a broad spectrum of political and religious viewpoints, including diverse Protestant, Roman Catholic, and Jewish representatives (signatories and resolution printed in: Recombinant DNA Advisory Committee, 1984). The resolution was accompanied by a discussion paper by Jeremy Rifkin, author of ***Algeny*** and head of the Foundation on Economic Trends, although the discussion paper was not endorsed by all signatories of the resolution (Nelson, 1984a; McCormick, 1984; Dorfman, 1983). The discussion paper warned of many potential abuses of intervening in human genetics (Foundation on Economic Trends, 1984; Recombinant DNA Advisory Committee, 1984). Delivery of the resolution, and the involvement of Rifkin and many of the signers attracted media attention, once again verifying the existence of public and religious apprehensions about the rapid advances of genetic technologies (Harden, 1984). Discussions following release of the resolution have failed to demonstrate a consensus, even among the signatories, but the document did generate the wide public discussion sought by many who signed it (Nelson, 1984a; McCormick, 1984).

OTA involvement and review process

OTA convened a workshop in September 1984, where potential consumers and experts in ethics, medicine, and genetics convened to discuss the technical feasibility and diverse implications of human gene therapy. The panel for the workshop and other workshop participants reviewed material prepared by OTA staff and contractors. Several drafts of the background paper were widely circulated for external criticism before and after the workshop, resulting in review by more than 70 ethicists, scientists, religious and civic leaders, and other concerned parties. Drafts were also distributed for review at the National Institutes of Health, the Food and Drug Administration, to all members of the Working Group on Human Gene Therapy of the Recombinant DNA Advisory Committee of the National Institutes of Health, and to other government agencies.

Types of gene therapy

Human gene therapy encompasses a broad range of technologies and may eventually be applied to a diverse group of genetic diseases. This variety requires that several distinctions be kept in mind when discussing the technology.

Different mechanisms of gene therapy

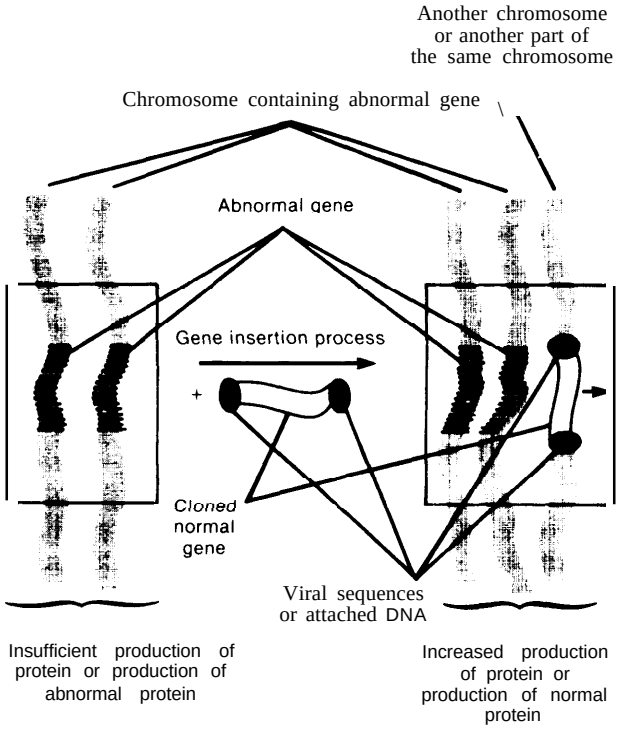
Gene therapy refers to the insertion of genetic material to correct a defect. Gene therapy can take several forms:

- gene insertion, in which a new version of a gene is introduced into a cell;
- gene modification, in which a gene already in place is altered; and
- gene surgery, in which a particular gene is excised and may also be replaced by its normal counterpart.

Such genetic alterations would involve insertion of new material that directly codes for proteins or that affects how existing genes are expressed by suppressing or enhancing production of particular proteins.

