NEWS AND VIEWS

REPRODUCTIVE HEALTH CARE POLICIES AROUND THE WORLD

Genetic Engineering: Moral Aspects and Control of Practice

INTRODUCTION

Since the time of Hippocrates, physicians have sought to understand the mechanisms of disease development for the purposes of developing more effective therapy. The application of molecular biology to human diseases has produced significant discoveries about some of these disease states. Gene transfer involves the delivery to target cells of an expression cassette made up of one or more genes and the sequence controlling their expression. The process is usually aided by a vector that helps deliver the cassette to the intracellular site where it can function appropriately. Human gene therapy has moved from feasibility and safety studies to clinical application more rapidly than was expected. The development of recombinant DNA technology brought science to the brink of curing previously untreatable diseases in a relatively short period of time. The ability to characterize gene defects at the DNA level, and the availability of vectors for the insertion of genetic information into normal and abnormal tissues of the human body, has made possible the initiation of genetic therapy of human disease. The Human Genome Project is expected to promote additional scientific advances. This raises the fear of much too rapid development leading to uncontrollable gene transfers being performed. It is the purpose of this article to

outline the concept of gene therapy with regard to the ethical aspects involved.

HISTORY

The following is a concise review of the history of gene therapy. Extensive reviews can be found elsewhere (1). The human species has for many generations practiced genetic manipulation on other species. Examples can be seen in the breeding of animals and plants for specific intent, such as, corn, roses, dogs, and horses. The term "genetics" was first used in 1906, and the term "genetic engineering" originated in 1932. Genetic engineering was then defined as the application of genetic principles to animal and plant breeding. The term "gene therapy" was adopted to distinguish itself from the ominous, germ-line perception associated with the term "human genetic engineering" (1).

"Gene therapy can be defined as the application of genetic principles to the treatment of human disease" (1). The 1944 discovery by Avery and colleagues that a gene can be transferred within nucleic acids is an important landmark (2). The capacity of viruses to transmit genes was first demonstrated in *Salmonella* species (3). Viral genomes were discovered to be able to integrate into cell genomes (4) and, later, were found to be responsible for cell transformation (5,6). The elucidation of the structure of DNA in 1953 and the subsequent discoveries of mRNA increased progress in the field of genetic research (7). In the interval preceding

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the recombinant DNA era, key aspects of gene therapy were elaborated. In 1966, Tatum predicted that viruses could be used to transduce genes (8). Another important milestone is the successful replication of DNA in a test tube by Kornberg (9). By the late 1960s and early 1970s, gene therapy became the subject of many articles and meetings. In 1970 Davis discussed human genetic engineering and explored the feasibility and ethics of somatic and germ cell alterations, cloning of humans, genetic modification of behavior, sex preselection, and selective reproduction. He stated then that "control of polygenic behavioural traits is much less likely than cure of monogenic diseases" (10).

Studies in the late 1950s and early 1960s revealed that cultured cells could take up radioactive DNA and that the DNA could enter into the nucleus of the cells. Naked viral DNA or RNA was demonstrated to be ineffective when applied to cells. Uptake of cellular or viral polynucleotides could be improved by complexing with various proteins, such as protamine (11). In the 1960s several studies asserted changes in cellular phenotype by the transfer of nonviral genes. Later, cell lines containing defined enzymatic defects and selectable systems were established, and thus, started the era of gene transfer (1). Later developments specialized a method of calcium phosphate-mediated transfection which became widely used (12).

The earliest predecessor of a direct in vivo approach to gene transfer was the use of vaccines with attenuated viruses, which permanently modify the body's response to infection and may persist for a long term (1). The ease of administration, relative cheapness, and long-lasting effect of vaccines are ideal qualities to which proponents of direct gene therapy aspire. An early attempt at treating bacterial infections by the injection of bacteriophages (13) was later dropped with the ascent of antibiotics. Other studies explored the ability of DNA to transfer the neoplastic state. The phenotype for neoplastic transformation was reliably transferred from mammalian DNA into cells in culture (14). The maturation of plasmid expression vectors, reporter genes, and better in situ detection systems prompted further attempts at direct in vivo gene transfer.

In the late 1960s, Rogers injected the Shope papilloma virus into patients with arginase deficiency, based upon studies indicating that the virus contained an arginase gene (15). However, three sib-

lings with arginase deficiency were injected with the Shope virus, without any effect on their arginine levels (16). In 1980 Martin Cline attempted gene transfer of the β -globin gene into human bone marrow cells and their transplantation into patients with thalassemia. The study, which was not approved by the Institutional Review Board, was severely criticized for scientific, ethical and procedural reasons (17). The indirect result of this was the NIH decision that all future gene therapy must be approved by the NIH Recombinant DNA Advisory Committee (RAC) (1). Unsound practices in these early studies in cell culture, animals, and humans made both the experimental results and the entire approach of gene therapy seem suspect, even though some of the basic concepts and approaches upon which the studies were based were eventually proven correct (1).

Major progress was made when early transfection techniques and selection systems for cultured cells were combined with recombinant DNA technology. The isolation of a single gene enabled both greater efficiency and better documentation of its transfer. Studies demonstrated that any gene can be transferred into mammalian cells along with a selectable marker (18). The early 1980s brought forth the development of retroviral vectors (19). In 1983 The Banbury Gene Therapy meeting set the course to further research into safe gene delivery applications (20). Another important development was that of the HPRT gene transfer by Szybalski (21). After several disease-related genes were transferred into various cells in culture, the possibility of efficient gene transfer into mammalian cells for the purpose of gene therapy became widely accepted (1). In 1989 the first approved human gene therapy trial was initiated (22).

The idea of gene therapy developed shortly after the discovery of molecular genetics, however, advancement was for a long period of time hindered by poorly designed studies. Progress has accelerated in recent years, as the field has gained greater credibility. The Human Genome Project is expected to advance the field further.

POSSIBLE APPLICATIONS OF GENE THERAPY AND CURRENT TRIALS

There are four potential levels for the application of gene transfer techniques.

1. Somatic cell gene therapy involves the correction of a genetic defect in somatic cells. This type of gene therapy is beneficial primarily for the replacement of a defective or missing enzyme or protein or a deficient circulating protein.
2. Germline alteration requires the insertion of a gene into the reproductive tissue of the patient, resulting in the correction of the disorder in the offspring as well.
3. Enhancement genetic engineering involves the insertion of a gene with the intent to enhance a certain characteristic, such as height.
4. Eugenic genetic engineering involves an attempt to alter or improve complex human traits, which are usually polygenic, such as personality or character.

Since presently only somatic cell gene therapy is feasible, the following discussion centers around it. The upcoming ethical discussion includes all the above aspects and their implications.

It is presently possible to insert a single gene, thus, recessive disorders are amenable to treatment. The obstacles which must be overcome are accessibility to the affected tissue; the precise regulation of the gene, and the possibility of the damage being irreversible by birth. Dominant disorders can be corrected by replacement either of the dominant gene or of the aberrant nucleotides within the gene, a feat that cannot be easily accomplished. Unfortunately recessive disorders are not the cause of the majority of serious human disease. Somatic cell gene therapy, the insertion of single genes into somatic cells, can be seen as a natural extension of commonly used medical procedures, similar to injection of medication, or organ transplantation. There are currently many undergoing trials involving gene modification at medical centers worldwide. The stated goals of these trials are to achieve short-term goals, as each clinical trial is to be considered as an intermediate step in a multistep process; to identify end points for toxicity and efficacy; and to define potential risks and benefits for participating patients (23). The genes are inserted by way of a delivery system, such as retroviruses, adenoviruses, liposomes, and direct injection of DNA (Table I).

