other medical technologies are handled by the courts or in new legislation at the State or Federal level.

patents and trade secrets

The techniques involved in gene therapy involve the use of recombinant DNA to clone and insert human genes. The early applications, if they involve the diseases listed in table Z, are unlikely to involve patentable agents or processes, because the methods under development have been openly published and developed at several centers, and the recombinant DNA involved is available in several laboratories. Eventually, however, the complexity and variety of approaches to gene therapy might result in products or processes that could be patented. Patents might be sought, for example, for genetically altered viruses designed to deliver the human gene to the target tissue or that permit controlled expression. The criteria for granting such patents will be patentable subject matter, novelty, utility, and nonobviousness, the same ones used for other recombinant DNA products (OTA, 1984, ch. 16). The public policy issues of fair access to the technology and encouragement of innovation would also be analogous to those for other medical technologies.

A few distinctive aspects of patents and trade secrets are especially relevant to gene therapy. The review process by the National Institutes of Health (NIH) for approving experiments involving proprietary information might require closed sessions, so that trade secrets were not disclosed publicly. The guidelines for human gene therapy formulated by the NIH (described below) are not binding on private firms that do not receive Federal research funds, although companies would be likely to seek NIH approval in any event to avoid adverse publicity and to assure due process for questions that arise about liability and insurance. Finally, the flow of scientific and clinical information to other investigators might be inhibited if trade secrets related to gene therapy must be protected.

Insurance

Gene therapy might eventually be covered by standard medical insurance, or it might require special provisions. Gene therapy, if it follows the model of other medical treatments, will not be covered by insurance companies until its efficacy has been established for its intended application. Coverage by insurance will likely depend on the particular disorder, the relative cost (for gene therapy and the alternatives), and the safety and efficacy of the techniques involved.

Social implications of gene therapy

Gene therapy, should it prove useful, would be like other technologies in changing the character and kinds of decisions that individuals make. It would provide new options for medical therapy and imply new responsibilities for making such decisions fairly and for the benefit of both individuals and society. In the view of many religious and ethical thinkers, gene therapy restricted to somatic cell corrections of single gene traits differs little from other medical therapies (Neale, 1983; World Council of Churches, 1983; Siegel, 1982; Fletcher, 1982, 1983a, and 1983b).

There are risks and benefits associated with beginning gene therapy, as with any new technology. Public policy, public education, scientific and technical advance, and other factors can all influence which applications are pursued and which eschewed. In an open and democratic society, new technologies are greeted by different social groups in different ways. Some may believe that beginning gene therapy too closely resembles “playing God” or is too dangerous, while others impatiently await its application to the disease affecting a loved one.

Background

The application of gene therapy to humans is likely to be regarded throughout society as a significant step, whether done in somatic or germ

line cells. It will be a focus of attention because it is unprecedented and technologically sophisticated, and because it permits alteration of something considered fundamental to each individual—his or her genetic constitution. While genetic changes have been technologically induced for years—for example, in the use of some vaccines--the changes have never been so premeditated nor so direct as deliberately inserting new human genes to cure a specific disease. As noted above, however, the main difference between gene therapy and other medical technologies may be perceptual more than actual. The risks and benefits of gene therapy are analogous to those for other therapies, and many believe that it presents no fundamentally new ethical problems, yet there remains a gnawing discomfiture with the prospect.

In the absence of gene therapy after birth, an individual has no role in the choice about which genes he or she carries, and so bears no responsibility for carrying them. Once gene therapy is available, this may not be the case, and individuals ma-y play some role in selecting their genes. This prospect is frightening to many because new choices bring new responsibilities; new technologies can be misapplied. The magnitude of the responsibility is, to a large extent, determined by the power of the new technology. If, as suggested above, gene therapy is not widely applied in the near future because of limitations on the range of diseases to which it is applied, then the social impact of gene therapy is likely to be less than that associated with many other accepted medical practices.

Most of the major social impacts of genetic knowledge will almost certainly derive less from gene therapy than from genetic screening or other genetic testing. Some fundamental choices about privacy of data on patients' genetic constitution must be made as the new technologies provide greater amounts of such information (see app. B). The new information will, however, not be directly related to developments in gene ***therapy***, but rather to diagnostic evaluations of patients' predispositions to genetic diseases or special health risks.

Some fear that increased knowledge about how genes work may further promote a cold, abstract, and mechanistic view of human life. To the extent that this is true, however, it does not relate directly to gene therapy but rather to genetics in general, and even more broadly to all of science.

Social aspects of gene therapy that are mentioned below fall into several general categories:

- What process will determine when to begin gene therapy?
- How important are evolutionary considerations? and
- What might be the impacts on social institutions?

Major social issues

WHAT PROCESS WILL DETERMINE WHEN TO BEGIN GENE THERAPY?