Current prospects for human gene therapy do not include either gene modification or gene surgery (Anderson, 1984) because these are more complex than merely adding new genes to cells, Such complicated manipulations can now be performed, however, in some viruses, yeast, and bacteria, and the necessary technologies may later be discovered that would permit gene surgery or controlled genetic modification in animals and humans. Through the remainder of this background paper, gene therapy will refer to gene insertion, because this is the form likely to be applied first. The distinction is technically relevant,

Gene Insertion



SOURCE: Office of Technology Assessment.

but does not significantly affect the discussion of public policy implications that will be addressed because gene modification and gene surgery do not raise moral or medical issues distinct from those raised by gene insertion.

Somatic versus germ line gene therapy

Gene therapy might be performed in either **germ cells** (sperm, egg cells, or the cells that give rise to them) or in ***somatic*** cells (cells that comprise all other body tissues). Alterations in somatic cells do not result in inheritance of the alteration, while modification of germ cells results in changes that could be passed on to subsequent generations if the recipient patient were to have children.

Genes are comprised of deoxyribonucleic acid (DNA). DNA, in turn, is composed of long chains of molecules called nucleotides. All the genetic information that is inherited by a cell is encoded by the sequence of nucleotides in its DNA (see Technical Notes). DNA ultimately controls formation of all of the substances that comprise and regulate the cell. Certain sequences of DNA contain information for specific proteins such as enzymes, hemoglobin (the oxygen-containing protein in red blood cells), or the variety of receptors on the cell's surface. Stretches of DNA that contain the information for a specific product are called genes. The DNA of the gene would not be different for somatic versus germ line therapy, although there might be different sequences added adjacent to the gene depending on how the gene would be regulated in a particular experiment or treatment. The difference between somatic and germ line therapy is which type of cell is treated with DNA.

Somatic cell gene therapy is illustrated by following how physicians might attempt to correct the genetic defects that cause ADA or PNP enzyme deficiencies. ADA deficiency is caused by absence or inactivity of the enzyme adenosine deaminase. PNP deficiency is a different disorder with some clinical similarities, It is caused by absence or inactivity of the purine nucleoside phosphorylase enzyme. In ADA deficiency, the DNA in the adenosine deaminase gene is abnormal, and for PNP deficiency, there is a corresponding defective PNP gene. The genetic defect is due to an incorrect DNA sequence caused by a mutation. The mutation could be in the form of errant replacement of one nucleotide by another or loss (or addition) of one or more nucleotides somewhere in the sequence. The altered sequence encodes an abnormal enzyme that does not function, or causes insufficient production of the normal protein.

Because there is either not enough enzyme, or it is present in a dysfunctional form, the chemical reactions mediated by ADA or PNP do not take place normally in the cell. This leads to accumulation of some chemicals that would normally be destroyed by ADA or PNP, and a paucity of those chemicals the enzymes are responsible for making. In the case of both ADA and PNP deficiencies, it appears that toxic chemicals accumulate that inhibit the action of cells that are involved in body defences.

The diseases are inherited as recessive genetic traits (the two diseases caused by the different enzyme deficiencies are slightly different, but not in a sense that is relevant here), and are usually fatal before age 2 if not treated (Kredich, 1983).

Severe immune deficiencies can be treated by bone marrow transplant (Friedrich, 1984), but not all patients are eligible for transplant, and the procedure is quite risky and costly. ADA or PNP deficiency might be treated instead by somatic cell gene therapy: removing an affected patient's bone marrow cells, inserting normal genes for the enzymes into them, and returning the treated cells to the patient where they could grow and perhaps produce enough of the needed enzyme to degrade the toxic chemicals, thus restoring immune function.

Although the details vary, most of the diseases that might be approached by gene therapy conform to this model: they are genetic defects that cause insufficient production of normal enzymes or production of dysfunctional ones. Gene therapy attempts to restore enzyme function by inserting DNA to produce normal protein.