1. Retroviruses are currently the most widely used means of gene transfer. The main advantage of retroviruses is permanent modi-

fication. However, these vectors must integrate into the dividing cell in order to expand, so that if a mutation occurs there will be permanent damage. The early cells that have the greatest potential to sustain the long term changes are often quiescent and nondividing. The genes, once inserted, do not always remain transcriptionally active. In vivo selection of cells with functionally active retroviral genes may assist in solving these problems. The risks are the potential for toxicity associated with chronic overexpression or insertional mutagenesis. For example, if the proviral DNA randomly disrupts a tumor suppressor gene or activates an oncogene.

2. Adenoviruses infect epithelial cells at a high frequency but they do not require a cell for proliferation. Adenoviruses do not infect the bone marrow, and they are immunogenic. Furthermore, they exist only temporarily in the cytoplasm of the host cell. Thus, adenoviruses are more suitable for populations of quiescent cells, especially in cases when a transient expression of the transgene is sufficient to achieve the therapeutic goals.
3. Adeno-associated viruses are used for the transduction of differentiated cells, where retroviruses, which are unable to infect nondividing cells, cannot be used.
4. HSV type I is applied mainly for central nervous system trials, due to the tropism of the virus.
5. "Naked" DNA does not involve the use of viruses. Naked DNA is easy to use and to develop, but there is a low integration frequency and a temporary expression only. They are used primarily in vaccine development.
6. Liposomes, likewise, do not involve the use of viruses. They enable unlimited gene transfer size and cause fewer inflammatory or immune responses due to the lack of proteins. They are, however, inefficient, requiring thousands of plasmids to be presented to the cell in order to achieve successful gene transfer. There is not sufficient data presently to assess the risks of repetitive administration.
7. Adenovirus coat proteins are not an infectious agent and enable targeting. Their use at present is limited.

Table I. Characteristics of Available Gene Delivery Systems

Vector	Advantages	Disadvantages
Retrovirus	Variable transduction frequency, permanent modification, infection of hematopoietic and epithelial cells	Instability, necessity for integration into dividing cells for expansion, size limit of 9–12 kb
Adenovirus	Infection of epithelial cells at high frequency, no necessity for cellular proliferation	No infectivity of bone marrow, immunogenicity, viral inflammation, size limit of 7.5 kb, temporary effect
Adeno-associated virus	Stability, low frequency of integration into nondividing cells	Low titers, small scale use only, size limit of 5 kb
Liposome	Not a virus, unlimited size, lower immunogenicity and inflammation	Low modification frequency, temporary expression
Herpes simplex virus type I	Wide infectivity range, high titers, prolonged expression	No integration into the genome of the infected cell, difficult development, toxicity
Naked DNA	Not a virus, easy to use and develop	Low frequency of integration, temporary expression
Adenovirus coat protein	No infectious agent, enables targeting	Difficult construction, limited use, modification frequency unknown

Both adenoviruses and retroviruses have been modified in order to reduce the elements which enable the production of a systemic infection. In order for gene insertion strategies to work, the gene must be inserted into a large number of cells, the therapeutic gene must be persistently active, and the biological effect of the gene product must match the biology of the target cells, in order to have an optimal effect on the disease process. The titers of the vectors must be very high in order to increase the probability of modification.

Human gene therapy studies fall into two main categories: marking and therapeutic (23). Marking trials use expression cassettes with bacterial antibiotic-resistant genes, which allow the genetically modified cells to be identified. These trials have been designed to demonstrate the feasibility of human gene transfer, to uncover biological principles relevant to human disease, and to evaluate safety. Therapeutic trials aim to transfer expression cassettes carrying genes that evoke biologic responses that are relevant to the treatment of human disease and to demonstrate that this can be accomplished safely. Some examples are given below.

Marking Trials

Retroviruses which have been rendered replication-incompetent may be used for marking hematopoietic cells, and are applied in several aspects, such as in vivo trafficking of lymphocytes in immunotherapy trials of cancer, in cancer vaccine trials and in immunomodulation (23). Retrovirus marking

trials have been used to discover the origin of relapse after autologous bone marrow transplantation. Data from trials in acute myelogenous leukemia (AML) (24,25), chronic myelogenous leukemia (CML) (26,27), and neuroblastoma (28) indicate that relapse occurs, at least in part, from leukemic cells left in the autologous bone marrow which is transplanted. From such knowledge comes the suggestion to use fractionation of cells prior to transplantation in order to remove the leukemic cells. Through marking trials also comes the knowledge that, the infused autologous bone marrow is the one responsible for the long term hematopoietic reconstitution following delivery of ablative levels of intensive therapy.

Cancer Genetic Sensitization Therapy

It is possible to inject viral particles containing a transcription unit into the center of a tumor, in order to render that tumor more sensitive to a therapeutic agent (23). This has been applied for the treatment of experimental brain tumors (29). Use of gene sensitization in animal studies has resulted in the complete suppression of the tumor through the intercellular transfer of the activated therapeutic agent. This is called "the bystander effect." Similar use has been made with ascitic fluid of ovarian cancer patients (30). The applicability of these methods is limited by the ability of the virus to access the tumor cells.

Gene Therapy for AIDS

The human immunodeficiency virus (HIV) is integrated into the genome of monocytes and lymphocytes whom it infects. The replication of HIV in T cells and monocytes results in the progressive loss of CD4 cells, leading to immunodeficiency and death, due to life-threatening opportunistic infections and cancer. The progression of the disease appears to correlate with expression and replication of the virus. The replication of the virus depends on the TAT protein, which binds to the TAT activation response element, and the REV protein (31). Gene therapy for AIDS may be performed in three categories: enhancement of the immune response, engineering the cells to secrete a factor that would either inhibit or assist the body's defense mechanisms in fighting the HIV infection, and engineering HIV-infected cells so as either to kill them or to inhibit replication of HIV within them. The use of retroviral vectors may be applied to modify genetically hematopoietic stem cells. These strategies would work by transdominant inhibition of the REV or TAT proteins by molecular traps that bind and inactivate the REV or TAT proteins or by competitive inhibition of the binding of these proteins to their recognition elements. Others have proposed direct intramuscular injection of genes that code for antigens of the HIV virus to which a response is sought (32). Success or failure depends on the ability to introduce nucleic acids for genes into somatic cells in a functional form and to maintain those genetically modified cells at a high percentage of the total number of cells in a tissue for a long period of time. Several trials are under way testing these principles.

Current Gene Replacement Trials

In most of the gene replacement trials using retroviruses, somatic cells are removed from the body and transduced with the retrovirus containing the functional replacement gene. The modified cells are then returned to the patient. Different strategies are used to ensure that the genetically modified hematopoietic cells will remain dominant and functional in the cells after transplant. Retroviruses can be used to replace missing or defective genes that are absent in disease processes, such as familial hypercholesterolemia (33), Gaucher's disease (34), and severe combined immunodeficiency disease (SCID) (35,36). Severe combined immunodeficiency is characterized by the lack of expression of

adenosine deaminase (ADA). Retroviruses which contain the ADA gene have been inserted into lymphocytes. Patients who were injected with these lymphocytes were shown to undergo an improvement coincident with the increases in serum levels of ADA. The genetically modified lymphocytes were retained in the patient's circulation for a prolonged period of time. This was the first approved gene therapy trial in the USA.