The process of deciding when to begin experimental human gene therapy includes several components. Some judgments are technical, involving assessment of the expression of the gene of interest, for example, and such decisions are left to scientific peers to examine experimental design or determine which studies are relevant to a proposed project. Other judgments involve assessment of quality of life for a particular patient; such decisions can only be made by the patient, his or her family, the physician, or others who are familiar with the details of a particular case. Other judgments may involve determination of acceptable risk to society, and these invite wider public participation.

Many of the questions raised will be answered only in the context of a particular patient in a particular family seen by an individual physician, and the judgments of the parties most directly affected will decide the case within the constraints set by laws, regulations, and local ethics and human research committees. The context for making individual decisions will thus depend on peer review and compliance with human subjects guidelines. The criteria for peer review and setting of guidelines involve, in turn, government agencies that must ensure fairness, completeness, and representation of diverse and often conflicting viewpoints.

Judgments about whether a given experiment conforms to the criteria will differ among individuals. Some of the differences will reflect life experiences. A physician accustomed to treating cancer patients will have different views from a scientist whose primary interest is developmental biology. A hospital attorney may hesitate to endorse an experiment that the parent of an affected child would eagerly embrace. One suspicious of technology in general might reject experiments involving any level of risk.

Some urge caution in approaching uses of gene therapy.

> Once we decide to begin the process of human genetic engineering, there is really no logical place to stop. If diabetes, sickle cell anemia, and cancer are to be cured by altering the genetic makeup of an individual, why not proceed to other 'disorders': myopia, color blindness, left-handedness? Indeed, what is to preclude a society from deciding that a certain skin color is a disorder? . . .
>
> With human genetic engineering, we get something and we give up something. In return for securing our own physical well-being, we are forced to accept the idea of reducing the human species to a technologically designed product. Genetic engineering poses the most fundamental of questions. Is guaranteeing our health worth trading away our humanity? (Rifkin, 1983, pp. 232-233).

In contrast, an urgent request for support of gene therapy research is found in the words of Ola Huntley, three of whose children suffer from sickle cell disease:

> I resent the fact that a few well-meaning individuals have presented arguments strong enough to curtail the scientific technology which promises to give some hope to those suffering from a genetic disease. I have faith to believe that genetic therapy research, if allowed to continue, will be used to give life to those who are just existing . . . .I, too, would like to ask the question, who do we designate to play God? Aren't those theologians and politician; playing God? Aren't they deciding what's best for me without any knowledge of my suffering? I am very angry that anyone would presume to deny my children and my family the essential genetic treatment of a genetic disease . . ..1 see such persons as simplistic moralists who probably have seen too many mad scientist horror films. It's like saying that someone can deny others the right to drive or ride in an automobile because there is an ever-present danger of an accident (Huntley, 1983, pp. 166-169).

Such conflicting views cannot be assuaged by empty assurances, and public policy decision will typically be made without consensus. There are dangers in premature application balanced against undue delays of useful medical benefits. Public policy will be decided amidst great uncertainty. As one doctor noted, "the ethical principle that physicians have to be concerned about is that we know what we're doing before we promise that we're going to try and treat someone" (Ryan, **1983, p.** 172). In deciding when to begin experiments on human gene therapy, the need for further knowledge must be weighed against the benefits that might accrue to patients with severe and fatal diseases.

Most of the social and ethical questions raised about gene therapy could also be raised in the context of other medical interventions, such as use of antibiotics or acceptance of surgery. It is not the questions that are new, but rather a new technology that forces their reconsideration. Disagreement about the seriousness of the new social and ethical consequences of using gene therapy in humans hinges on incompatible judgments of how widely it will be used and how revolutionary will be its perceived impact on how humans view their own sanctity. Most scientists and clinicians believe that gene therapy will be only a small incremental medical advance applicable to a few patients, while religious and social commentators may reflect on its cumulative effects over generations. The general interest in human gene therapy has led some scientists and medical providers to urge caution so as to avoid political reaction against gene therapy among the general population (Rosenberg, 1983; Grobstein, 1984).

Public policy will have to be based on consideration of patient welfare, social impacts, religious precepts, and political realities. There is little reason to believe that differences in opinion about the appropriateness of human gene therapy will resolve spontaneously, or even after extensive public discussion. Where there is no agreement

on what decision to make, the only alternative is a process for making the decision, and government agencies must demonstrate that the process is rational and fair (Bazelon, 1983).

Wide public discussion and agreement on a process do not guarantee fair decisions or correct assessments of risk and benefit. Errors of judgment may occur even with unassailable expertise and completely democratic participation. Resort to fair and open process is not, therefore, perfect, but merely the best practical solution **to** assure fairness.