Rather than treating only bone marrow or other somatic cells, germ cells or cells of an early embryo might be treated to correct a genetic defect. Such germ line treatment would affect all cells in the body, including both somatic cells and germ line cells. In the case of ADA or PNP deficiency, germ line therapy would likely be done by inserting the correct genes into an affected embryo within hours of fertilization. This might lead to presence of a normal ADA or PNP gene in all cells, and expression of the normal gene with production of a normal enzyme in the tissues where it would be needed to correct the immune deficiency.

In somatic cell therapy, treatment affects only cells in the patients' organs and would not be passed on to children, while germ line correction would produce genetic changes that could be detected in all cells in the body and could be passed on to children.

TREATMENT OF SOMATIC CELLS

Many of the ethical and religious reservations expressed about human gene therapy refer only to alterations that might affect the germ line to produce inherited changes, In the opinion of several ethicists and religious thinkers, treatment of somatic cells by genetic methods does not pose ethical problems different in kind from those presented by other types of experimental therapy such as new drugs or novel surgical techniques (Fletcher, 1983a, 1983b; Siegel, 1982, 1983). The questions that need to be addressed in assessing the appropriateness of treating ***somatic*** cells include:

- What is the likely impact on people's *regard* for the sanctity of human life? (World Council of Churches, 1983; National Council of Churches, 1984).
- What are the risks of inadvertently affecting the germ line?
- What are the precautions taken against deliberate misapplication?
- What scientific data are available to suggest that the treatment might work to the patient's benefit?
- How serious is the disease? What are the realistic possibilities of benefit to the patient? What are the risks to the patient? What is the prognosis if there is no treatment?
- What are the alternative methods of treatment? Is gene therapy likely to be more effective, less costly, safer, or otherwise more acceptable than available alternatives?
- How safe is the procedure, based on the best available evidence? What are the data on short-term effects and long-term consequences?
- Are patients or their surrogate decisionmakers properly informed about the risks and benefits of the therapy?
- Are the side effects of the treatment reversible or treatable in the patient and in the population?

These concerns are analogous to those that would be raised for any other new medical treatment. The likelihood of inadvertently affecting the germ line, however, is of greater concern for gene therapy than for most other treatments. The risk of genetically altering the germ line is not unique to gene therapy because several other medical practices —such as vaccination, cancer chemotherapy and radiation therapy—also carry this risk (see "Safety" below).

A concern for deliberate misapplication of gene therapy derives, in part, from a historic association between eugenics and oppressive political movements (see below). Genetic "purity" or preservation of "superior" characteristics by genetic

means has been advocated by several political and scientific groups in the past (Kevles, 1984), and some fear that gene therapy technology might become part of a coercive social program. The rationale for gene therapy as currently contemplated–insertion of single genes to correct severely debilitating specific genetic diseases (Anderson, 1984)—is extremely remote from such eugenic motivations.

The question regarding the sanctity of human life is one that has been addressed by religious thinkers and philosophers (Siegel, 1982, 1983; President's Commission, 1982). This concern for human dignity underlies the great care with which proposals to undertake human gene therapy are now being scrutinized. Such concern suggests that public education and discussion must precede and attend clinical application (Working Group on Human Gene Therapy, 1984; President's Commission, 1982; Capron, 1984a,b).

TREATMENT OF GERM CELLS

If ever applied to humans, germ line therapy could be done in several ways. Such therapy could be directed at sperm or ova, or cells that produce them, before the germ cells join to produce a fertilized egg. It could also be targeted at the early stages of development, currently practical only if performed within hours after fertilization, days before the embryo is implanted in the uterus.[6] Human gene therapy affecting germ line cells raises several concerns in addition to those listed for somatic cell therapy. These have been noted by religious and civic commentators (Foundation on Economic Trends, 1984; National Council of Churches, 1984; President's Commission, 1982), and include:

- propagation of unpredictable effects (both positive and negative) into future generations,
- diminishing genetic diversity among human populations, and
- long-term effects of changing genetic characteristics in human populations.