Adenoviruses have been used for the transfer of replacement genes. Adenoviruses containing the cystic fibrosis transmembrane conductance regulator (CFTR) cDNA, were administered in vivo to patients with cystic fibrosis. This is possible since the adenovirus is particularly tropic for the respiratory bronchial mucosa that is involved in the pathogenesis of cystic fibrosis. In a recent controlled study in patients with cystic fibrosis, adenoviral vector-mediated transfer of the CFTR gene did not correct functional defects in the nasal epithelium. Furthermore, local inflammatory responses limited the dose of adenovirus that could be administered to overcome the inefficiency of gene transfer (37).

FUTURE STRATEGIES

Improvements in vector design are likely to illuminate new treatment strategies in the future. We will give but a few examples.

Adeno-associated viruses are being studied as an alternative to retroviruses for the introduction of genetic elements into the hematopoietic stem cell (38). Adeno-associated virus, in its native form, exhibits nonrandom into the short arm of chromosome 19, and integrates into nondividing cells (39). The recombinant vectors made for gene therapy integrate randomly into the genome in a process stimulated by proliferation. The nucleic acids from these vectors persist in the cytoplasm for several weeks and their DNA is replicated by the cells in which they reside after integration into the genome. Further research is necessary before these vectors may be used safely (22).

Chemotherapy of solid tumor neoplasms is limited by the toxicity of the drugs to normal tissues and particularly to the bone marrow. The use of intensive chemotherapy for the treatment of invasive epithelial neoplasms has been associated with dramatic reductions of total tumor burden but necessitates the use of autologous bone marrow for rescue of the marrow function of the treated

patients. Several studies have proposed the use of retroviruses that contain chemotherapy resistance genes, such as the multidrug resistance gene (MDR-1), for modification of the bone marrow. When modified bone marrow is transplanted into ovarian or breast cancer patients, it becomes more resistant to chemotherapy, and larger dosages may be used overall without fear of life-threatening suppression of its function (40,41). Furthermore, treated marrow cells will become progressively more resistant to chemotherapy with each succeeding course of chemotherapy due to the increasing fraction of cells that are genetically modified with the MDR-1 virus. This method may in the future enable the use of bone marrow transplantation as a conduit through which to introduce therapeutic molecules into the systemic circulation of patients with diseases such as hemophilia, diabetes, heart disease, storage diseases, and cancer (22).

Human cord blood has previously been demonstrated to contain a large number of primitive progenitor cells. Single cord blood collections are capable of reconstituting the lymphohematopoietic system of infants and children following transplantation in vivo after myeloablative therapy (42). Single cord blood samples may also be sufficient to reconstitute hematopoiesis in adult recipients (43). Committed and primitive hematopoietic cells from human cord blood are efficiently infected using retroviral vectors. The introduced sequences are expressed at high levels in progeny of transduced stem cells. Gene transfer efficiency is significantly higher into cord blood committed progenitors compared with adult bone marrow cells (44).

POTENTIAL PROBLEMS

Theoretical safety concerns in gene therapy include the possibility of vector induced inflammation and immune responses, of complementation of replication-deficient vectors leading to overwhelming viral infection and, for retroviruses, of insertional mutagenesis (45). Other theoretical social concerns include concerns about germ line modification and about protecting the environment from new infectious agents generated from gene transfer vectors carrying expression cassettes with powerful biologic functions. Rare adverse effects have been encountered, such as inflammation

induced by airway administration of adenovirus vectors and by administration to the central nervous system of a xenogenic producer cell line releasing a retrovirus vector (45). These effects were mostly related to the dose and the manner in which the vectors were administered. Human gene transfer has to date not been implicated in initiating malignancy. A major disadvantage of all human gene therapy studies is inconsistent results, the basis of which are unclear (45). Furthermore, the trials are plagued by problems of vector production, the problem of finding the perfect target-specific vector for each application, and the inability to derive complete conclusions from animal studies due to differences in characteristics and toxicology.

Finding the perfect vector for each application may be difficult. The current vectors in use all need refinement. The technology is now available to create designer vectors that can be optimized for each application. It is necessary to increase the efficiency of gene transfer, to increase target specificity, and to enable the transferred gene to be regulated. It is also necessary to decrease the insertional mutagenesis of retroviruses, to minimize immunity and inflammation associated with adenoviruses, and to enhance translocation of the gene to the nucleus for the plasmid-liposome complexes. New classes of vectors that incorporate features of viral and non-viral vectors are under investigation.

CURRENT CLINICAL PROTOCOLS

More than 100 gene therapy protocols are presently approved worldwide, in the following countries: Austria, China, France, Germany, Italy, the Netherlands, Sweden, Switzerland, the United Kingdom, and the United States. There have not been any reports of adverse outcomes on any protocol. Ongoing trials include gene therapy for several inherited disorders such as ADA deficiency, cystic fibrosis, Gaucher's disease, hemophilia B, and familial hypercholesterolemia as well as acquired disorders such as arthritis and AIDS.

To summarize, gene modification techniques are being implemented at a rapid rate for the treatment of genetic and acquired disease states. At the present time the expectations of the public surpass the feasibility of these procedures. No human disease has so far been entirely cured by gene transfer, and it is not clear when this will be accomplished (45). The Human Genome Project will likely provide sev-

eral hundred thousand genes that will greatly illuminate our present knowledge of the human genetic composition.

The Human Genome Project is a coordinated effort to characterize the entire human genome. The goals of the project are mainly to construct a map of the human genome so that the entire human DNA could be sequenced. In order to achieve this goal appropriate technologies must be created. For that purpose selected model organisms are used and their genome sequenced. The project also entails the development of capabilities for collecting, storing, distributing, and analyzing the data produced. Ethical, legal, and social implications of the genome project are also considered, in order to develop future policy options. The genome project has profound consequences for the field of medicine with improved diagnosis and the prospect of novel therapies (46). The attained knowledge could potentially be used for human gene transfer. Substantial benefits can be gained by careful clinical investigation and basic laboratory research.

ETHICAL CONSIDERATIONS

The public perception of human gene therapy is greatly misinformed and, thus, influenced easily by extreme opinions, expressed by the media. It is easier for prophetic alarmists to gain public attention than for persons who are prudently complex about both the medical and moral dimensions. As Baird points out, "mixtures of fact and fiction are used by opponents to portray the allegedly disastrous effects of using genetic knowledge to alter human DNA, with extrapolation to emotionally charged nightmare scenarios, usually making reference to Nazi Germany, to corporate conspiracy, or to agri-business. Proponents also extrapolate with statements that many diseases will be wiped out or with assumptions of understanding human nature once the human genome is sequenced. Gene therapy is regarded by some as miracle medicine, by others as tampering with nature and tempting fate". (47). Some of this debate is prompted by misuse of the term gene therapy to include also gene alteration of somatic or germlines for prevention or for improvement by enhancement, where actually no treatment of a specific disorder is involved. At the present time gene therapy is primarily relevant for single gene disorders. Present progress strongly

suggests that within ten years many diseases will be treatable, at least partially, by means of gene transfer. What remain untreatable are dominant disorders, in which a harmful product is usually synthesized, for example, CAG sequence repeats in Huntington's disease. Modern ethics must determine a morality with regard to these developments, in order for them to be regulated. We outline important ethical considerations with regard to feasible gene therapy techniques, as well as possible futuristic techniques which are not presently feasible.