Given the anticipated public interest in and controversy about human gene therapy, any successful mechanism for permitting its commencement will involve a public process including discussion among individuals with different informed perspectives. Such discussion may arrive at consensus, but if it does not, documentation of the fairness and rationality of the decisionmaking process will be the only practical course. The Federal Government will be involved in decisions about human gene therapy because of its involvement in medical research, health care, and issues that attract wide public interest.

There are several Federal agencies already in place that can educate the public and make decisions about when to begin human gene therapy. These include the Recombinant DNA Advisory Committee of the NIH, the Food and Drug Administration, and several other bodies within the department of Health and Human Services. These will be described below in the section on the Federal Role in Gene Therapy.

HOW IMPORTANT ARE EVOLUTIONARY CONSIDERATIONS?

Direct manipulation of the genome inspires visions of mankind controlling its own evolution, depleting the diversity of genes in the human population, and crossing species barriers to create new life forms. The magnitude and rapidity of change caused by direct genetic intervention, however, are likely to be far smaller than the large effects caused by relaxing historic selection pressures on the human population through changes in the environment, sanitation, and health care.

Discussion of ***germ line*** gene therapy is most relevant to permanently changing the human gene pool because it would lead to inherited changes. At present, however, such discussion is necessarily vague and speculative because the technology does not exist and may never be used. There will doubtless be continued public interest in ensuring fair and open debate on whether human germ line gene therapy would be appropriate. It is impossible, however, to make estimates of the potential magnitude of its impact on human populations now.

The effects of somatic cell gene therapy will depend on how many patients receive such therapy, and to which conditions it is applied. It is not possible to make firm predictions about how many patients might eventually be treated by gene therapy, because it is not now certain that even somatic cell gene therapy will prove medically useful. The effect that somatic cell therapy would have on human population genetics would be no different in kind than that from other technologies that affect the patient and do not lead to inherited changes, Most of the changes would be due to preservation of the lives of those who would otherwise die before reproducing, the same effect that results from diet therapy in PKU, or clotting factor replacement in hemophilia.

While it is not possible to estimate the number of patients that might eventually be aided by somatic cell gene therapy, it is possible to estimate the impact of correcting those genetic defects that are currently targeted. These will be the potential genetic impacts that must be assessed by those approving the early experiments in gene therapy. As can be seen in table 2, the diseases for which gene therapy is now contemplated are quite rare. The total number of patients with these conditions that might be treated using somatic cell gene therapy would likely be less than 300 per year in the United States, and would probably be far fewer until the technology were accepted. This figure compares to the approximately 4 million births in the United States each year.

Changing the Gene Mix in Human Populations.—Somatic cell gene therapy would have no direct effect on the mix of genes in human popula-

tions, and would have only the indirect effects noted above. Germ line therapy, in contrast, would alter the prevalence of some genes, although the magnitude of such effects is impossible to predict because so many factors are involved.

Direct germ line gene therapy of recessive disorders would, for most diseases, have a noticeable effect on human evolution only if widely practiced for hundreds of generations. The number of generations needed to have a significant effect would depend on the type of gene being corrected, its prevalence in the population, when the disease were expressed (in adulthood or childhood), the severity of the disease caused by it, and many other factors. If gene therapy were used only to treat single gene recessive traits, then it would take several hundred generations measurably to alter the prevalence of the gene in the population. For defects that are present on one percent of chromosomes in the human population, for example--corresponding to a genetic disease much more common than any under consideration for gene therapy now—it would take 1,500 years to increase the frequency to 2 percent.[14] If germ line gene therapy were widely practiced for a large number of diseases, including common dominant traits, then alterations might be noticed much more quickly, but such applications are not now envisioned.

Depletion of Diversity in the Gene Pool.-– There is excellent evidence that some genetic diseases are common because of an advantage conferred to those individuals who carry ***one*** copy of the aberrant gene. Those who carry one copy of the sickle cell anemia gene, for example, are better able to combat malarial infections. The genetic disease is the price paid to preserve this advantage for the population on average, mitigated only by the statistical rarity of having two abnormal genes (and thus the disease) (Vogel, 1979).

[14]This example is based on discussion of eliminating rare genes for recessive disorders in several references (Li, 1961; Vogel, 1979). These assume that those who carry two copies of a defective gene would not reproduce. In considering the impact of human gene therapy for those who would otherwise die before reproducing, the situation is reversed but the time scales would be comparable,

Genes causing other genetic diseases may also serve a purpose that has not been discovered, and so elimination of such genes might prove deleterious to the human population in the long run. In somatic cell gene therapy, the patient own genes would not be deleted, but new information would be added in such a way that it would not be inherited. This would have no impact whatever on the population's reproductive gene pool. If gene therapy permitted the survival of patients who would otherwise die, however, then genes causing diseases might slowly become more widespread because they would not be eliminated.