The different social and ethical considerations that arise from somatic versus germ cell manipulations are elaborated further in the sections below on medical and social aspects of gene therapy.

COMPARISON OF SOMATIC AND GERM CELL GENE THERAPY

There are several technical and practical advantages to performing gene therapy on somatic cells as opposed to germ cells. The primary advantage of somatic cell therapy is that it can be performed on individuals at any stage of development, while germ line therapy as currently envisioned would have to be performed early in embryonic development. Experiments on somatic cells may be done on samples or parts of organs, rather than an entire organ, lowering the risks of failure because a failed experiment does not cause loss of the organ. Experiments involving somatic cells may also be repeated in the same individual if they fail, and the reliability of the gene transfer procedure does not have to be as high. Somatic cell gene therapy is also advantageous because it directly benefits the person to whom it is administered, rather than a person (who cannot consent to therapy) who develops from a treated embryo.

Despite these advantages of somatic therapy, there are several disadvantages. Somatic cell therapy may not be applicable to some disorders that affect multiple tissues, because cells of each organ would have to be altered. It may also not be effective for those tissues composed of cells that do not divide, such as brain and muscle (although symptoms of some diseases of nerve and muscle cells might be treated by gene therapy in other kinds of cells that influence brain and muscular function). Which diseases and which tissues might prove refractory to gene therapy of somatic cells will be determined only by further study of the specific genetic diseases in question.

There is at least one potential advantage to heritable correction of germ line cells. Once a defect were fixed, it would be less likely to plague the direct descendants of the person who developed from the treated embryo. This would not eliminate the risk, however, because new mutations causing the same disease could spontaneously arise.

[6] For further details on stages of fertilization and human development, see Technical Notes.

TREATMENT OF SPERM, OVA, AND CELLS THAT PRODUCE THEM

While germ line therapy, until now, has been performed on early embryonic cells, it is theoretically possible to perform it by inserting new genetic information into gametes (sperm, ova, or the cells that produce them).

Sperm may be difficult to genetically alter, because they are small, difficult to penetrate by physical or chemical manipulations, and would have to be treated in vast numbers. Millions of sperm are usually inseminated before fertilization, although only one actually fertilizes the egg; every sperm would have to be treated if gene therapy were to be assured. It would be technically easier to genetically alter sperm by treating the cells that produce them because such cells are larger and less difficult to manipulate. There are several complications with this strategy, however, including the necessity to use invasive procedures to obtain testicular cells, unavailability of methods for artificially inducing maturation of sperm, and uncertainty over whether genetic changes in sperm precursors would lead to genetic correction in all sperm. Substantial technological advances would thus be required for reliable gene therapy of sperm or their precursor cells.

In contrast, ova, or egg cells, might be altered after they were extruded from the ovary, and before fertilization. Egg cells are larger and more easily manipulated than sperm, suggesting that eggs might be easier candidates for gene insertion. Methods for obtaining human ova are now routinely practiced for in vitro fertilization techniques, and many do not involve highly invasive techniques (Andrews, 1984c). Manipulations of egg cells and early embryos differ primarily in that the eggs could be altered before fertilization, eliminating some ethical concerns of those who regard fertilization as the beginning of human life. Unless the gene therapy technique were extremely reliable, however, methods would have to be found for confirming that the desired alterations had actually occurred. This would involve sampling of embryonic or fetal tissue, and would thus not avoid all of the ethical questions that beset embryonic manipulations.

Gene therapy of gametes thus offers some advantages in restricted applications, but it would affect the germ line, and would not avoid the ethical dilemma associated with heritability of genetic changes. The technical prospects for such therapy, however, are less promising than treatment of either early embryos or somatic cells. For both technical and ethical reasons, therefore, gametic gene therapy is not imminent.