SOMATIC CELL GENE THERAPY

Somatic gene therapy for the treatment of severe disease is considered ethically acceptable because it can be supported by the fundamental moral principle of beneficence, namely, it would relieve human suffering. It is therefore a moral good. Many observers feel that somatic cell gene therapy for a patient suffering a serious genetic disorder may be ethically acceptable, if carried out under the same strict criteria that cover other novel experimental medical procedures. In order for this to be done, Anderson believes that there are three requirements that must be met (48): Previous animal studies should show that the new gene can be inserted into the correct target cells and will remain there long enough to be effective. The new gene must be expressed in the new cell at an appropriate level, and it must be safe. When the probable benefits for the patient are expected to exceed the possible risks, then attempts at gene therapy are ethical. Somatic gene therapy is not necessarily subject to objection, but its application does raise several important issues, such as assessment of risks, informed consent, confidentiality, and appropriate use of resources (47). These issues are not new or unique to gene therapy and are usually applied to any medical therapy.

Risks of Gene Therapy Applications

The current methods which are used to insert genetic material may expose the patient to an increased risk of cancer, as a result of the inability to precisely control the integration of the DNA into the host cell. The integration of the inserted genes could result in the inactivation or deactivation of genes that influence susceptibility to cancer or that

promote suppression of tumor generation or growth (49). Again, this is not unique to gene insertion; it occurs also in other life-saving treatments, such as immunosuppressive medications or aggressive chemotherapy (47). One risk of using retroviral vectors to deliver genes is that recombination may occur between another virus in the recipient and the retroviral vector resulting in disseminated retroviral infection (49). This would be particularly devastating in patients who are unable to mount an immune response. This possibility would also permit the insertion of exogenous genes into germ cells where these altered genes could be passed to future generations. The effects of this in all tissues may be deleterious.

Another problem is that the integration of genetic material may be successful but insufficient, thus prolonging the course of a severe disorder, without actually curing the disease or even alleviating the suffering (47). On the other hand, the course of the disease may be so devastating and the potential benefits so overwhelming that the patient and the family are willing to risk many uncertainties in the protocol. The use of somatic gene therapy is most appropriate for diseases that lead to severe debilitation or death, for which no other successful treatment exists (48).

It is necessary to weigh the potential risks to the patient against the anticipated benefits to be gained from insertion of the functional gene. This risk to benefit determination must apply to each patient individually.

Alternatives

Alternatives to gene therapy are to do nothing, or to use other available interventions. When regarding ADA-deficient SCIDs patients, for example, this would mean providing a sterile hospital environment while waiting for a sufficiently matched bone marrow donor to prevent graft-versus-host disease in the recipient. Other human genetic disorders in which the patients do not live past puberty often have fewer alternatives. For example, Lesch-Nyhan syndrome, where self-mutilation proceeds in spite of protective devices. The more severe the disease and the fewer medical interventions available, the more likely that potential benefits will outweigh the risks of gene therapy.

Another alternative to gene therapy is to test at-risk fetuses and offer abortion to those couples who request it. Prenatal diagnosis is generally the

first active medical intervention available to couples when a genetic disease is discovered and the mutations are defined. The cost of prenatal diagnosis is sufficiently high so that this alternative is offered only to couples known to be at risk for a genetic disease. These couples are identified by the presence of an affected family member. A significant percentage of autosomal recessive genetic disease cases cannot be prevented because they appear in families with no previously known genetic risk. Thus, a significant number of affected patients will remain that could benefit from successful gene therapy. The prospect for human gene therapy might represent the best hope for those families who do not consider prenatal diagnosis and pregnancy termination an option.

Obtaining Informed Consent

The candidate for involvement in a gene therapy trial must be informed and voluntary, as with all medical research. In order for this to be accomplished, sufficient information must be provided about the proposed treatment in an understandable form, to enable the patient to decide whether to participate without introducing coercion. The level of disclosure to the patient should include all adverse consequences, even those with a remote chance to occur. One consequence of the context of gene therapy is that the party involved is often a very young child, unable to give informed consent, except via a proxy. It is of the outmost importance to supply the proxy, often the parents, with the necessary information (47). A theoretical problem which arises is in obtaining informed consent for germline therapy. Since the procedure is expected to influence future generations, should they not be consulted too and asked to give informed consent? This is not possible since some of these generations do not exist yet. Furthermore, the techniques to achieve germ line therapy are not feasible yet. It is expected that similar ethical problems will be addressed by the Human Genome Project.

Confidentiality

The wide public interest in gene therapy research trials may impose a difficulty in maintaining anonymity. This should be explained when obtaining informed consent, and all possible measures to ensure confidentiality must be taken (47).

Use of Resources

Gene therapy is expensive, requiring considerable expertise and laboratory appliances. Likewise, treating severely diseased individuals is also associated with substantial costs. In this are included expensive treatments such as bone marrow transplantation for children with immunodeficiency disorders, lung transplantation for patients with cystic fibrosis and other treatments. It is therefore appropriate to provide public funding for somatic gene therapy research for serious disorders for which there is no alternative treatment (47). The Human Genome Project is expected to make prenatal diagnosis and abortion a safe, feasible, and definitive approach to therapy of genetic disease. This is a cheaper approach compared to gene therapy, and would possibly be a preferred use of resources. However, not all members in society consider abortion an option and, thus, are likely to prefer gene therapy.

Goals

Institutional and national review boards should carefully evaluate therapeutic protocols to ensure that the delivery system is effective, that sufficient expression can be obtained in bone marrow cultures and in laboratory animals to predict probable benefit for the patient. Safety protocols must demonstrate that the probability is low for the production of a malignant cell or a harmful infectious retrovirus. Patients with serious genetic disease have little hope other than gene therapy for alleviating their medical problems. As Anderson points out, arguments that someday gene therapy might be misused do not justify the needless perpetuation of human suffering that would result from an unnecessary delay in the clinical application of this potentially powerful therapeutic procedure (48).

Current Safeguards

The current safeguards are an extension of similar safeguards which were established when recombinant DNA experiments first became possible. At the time, an international meeting was called where a moratorium was voluntarily placed on all experiments until suitable safety guidelines were promulgated. At present every major university has a recombinant DNA committee that reviews proposed experiments and maintains safety protocols

consistent with agreed upon standards. Gene therapy trials are defined as a research protocol to distinguish it from innovative treatment. The trial is further admitted for the approval of a federal advisory committee. The advisory committee has two main tasks: To review the risk-versus-benefit ratio and ensure that for any experiment the proposed benefits outweigh the risks; to ensure that voluntary informed consent is obtained from each research subject or his representative. These protocols also must maintain patient confidentiality (50).

Long-Term Clinical Follow-up and Care

It is necessary to offer effective follow-up for patients who receive somatic gene therapy to fully assess potential adverse effects resulting from these therapies. It is also necessary to provide continuous clinical care to patients who are treated with somatic gene therapy. Patients with adverse experiences must receive appropriate care for these complications. The investigators and institutions involved are responsible for providing continuing therapy to patients who may benefit from clinical trials. This is not easy to achieve, since voluntary participation in clinical follow-up is poor, and since institutions may not be in a position to assume responsibility for ongoing care, particularly if gene therapy is administered as a clinical research project (50).

The relatively small number of patients enrolled in clinical trials does not allow any meaningful conclusion to be reached regarding adverse experiences having a low incidence. Survivors of clinical trials may suffer from a variety of common disease processes, some of which are unrelated to the gene transfer. It is difficult to design clinical studies with sufficient power to make significant statistical inferences about the incidence of adverse experiences against a background incidence of similar disorders in the general population. A proper assessment of the risks of gene therapy trials is an important research problem. It is necessary to have databases that are secure and flexible as well as algorithms for analysis of data that allow statistically significant conclusions to be drawn up (50).

