to prepare the patient to receive the transplanted cells or organs. A final disadvantage of transplantation is its extraordinary cost.

There are thus several existing and prospective treatment for genetic diseases that do not require direct gene replacement or supplementation, but all have limitations and many genetic diseases have ***no*** treatment. As one physician summarizes the status quo, "therapy of most genetic disorders is still ineffective and inadequate" (Friedmann, 1983).

Gene therapy of somatic cells will therefore probably prove technically superior to alternative treatments for selected patients with some disorders.

SEVERITY OF SYMPTOMS **AND PROGNOSIS**

The patient expected quality and length of life directly affect the potential benefit and acceptable level of risk of any medical or experimental intervention. Extremely serious disorders, such as Lesch-Nyhan disease and ADA and PNP deficiencies, have such poor prognoses that even small potential benefits are welcome and large risks may be acceptable to the patient and his or her family because they pale in comparison to continued life with the disease.

Some examples of diseases likely to be targets for gene therapy are noted by category in table 1. The number of patients likely to be treated are noted in table z.

DATA MONITORING

For clinical trials to be optimally productive of new knowledge, investigators must have mechanisms for following patients, and have a protocol for obtaining whatever tissues may be needed and for analyzing them. Advance thought about how data monitoring will be done and disclosure of what it will involve to the human research Subjects should be an important aspect of any human gene therapy experiments. Attention to data monitoring will thus be one requirement for approval to begin clinical trials.

INFORMED CONSENT

Assurance that informed consent will be freely and appropriately obtained is required for all ex-

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Table 1.—Examples of Diseases for Which Gene Therapy Might Be Considered

1. **Protocols** for human gene therapy in somatic cells expected in next several years:
   - immunodeficiency caused by adenosine deaminase or purine nucleoside phosphorylase deficiencies (ADA or PNP deficiencies)
   - Lesch-Nyhan syndrome (complete hypoxanthine-guanine phosphoribosyl transferase deficiency)
   - urea cycle defects caused by deficiencies of arginosuccinate synthetase (citrullinemia) or ornithine carbamoyl transferase (OCT, also known as ornithine transcarbamylase)
2. Might be attempted in foreseeable future:
   - phenylketonuria (as improvement on current dietary treatment)
   - familial hypercholesterolemia
   - defects of the urea cycle other than citrullinemia and OCT deficiency:
     - arginemia (arginase deficiency)
   - mucopolysaccharidoses and other defined metabolic defects:
     - Gaucher disease (some forms)
     - metachromatic leukodystrophy (arylsulfatase B deficiency type with little brain involvement)
     - Hunter syndrome (enzyme detectable in normal blood)
     - branched chain ketoaciduria (severe grades)
3. Farther off because protein expression may require regulation:
   - hemoglobinopathies: (see *Technical Note 5)*
     - sickle cell disease, hemoglobin SC disease
     - alpha and beta thalassemia
   - hormone production defects
4. Farther off because gene product may be easily available for administration (diminishing the need for gene therapy):
   - growth hormone deficiency; some other hormone production defects
   - hemophilias
5. Unlikely unless new discoveries provide clues on how to approach gene therapy:
   (Some may require germ line therapy because of access to tissue sites or immunologic problems with gene product.):
   - Tay-Sachs disease and other metabolic defects that primarily affect brain
   - cystic fibrosis
   - type 1A growth hormone deficiency
   - most diseases inherited in dominant pattern (e. g., Huntington disease, Marfan syndrome, achondroplasia, etc.)
6. May not be applicable:
   - chromosomal disorders:
     - Down syndrome
   - environmental and multigenic disorders:
     - hypertension
     - diabetes

"Cloned human gene available

SOURCE: Wissow, 1984.

Table 2.—Numbers of Patients Who Might Be Treated by Somatic Cell Gene Therapy in the Near Future

Disorder	Number of patients with the disorder
Adenosine deaminase deficiency	40 to 50 reported worldwide
Purine nucleoside phosphorylase deficiency	9 patients in 6 families reported worldwide
Lesch-Nyan syndrome	1:10,000 males, estimated 200 new cases in the United States per year
Arginosuccinate synthetase deficiency	53 cases reported
Ornithine carbamoyl transferase deficiency	110 cases reported

SOURCE: Stanbury, et al., 1983, as modified by OTA.

periments involving humans (Code of Federal Regulations, 1983). In the case of human gene therapy experiments, this will include disclosure of what can reasonably be expected about:

- risks of new mutations,
- possible effects on the germ line,
- reversibility of side effects in the patient, and treatment for them,
- relative costs of alternative therapies,
- relative risks and benefits of alternative therapies,

procedures that will be done to obtain clinical data on the gene therapy experiments, procedures for dropping out of the study, and assurance that it is the patient's right to do so.

All human experimental protocols should be reviewed by local Institutional Review Boards (IRBs), as is the case with all experiments involving humans. In the case of human gene therapy, however, the NIH recently revised the Guidelines for use of recombinant DNA to state that research proposals involving human gene therapy (proposed by institutions that receive Federal funds for recombinant DNA research) must be submitted to NIH for approval, in addition to local IRB review. These protocols will be reviewed first by a Working Group on Human Gene Therapy, then by the Recombinant DNA Advisory Committee, and finally by the NIH Director before ap-