IN VITRO VERSUS IN VIVO

Gene therapy can theoretically be performed either on cells that have been removed from the body (in vitro), or on cells that are in their usual place in the body (in vivo). The first attempts at human gene therapy will be performed on cells that are removed from the body, genetically altered in vitro, and restored to the patient, as in the example of ADA or PNP deficiencies (Anderson, 1984). This procedure makes the chances of altering the germ line of the patient quite low, and also reduces the probability of unintentionally affecting other tissues that need not be treated (Working Group on Human Gene Therapy, 1984).

Several disorders in addition to ADA and PNP deficiencies are currently under discussion for somatic cell gene therapy. Citrullinemia is caused by deficiency of the enzyme arginosuccinate synthetase involved in protein and amino acid metabolism and nitrogen excretion (Walser, 1983). The gene has been isolated and cloned (Freytag, 1984), and citrullinemia is considered a promising candidate for early application of human gene therapy. Ornithine carbamoyl transferase deficiency can be quite severe, and the gene that codes for it has been cloned (Horwich, 1984), making it also a potential candidate for gene therapy. Lesch-Nyhan disease is a rare genetic disorder. It affects primarily boys who appear normal at birth but soon show abnormal uncontrollable movements. Abnormal behaviors of self-mutilation such as biting off fingers or otherwise inflicting painful injuries are part of the syndrome, as well as aggression towards others. These bizarre symptoms are extremely distressing to the patient and his family. Lesch-Nyhan syndrome is caused by complete deficiency of the enzyme

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hypoxanthine-guanine phosphoribosyl transferase (HPRT), the same enzyme that is partially deficient in gout (Wilson, 1984). The gene has been cloned (Miller, 1984; Jolly, 1982; Yang, 1984), and proposals for human experimentation on gene therapy for Lesch-Nyhan syndrome have been submitted to at least one local Institutional Review Board (Baskin, 1984; Merz, 1984). Proposals to begin human experiments on Lesch-Nyhan syndrome are expected to be referred soon to the National Institutes of Health (Anderson, 1984; Jenks, 1984; Merz, 1984).

It may be possible in the future to alter specific tissues while they are still in the body. It would be desirable, for example, to selectively alter nerve cells to treat diseases caused by metabolic disruption of brain cell function, or to correct only liver cells in genetic diseases that primarily affect proteins produced by the liver. The worst behavioral symptoms of Lesch-Nyhan syndrome, for example, presumably involve disruption of normal neural processes, and it might prove necessary to directly treat nerve cells. While methods for specifically targeting particular cells for directed gene therapy are theoretically possible, they have not yet been developed. Several possible methods of delivering specific genes to targeted cells may be found in the future, however, by use of tailored viruses or antibodies attached to artificial membrane sacs that contain the appropriate genes (see Technical Note 2).

Stages of development of gene *therapy technology*

If human gene therapy becomes a viable medical technology, its development will fall into several stages.

- Feasibility ***testing,*** involves animal studies and in vitro experiments on human cells, but not with patients.
- ***Early clinical research*** involves a few human patients with rare and severe diseases for whom other treatment alternatives are too risky, inapplicable, or less likely to be beneficial.
- Clinical ***testing*** will occur only if a potential for success has been demonstrated in early clinical research and feasibility testing. Clinical testing might involve a wider range of diseases and larger number of patients than early clinical research if experience with more severe diseases is fruitful. The final stage would be
- ***Standard medical practice*** in those specific instances where gene therapy has been shown safe and efficacious for a particular disease or type of patient. Issues of fair access to the technology, methods of paying for it, and proper quality assurance would emerge as the technology made the transition to this final stage.

Somatic cell therapy is now in the first stage, verging on the second. Germ line gene therapy has not even undergone feasibility testing in a form that might be applied to humans. Gene therapy for different disorders or specific kinds of patients will beat different stages of development; only a few diseases are now being tested for feasibility of somatic cell therapy (Working Group on Human Gene Therapy, 1984; Anderson, 1984).