There is a growing consensus among ethicists and investigators that subjects should receive compensation for injuries associated with clinical gene therapy trials. It may be impossible to make a critical and correct assessment of the origin of many potential adverse experiences and their relationship

to the gene therapy trial. It is necessary to identify the individual or institution responsible and capable of assuming the costs or compensation and follow-up care (50).

As Ledley concludes, "Considerable safeguards are required in designing protocols for follow-up to ensure that the individual's confidentiality and privacy are not violated, that the benefits of follow-up balance the risks, and that appropriate informed consent is obtained. Mechanisms should be established which allow individuals to withdraw from follow-up at any time. If children participate in these studies, it will be necessary to obtain their assent at the time the study begins, as well as their consent upon reaching the age of majority" (50).

In summary, few writers have any doubt that somatic cell gene therapy is ethically acceptable. However, the other potential uses of gene alteration require more scrutiny. When these are considered one is inevitably drawn into a philosophical debate regarding the concept of humanness in its broadest sense. Extensive elaboration of this issue can be found by Gustafson (51) and Anderson (52). It is not within the scope of this article to go into the philosophical issues. We, however, discuss some religious aspects, as well as some major secular views.

GERMLINE GENETIC ALTERATION

Germline genetic alteration involves the introduction of a genetic change that is passed on to subsequent generations and inherited by them, in an attempt to prevent diseases in future individuals. This is a preventive strategy and not a specific therapeutic measure (47). It applies to individuals who are affected by, or are carriers of, a genetic disorder. Altering human gametes is associated with enormous difficulties, requiring precise gene replacement in all the affected cells, with actual taking out of the affected gene. Gene therapy of the zygote or preembryo is theoretically feasible, as preimplantation diagnosis, usually in the context of in vitro fertilization. Such therapy would not only alter the genetic composition of the preembryo but also prevent the transmission of the affected gene to future generations. Since this is risky, it may be a better option to simply not transfer the affected zygote into the maternal uterus (47). It is presently not feasible to perform genetic alteration on

gametes, and therefore, the following discussion is theoretical at present.

Germ line gene insertion has been attempted in animals by microinjection into eggs. This technique has a high failure rate, it can produce deleterious results because there is no control over where the injected DNA will integrate in the genome, and it has limited usefulness. It is ethically questionable to experiment on human eggs because of the expected losses. Even if the process was successful it would be applicable primarily when both patients are homozygous for the defect, which would mean that all their children would be affected by the disorder, but this is an extremely rare situation. Most of the serious genetic disorders result in infertility or death before reproductive age in homozygous patients. Another situation where there is a 100% chance for the offspring to be affected is in the case of maternally inherited mitochondrial defects, but there is no present technology to approach the problem. In the other situations the chances of couples who are carriers for having children with the disease is either one in two in cases of autosomal dominant disorders or one in four in cases of autosomal recessive or X-linked disorders. Consequently, there would be little use for the procedure even if it were feasible. The Human Genome Project may eventually make germline gene therapy feasible and safe.

There can be five possible arguments in favor of germline modification, according to Juengst (53).

1. Medical utility: Germline gene therapy offers a true cure for many genetic diseases.
2. Medical necessity: Such therapy is the only effective way to address some diseases.
3. Prophylactic efficiency: Prevention, in the form of germ line alteration is less costly and less risky than cure, namely, somatic cell gene therapy.
4. Respect for parental autonomy when parents request germline intervention.
5. Scientific freedom to engage in germline inquiry.

Anderson points out that, even when it becomes technically feasible to perform germ line intervention in humans, there are major concerns which must be considered (48). Medical concerns center primarily around whether the transmitted gene itself, or any side effects caused by its presence, adversely affect the immediate offspring or their descendants. Several generations of progeny must

be studied in order to obtain an answer. Furthermore there is little chance to ensure that the inserted gene will incorporate into the target DNA in exactly the desired place. The odds are at least 1 to 23 against the inserted DNA being incorporated into the chromosome that carries the mutant gene, and more than 100 to 1 against the site of insertion being close enough to the disease-causing gene for both to be passed on together after genetic recombination has taken place (54).

Germline therapy deserves careful ethical consideration well in advance of the time of technical feasibility. The critical question is whether such a treatment should even be undertaken, considering the consequences. Before germline therapy is attempted in humans, Anderson believes that at least three conditions must be met (48).

1. There should be considerable previous experience with somatic cell gene therapy that clearly establishes the effectiveness and safety of treatments of somatic cells.
2. There should be adequate animal studies that establish the reproducibility, reliability, and safety of germline therapy, using the same vectors and procedures that would be used in humans. It would be of the outmost importance to demonstrate that the new DNA could be inserted exactly as predicted and that it would be expressed in the appropriate tissues and at the appropriate times.
3. There should be public awareness and approval of the procedure. Germline therapy is expected to affect unborn generations and, therefore, has a greater impact on society as a whole than treatment confined to a single individual. The gene pool is a joint possession of all members of society. The public should be made aware of the procedure, as it may affect the gene pool. An informed public must indicate its support before clinical trials begin.

One of the arguments in favor of genetic germline alteration is that society should pursue the development of strategies for preventing or correcting such genes at the germ line level as a way of ensuring that present and future couples can "exercise their rights to reproductive health." The idea of eliminating the risk of transmitting genetic disease may appear as an attractive option, but this would involve genetic alteration of virtually all adults who may theoretically be carriers of a genetic disorder (47). As Baird points out, the risk of passing genetic

disease is inherent in the human condition, by the occurrence of mutations, and it may be impossible to change. Furthermore, from an evolutionary perspective, it may not be desirable to perform such changes. Having carriers of certain genetic disorders has benefits in some populations, such as the gene for sickle cell disease, which provides greater resistance to malaria. "Germ line genetic alteration is unique in that it involves intentional interference in human evolution," which imposes a great responsibility on those involved in it. The impact on our species and on the interests of future generations must be considered (47).

The arguments against human germline therapy can be summarized as follows.

1. The risk argument—Too many long and short term risks are involved affecting the subjects and their offspring (55).
2. The consent argument—The subjects under study are not able to give informed consent (56).
3. The cost argument—The procedure is so costly that it will never merit a high priority in the allocation of resources (55).
4. The integrity argument—It would violate the rights of future generations who would like to inherit genetic material whose integrity has not been violated through intentional modification (56).
5. The theological argument—Germ-line alteration is "playing G-d". It tampers with material that is sacred and should not be altered by humans (57).
6. The slippery slope argument—Another element of concern is the slippery slope argument.

Allowing somatic cell therapy may in the long run bring the performance of germline gene therapy. The downside of the slope would be genetic enhancement (58). As put by Anderson, whatever our humaneness may be we fear the possibility of its being tampered with (48). Human germline therapy might begin as an attempt to eradicate genetic diseases, namely negative eugenics, and eventually lead to the alteration of human beings for various purposes, namely, positive eugenics (59). Since the prospect of genetically altered human beings brings to mind the eugenics programs of the Nazis, Aldous Huxley's *Brave New Worlds*, and other scenarios, many writers argue that we must never attempt human germline gene therapy. Other

writers argue that the slippery slope argument is unsound because we can avoid sliding down the slope to ethical and social disaster with adequate regulations and safeguards. Others yet argue that regulations and safeguards will not stop the slippery slope; that once the Pandora's box of human germline therapy is opened, there will be no turning back (59).