Even if gene therapy did have an effect on genetic diversity, this might not prevent its use, The risk of slightly reducing diversity in the entire human population would likely seem insignificant to those patients for whom the potential benefits loom large and immediate. Perpetuation of genetic disease, particularly of the severe childhood diseases that are now the targets for gene therapy, would seem a cruel means to an end of uncertain import.

The sickle cell example is instructive in this sense, as well. While it is widely accepted that the sickle cell gene conferred certain advantages in combatting malaria among Mediterranean populations, it is also true that current antibiotics and sanitation technologies have been much ***more*** effective in protecting the same populations. In the era of modern medicine, sickle cell disease is no longer a necessary price to pay for genetic protection from the ravages of malaria.

The arguments for refraining from gene therapy in order to maintain genetic diversity are also weakened when raised in a population whose main long term problem may be the very rapidity of its growth. When a population is rapidly expanding, the diversity of genes generally increases because there are more individuals who can carry new genes.

Crossing Species Barriers. -Recombinant genetic technologies permit genes from one species to be inserted into another. In the animal experiments cited, for example, rat growth hormone genes were put into mice and rabbit globin genes

into rats. It is unlikely that an animal gene would be used for human gene therapy, because if an animal gene is available, then isolation and cloning of its human counterpart would be routine. Human genes will be used in animals, however, to test the safety and efficacy of gene therapy before it is tried in humans. What would be the significance of using human genes in animals?

Mythology and literature contain numerous examples of hybrid creatures that combine the characteristics of man and beast or involve engineering completely new organisms (Capron, 1984c; Siegel, 1982). One need only think of the minotaur (the apocryphal man-bull hybrid of Crete who devoured fair youths from ancient Greece), the golem (a creature of Jewish lore created to protect the residents of Prague; the golem eventually turned against them and had to be destroyed), or Frankenstein's monster to note the horror associated with semi-human creatures, It is widely accepted in the religious and professional ethics communities that attempting to create such creatures would be immoral (World Council of Churches, 1982; National Council of Churches, 1984; Siegel, 1982,1983); it is also impossible to create such creatures by attempting to alter single gene defects. Some of the issues raised by interspecies transfer of genes are further discussed in Technical Note 3,

FETAL RESEARCH

Research involving human fetuses is a topic of controversy in the United States, and 25 States have statutes that limit or prohibit it (Andrews, 1984b; Quigley, 1984). Fetal research bears on gene therapy primarily if germ line gene therapy is considered. If germ line gene therapy on human embryos is to be undertaken, it must rest on a foundation of knowledge about development and genetic expression in very early human embryos. Such knowledge can only be obtained using such embryos.

Even if germ line therapy is not considered, there may be instances in which fetal research would be useful in establishing safety or efficacy of somatic cell gene therapy. The history of research on Rubella during the 1960s may illuminate the utility of fetal investigation in several respects.

Concern about Rubella infection, particularly its proclivity for causing congenital malformations, intensified following the epidemic of 1964, It was well known that Rubella infection during pregnancy could cause malformations, but the mechanisms were not clear. Investigation of the epidemic was advanced by research on fetuses that either spontaneously aborted or were aborted because an infected woman chose to avoid the risk of bearing a deformed child. Fetal research showed that a majority of fetuses in women known to be affected had been directly infected by the Rubella virus, that the deformations were likely due to direct fetal infection, and that fetal infection often persisted long after the woman was no longer symptomatic (Horstmann, 1965).

Fetal investigation also led to the development of Rubella vaccines. Many vaccines were developed during the mid-1960s, including the RA 27/3 vaccine derived from an infected human fetus and propagated in tissue culture of human cells (Plotkin, 1965; Plotkin, 1969). This strain is now the only Rubella vaccine licensed for use in the United States (Plotkin, 1981).

Finally, the guidelines for use of Rubella vaccines were influenced by human fetal research. Animal experiments showed that Rubella could infect fetuses of pregnant females (Parkman, 1965), as was expected from human studies. Preliminary experiments in monkeys, however, did not show fetal infection by the weakened Rubella used in vaccination (Parkman, 1966). The number of monkeys tested was necessarily small because of the expense and difficulty of animal experiments, and investigation of humans proved necessary. Scandinavian workers showed that in contrast to the monkey experiments, vaccine strains might infect the human fetus (Vaheri, 1969). These experiments could only be done on aborted fetuses. The findings were considered in drafting the recommendations for use of vaccines in pregnant women (Recommendations, 1969).

The strains of vaccine now in use are different from those used in the Scandinavian experiments, and further research on current strains (involving women who have inadvertently been vaccinated during pregnancy) has demonstrated that