The force of the slippery slope argument depends on the availability of safe and cost-effective human germline gene therapy. One of the concerns of this argument is incurring harm to future generations. This is difficult to assess because it is problematic to grant rights to nonexistent people, especially since we do not know what they need or want. Harm can be caused to the engineered persons, through the feeling that they are designed. The persons who are not engineered will be viewed as less than perfect and feel inferior. But Resnick points out, the psychosocial harms experienced as a result of someone else's benefits do not justify denying goods to the benefited persons. Society already accepts many things which contribute to social injustice or discrimination, such as higher education, fancy cars and clothes, and others. Eliminating these will not prevent discrimination (59).

Germ line therapy can pose a threat to social justice by threatening equality, equal opportunity, and the distribution of economic and social goods. The threat to society would be great if the enhanced persons were given more rights than the nonenhanced. Furthermore, since enhancement would not be available for all, it may be unjust. If germ line therapy were ever to be permitted, society must take steps to prevent any social injustice.

GENETIC ENHANCEMENT

Genetic enhancement refers to nontherapeutic genetic alteration, aimed at enhancing particular desired qualities such as intelligence or appearance. This would entail a process of improvement of an already healthy genetic makeup (47). As Baird points out, performing such feats is far beyond the technical feasibility at present and will likely remain so in the following generations. Present knowledge is insufficient to understand the effects of attempts to alter the genetic makeup of a human. Genetic enhancement may theoretically be possible for simple traits, such as height, but the risks involved far

surpass the benefits that might be gained (47). The insertion of additional genes to a normally functioning system may endanger the overall metabolic balance of the individual cells as well as the entire body. The motivation for nontherapeutic gene alteration requires close examination, since it is reminiscent of Nazi philosophy. Baird states that enhancement is a form of commodification of individuals, according to someone's perception of what is perfect or even what is normal. "This shows a lack of respect for human life and dignity and an intolerance for human diversity, which will likely lead to discrimination against, and devaluing of, certain categories of people" (47). When considering gene therapy of disease states it is clear who would receive the genetic alteration. However, the selection process for genetic enhancement cannot be based on medical need, where such need does not exist. It would be based on some other criteria, and would most likely be related to pecuniary ability. The goal of genetic alteration would be to pursue nonmedical objectives, such as, economic, social, cultural, ethnic or other. People might be pressured to undergo such a procedure and be subject to discrimination in case they refuse. Nontherapeutic use of genetic alteration technology would draw away needed resources and skilled personnel from real medical problems. It would be irresponsible and unethical to allow DNA alteration of healthy individuals when there are other pressing calls on social attention and resources. "Improvement of longevity, talents, and vigor of individuals and their descendants can be best achieved by improving social and environmental factors that affect our society" (47).

Anderson (48) recognizes a set of circumstances in which enhancement genetic engineering may be ethical. This is in the context of preventive medicine. For example, the insertion of an additional LDL receptor gene in "normal" individuals could significantly decrease the morbidity and mortality caused by atherosclerosis. The purpose of intervention in this case would be the prevention of disease, not simply the personal desire of an individual for an altered characteristic.

The justification for drawing a line where enhancement is concerned is founded on the argument that, beyond the line, human values that our society considers important for the dignity of man would be significantly threatened. Enhancement therapy could be medically hazardous when the risk might exceed the potential benefit. Adding a normal gene

to overcome the detrimental effects of a faulty one does not produce major problems. Inserting a gene to enhance an existing product might adversely affect numerous other biochemical pathways. Enhancement therapy could also be morally precarious, in the way that it would require moral decisions that present day society is not prepared to make (58). It would lead to increased inequality and discriminatory practices in an already unequal society.

Some important issues must be considered before enhancement therapies are even proposed. The first is the issue of which gene should or should not be provided upon request. The seriousness of a disease must be considered, but what distinguishes a serious disease from a minor disease, from cultural discomfort, or how does one quantify the suffering involved. Different observers inevitably have different lines to draw. The second issue is the determination of who should receive the gene. Those best able to benefit society, those most in need, those chosen by lottery, or those who can afford to pay for the gene. Since presently there is no consensus on this issue, decisions should be based on objective medical need rather than personal whim or resources of an individual. The third issue is the prevention of discrimination. People with a certain debilitating disease may be pressured into receiving treatment and if they refuse may be discriminated against, through difficulty in obtaining health insurance, or being requested to pay higher premiums. The fundamental right of autonomy would be threatened in these circumstances.

Once enhancement therapy begins it would be difficult, if not entirely impossible, to determine where to draw the line. Such a line should be those diseases that produce significant suffering and premature death, initially, and with growing experience, would be extended to include a wider range of diseases. Anderson believes that in the future germline therapy for specific diseases may be considered, however enhancement therapy should not be undertaken (58). Both nations and parents have strong incentives to defect from a ban on genetic enhancement, because enhancements would help them in competitions with other parents and nations (60). It is likely that any prohibition on enhancement engineering will eventually collapse. Any such prohibition must be followed by appropriate effective measures of control.

EUGENIC GENETIC ENGINEERING

Eugenic genetic engineering might be used to improve upon complex human traits. According to Webster's dictionary, eugenic means improving race and bearing healthy offspring while eugenics refers to the "discipline that deals with the improvement (as by control of mating) of hereditary qualities of race or breed in a series of generations by social control of human reproduction" (61). Eugenic schemes go as far back as Plato, whose ideal republic would have encouraged "union between the better specimens of both sexes" while limiting the reproduction of the less desired ones. The eugenics movement of the late 19th and early 20th centuries was originally a socially progressive movement that embraced the ideals of a better society. In England and America it became tied to ethnocentrism and the blindness of class interests, leading to forced sterilization of feeble minded prisoners. In Germany the eugenics movement became tied to antisemitism, resulting in the racial hygiene program of the Nazi SS (*Rassenhygiene*), and the atrocities of the so-called "final solution" (62). These occurrences must constantly be in our minds when considering eugenics.

Traits, such as personality, character, formation of body organs, fertility, intelligence, physical, mental, and emotional characteristics, are enormously complex. These traits are polygenic and the interactions between the different genes is unknown. The extent of environmental influence is unknown, as well. Complex polygenic traits are not likely to be influenced in a predictable way by genetic intervention. Developing the techniques for producing such changes will take many years, but undoubtedly will be advanced by the Human Genome Project. A discussion on eugenics can therefore be done on a theoretical level only at present, since it is not feasible.

The main objection to eugenics is that it is not ethical to meddle in areas where we are so ignorant. Society disagrees about what constitutes humanness. The insight into the genetic components which might play a role in our spiritual side is almost nonexistent. The understanding of how the mind functions or the genetic basis for instinctual behaviour are unknown. Eugenic engineering might be applied to less adaptive individuals like those who are mentally retarded to allow them to learn to read and contribute more to society. Another application might be to enhance complex

characteristics in normal individuals to promote elitism and concentrate power. Or worse, to insert certain traits desirable to some power group, such as violence in cloned soldiers. Regardless of how fast our technological abilities increase, there should be no attempt to manipulate the genetic framework, for other than pure therapeutic reasons.

CLONING

Cloning refers to the production of two or more genetically identical individuals. The production of multiple offspring with identical genotypes is now feasible in a range of animals. Mammals have proved more difficult to clone. This can be performed by embryo splitting and nuclear transplantation. Cloning by nuclear splitting is time-consuming and the potential number of cloned offspring is limited. Nuclear transfer may produce, at least theoretically, an unlimited number of clones, since embryos at the embryo culture stage could be recycled into further nuclear transfers. Cloning of the human is technically achievable and theoretically need not lead to adverse effects. The availability of preimplantation diagnosis has proven this.

There are sufficient unknowns in genetics which would be absolute contraindications to the cloning of humans. Cloning in the human could not even be considered until the full implications of genetic imprinting are known. In terms of evolution, the complex interactions between genes and the environment would be bypassed if cloning were undertaken. For example, the obvious advantage of having a sickle cell gene in a region endemic for malaria would be circumvented. Cloning would inevitably affect diversity and, in the long term, evolutionary progress. The ability to produce "elite" herds of domestic animals has considerable economic appeal. A consequence of this will be the enhancement of other genetic traits, some of which will be unfavourable. Human cloning would, likewise, lead to fixation of certain traits including potentially undesirable DNA or gene sequences. The genetic problems might not be apparent until the cloned individual reproduced (63).

Some of the reasons why people might wish to clone would not arouse much opposition. Cloning of the preembryo stage for the purpose of genetic screening enables the discarding of a defective embryo before it has been transferred to the womb. This is preferable to the birth of a severely defective

child or to an abortion after a test during pregnancy has shown that the child will be defective. Clones made from early embryonic organs can be used for transplantation in the same individuals, should that be required at a later point in life. The provision of tissues or organs that will not be rejected is unquestionably a desirable goal.

Human cloning would raise many ethical and legal considerations. Who takes responsibility for the clones? What will be the legal status and rights of a clone? What are the inheritance rights of a clone? These are but a few questions. Cloning, like germline gene therapy will influence both somatic cells and germ cells so that any undesirable characteristics present or produced will be transmitted to future progenies. The ethics of identity and individuality are integral components of the ethics of cloning. It is a complex situation when one considers the unlimited number of clones that can be generated and a spatial-time relationship between clones produced at different generations in time. The term "parent" and the concept of parenthood could also need redefinition in the cloning circumstance. If a line of clones was to be propagated ad infinitum, the original parents would cease to have direct relevance. These provide sufficient forceful arguments against the cloning of humans. Cloning of cells is and will remain an important research tool. It should be taken no further in the human (63).

RELIGIOUS ASPECTS

Genetic alteration may be regarded by some as an interference in creation by "playing G-d" or as the rightful application of our G-d-given intelligence to heal our earthly bodies and minds by others. It is important to make a distinction between using genetic intervention to heal a disease and using it to enhance human characteristics. Due to the relative novelty of the issue of genes, previous theological writings have not dealt extensively with gene transfer. Present-day writings by theologians center mostly on the ethical aspects described above. Since somatic cell gene therapy may be regarded as simply a therapeutic procedure, comparable to other therapies, then it may be considered acceptable according to religion. The Judeo-Christian heritage has produced a spectrum of opinion on genetic disease interventions and gene therapy that has uniformly admonished scientists to be cautious (64).

The Christian View

The spectrum of opinion among the protestant sects encompasses the entire range of religious analyses. The World Council of Churches of 1975, dealing with prenatal diagnosis and in vitro fertilization, concluded that Christianity demands a highly sensitive wariness toward any genetic modification other than whatever is healthgiving (65). A president's Commission with representatives from each religious organization concluded that government oversight was appropriate. The report describes distinguishing somatic from germline gene therapy. The outcome of this report concluded, "In view of the theologians, contemporary developments in molecular biology raise issues of responsibility rather than being matters to be prohibited because they usurp powers that human beings should not possess. The Biblical religions teach that human beings are, in some sense, co-creators with the Supreme Creator. Thus, as interpreted for the Commission by their representatives, these major religious faiths respect and encourage the enhancement of knowledge about nature, as well as responsible use of that knowledge. Endorsement of genetic engineering, which is praised for its potential to improve the human estate, is linked with the recognition that the misuse of human freedom creates evil and human knowledge and power can result in harm." Another report, "Splicing Life" stated that technical and ethical difficulties are strong contraindications to germline therapy in the future (87). The Central Committee of the World Council of Churches in 1986 added that because of human infallibility, self-confidence, and arrogance, appreciation of science must be tempered by humane and ethical considerations (67). In a later instruction by the pope in 1986 on Respect for Human Life in its Origin and on the Dignity of Procreation, the following statements appeared, "Techniques of fertilization in vitro can open the way to other forms of biological and genetic manipulation of human embryos . . . attempts . . . for obtaining a human being without any connection with sexuality through "twin fission", cloning or parthenogenesis are to be considered contrary to the moral law, since they are in opposition to the dignity both of human procreation and of the conjugal union. . . . Certain attempts to influence chromosomal or genetic inheritance are not therapeutic but are aimed at producing human beings selected according to sex or other predetermined qualities.

These manipulations are contrary to the personal dignity of the human being and his or her integrity and identity. Therefore, in no way can they be justified on the grounds of possible beneficial consequences for future humanity" (68).

The Jewish View

Life, in the Jewish faith, is of infinite value. All biblical and rabbinic commandments are set aside for the overriding consideration of saving life. Nature was created by G-d for man to use to his advantage and benefit. This makes animal experimentation permissible in Jewish law. The production of hormones in animals for the benefit of man by recombinant DNA techniques is also permissible. Gene therapy for the replacement of a missing or defective gene in Tay-Sachs disease or hemophilia is also sanctioned in Jewish law because it can restore health and preserve and prolong life (69). Ancient Jewish writings, including the Bible and the Talmud, contain some material relating to genetics. The laws of Mendelian genetics were applied by Jacob in the biblical narrative of the speckled and spotted sheep (70). The Talmud and subsequent rabbinic writings describe the precise sex-linked genetics of hemophilia (71). The literature on cloning, recombinant DNA technology, and genetic engineering, as viewed in Jewish law is sparse (72). One rabbi contends that gene therapy would be permissible in Jewish law because genes are submicroscopic particles and no process invisible to the naked eye is forbidden in Jewish law (73), but this is not a widespread opinion. Gene manipulation cannot be considered as tampering with an existing human being but only with a potential one. However, others will argue that the destruction of even a potential human being is prohibited in Jewish law. Rabbi Herschler is of the opinion that gene therapy and genetic engineering may be prohibited because "he who changes the divine arrangement of creation is lacking faith in the Creator" (74). He supports this by the prohibition against mating diverse animals, sowing together diverse kinds of seeds, and wearing garments made of wool and linen (75). But genetic engineering does not seem to be comparable to the grafting of diverse types of animals or seeds. Its main purpose is to cure disease, restore health, and prolong life, all of which are within the physicians' divine license to heal. Gene therapy may not be different from organ transplantation which nearly

all rabbis consider permissible. Somatic cell gene therapy may be considered as permissible according to these writings.

The Muslim View

From a Muslim perspective human gene therapy should be restricted only to therapeutic indications. Somatic cell gene therapy is encouraged as it involves remedy and alleviation of human sufferings. Enhancement genetic engineering or eugenic genetic engineering would involve change in the creation of G-d, which may lead to imbalance of the whole universe and should be prohibited. Gene therapy to manipulate hereditary traits, such as intelligence, stupidity, stature, beauty, or ugliness is a serious attempt, as it may imbalance the life of man (76).

REGULATORY ADVANCES AND PUBLIC OPINION

More than 100 gene therapy protocols are presently approved worldwide. Countries with active protocols include Austria, China, France, Germany, Italy, the Netherlands, Sweden, Switzerland, the United Kingdom, and the United States. The premature and unapproved gene therapy experiment by Martin Cline in 1980 generated a scandal that captured public attention. There have been many debates and surveys regarding the use of gene therapy. Opinion surveys are prone to bias and numbers may be misused in order to provide a scientific aura to reinforce preexisting views (77). There is a call for international approaches at regulating gene therapy trials. This is based on several arguments, including shared biological heritage and destiny of human beings in all nations, and the transitory nature of nations and the precedents for international law to protect common interests of humanity. There are currently efforts to make international guidelines for gene therapy, particularly by UNESCO (78). Those calling for national guidelines argue that each culture should make its own standards because of national autonomy, and because people in each country have different attitudes (79). The UNESCO International Bioethics Committee is drafting general guidelines and an international declaration on the human genome and human genetics, which will be put to the approval of the United Nations General Assembly in 1998 (78). The

positions adopted in the 1994 report on gene therapy may be summarized as follows.

1. Encouraging somatic cell gene therapy for any disease, not only genetic disease.
2. Not outlawing somatic cell gene enhancement or germline therapy.
3. Outlawing germ line gene enhancement.

The UNESCO conclusions are more liberal than some national guidelines.

This report has prompted an international survey to explore the public's reasoning about gene therapy (77). Interestingly, the diversity of comments was generally found to be the same in different countries, suggesting that reasoning about gene therapy goes deeper than cultures and religions. The survey included the general public, university students, and high-school teachers. About three quarters of all samples supported personal use of gene therapy trials, with higher support for children's use of gene therapy. The major reasons given were to save life and increase the quality of life. About 5–7% rejected gene therapy, considering it to be playing G-d, or unnatural. There was very little concern about eugenics, and more respondents gave supporting reasons like improving genes. Support for specific applications was significantly less for improving physical characteristics, improving intelligence, or making people more ethical than for curing diseases like cancer or diabetes, but there was little difference between inheritable or noninheritable gene therapy. The Eurobarometer survey of 1993 discussed biotechnology and genetic engineering. A total of 72.5% of Europeans approved of gene therapy, and 91% opted for government control (80). There are differences of opinion in different European countries, for example Germany, which has the highest general opposition to genetic engineering (81).

As early as 1980, criteria for experimental gene therapy in animals were set forth for a fitting scientific prelude to the ethical acceptability of human trials (82). A strong consensus in favor of somatic gene therapy exists within medicine and among authorities in religious and philosophical ethics (20,83,84). Current regulations governing research require the review body to determine that "where some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as persons with acute or severe physical or mental illness . . . Appropriate additional safeguards have been

included in the study to protect the rights and welfare of these subjects" (85).

Rifkin, one of the opponents of gene therapy, argues, that "ethics are designed to be compatible with the way people organize the world around them. Moral codes keep people's future behaviour in line with the way society goes about organizing and assimilating its environment" (86). A resolution composed by him and signed by 75 prominent Protestants, Jewish, and Catholic clergy, asked for a public policy to prevent genetic alteration of inheritable genetic change (87). This resolution referred to germ line therapy alone. Other writers have questioned the prohibition on germline gene therapy in the NIH guidelines, and called for formal discussion of germline therapy (88,89). The public opinion data, especially from the International Bioethics Survey, and the United States, suggest that the public is ready for a discussion of germ line gene therapy.

In the United States National Institute of Health (NIH) and Food and Drug Administration (FDA) guidelines, the only class of gene therapy that is generally approved is somatic cell gene therapy for treating a disease or somatic cell gene transfer as a marker involved in development of medical therapy (90). This also pertains to all European, Australian, Japanese, and Canadian guidelines and reports (91-93). In the United States the Human Gene Therapy Subcommittee of the NIH's Recombinant DNA Advisory Committee (RAC) has established a *de facto* line in 1986, stating that proposals for germline alteration will not be considered. Protocols for somatic gene therapy must justify why the disease selected is a good candidate, including the seriousness of the disease and the lack of effective alternative therapy (94). Requests from public interest groups to provide specific guidelines were rejected by the subcommittee. This is an advantage, since such criteria could become inappropriately restrictive. Since September 1994 investigators are no longer required to submit their protocol to the RAC in addition to the FDA. The RAC is used for all protocols involving new technology, novel approaches, new diseases, unique applications of gene transfer, and other issues that may require further public review. The RAC recommendations are thus part of the FDA review process.

The 1994 Council of Europe Draft Bioethics Convention banned germline intervention but noted that possible future exceptions could be permitted (95). There is no one regulatory body in Europe. Coun-

tries, such as France, the United Kingdom, and Germany have national regulatory agencies; other countries require local and state approval only. In the United Kingdom a committee on the Ethics of Gene Therapy (CEGT) was established in 1989 to draw up ethical guidance for the medical profession. It was later replaced by the Gene Therapy Advisory Committee (GTAC), of the same goals. In France a National Advisory Committee on Ethics (CCNE) was created in 1982. Somatic cell gene therapy is allowed, but germline modification is strictly forbidden. Several countries in Europe are currently working toward establishment of gene therapy review processes. In Italy and The Netherlands clinical trials were initiated some years ago, after their protocol was extensively reviewed. The Italian protocol was sent to be reviewed by the U.S. RAC, as there is no official body in Italy yet, but official guidelines are under way. In Austria official guidelines dealing with gene therapy were released recently and one clinical trial has been initiated in Vienna. In Belgium regulations are under way. Several trials are currently performed for cancer therapy, one in collaboration with the Vienna trial. In Germany experimental work is regulated by the gene technology law, and any study requires authorization by the Federal Committee for Biological Safety. In Switzerland gene therapy trials have to be approved first by the Hospital Ethical Committee and, later, by two federal commissions. A more stringent and federal regulatory process is currently being worked out. Denmark, Sweden, and Israel are on the way to adopting the U.S. RAC protocols (96). The European Working Group on Human Gene Transfer and Therapy (EWGT) was founded in 1992, aimed at developing and coordinating pre-clinical and clinical research in the field of gene therapy in Europe. Fourteen countries have participating members, including Israel. Guidelines for commercial use of gene therapy products were also established. There are approximately 20 clinical trials in progress in Europe (97).

Any proposal for somatic cell gene therapy research in Canada is carried out within the context of the Medical Research Council of Canada's Guidelines for Research on Somatic Cell Gene Therapy in Humans (98). The recommendation is that these guidelines be implemented at the local hospital level, as well as the national level. Germ line gene therapy is prohibited.

There is a high support for therapeutic purposes of gene therapy in all societies. International guide-

lines could provide minimum standards for ethical protection of users and enable availability of service. However, these cannot be enforced in countries who oppose them. Such guidelines are under way.

CONCLUSIONS

Present-day scientific advances have made it possible to use somatic cell gene therapy for the treatment of serious human genetic disease. Gene therapy is enormously important for curing some diseases, otherwise untreatable. The technical ability to perform germline gene alteration is also under way. Society must determine its attitude toward germline alteration and toward intervention for the purpose of genetic enhancement. Eugenic genetics is purely theoretical at present and is likely to remain so for a long time. Articles in the press, sometimes influenced by specific pressure groups, generate public fear that is in most cases unfounded, due to the lack of feasibility of performing the claims voiced in them. Still, society must be concerned about the possibility that gene therapy will be misused in the future. Gene therapy should only be used in ways that maintain human dignity. The best insurance against misuse is a public well informed and not unnecessarily frightened. With proper safeguards imposed by society, gene therapy can be ethically used.

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