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HUMAN GENE THERAPY: SCIENTIFIC AND ETHICAL CONSIDERATIONS

ABSTRACT. The term 'gene therapy' encompasses at least four types of application of genetic engineering for the insertion of genes into humans. The scientific requirements and the ethical issues associated with each type are discussed. Somatic cell gene therapy is technically the simplest and ethically the least controversial. The first clinical trials will probably be undertaken within the next year. Germ line gene therapy will require major advances in our present knowledge and it raises ethical issues that are now being debated. In order to provide guidelines for determining when germ line gene therapy would be ethical, the author presents three criteria which should be satisfied prior to the time that a clinical protocol is attempted in humans. Enhancement genetic engineering presents significant, and troubling, ethical concerns. Except where this type of therapy can be justified on the grounds of preventive medicine, enhancement engineering should not be performed. The fourth type, eugenic genetic engineering, is impossible at present and will probably remain so for the foreseeable future, despite the widespread media attention it has received.

Key Words: genetic engineering, somatic cells, germ cells, enhancement, eugenics, humanhood.

There are four potential levels of the application of genetic engineering for the insertion of a gene into a human being (Anderson, 1982):

(1) Somatic cell gene therapy: this would result in correcting a genetic defect in the somatic (i.e., body) cells of a patient.

(2) Germ line gene therapy: this would require the insertion of the gene into the reproductive tissue of the patient in such a way that the disorder in his or her offspring would also be corrected.

(3) Enhancement genetic engineering: this would involve the insertion of a gene to try to 'enhance' a known characteristic; for

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example, the placing of an additional growth hormone gene into a normal child.

(4) Eugenic genetic engineering: this is defined as the attempt to alter or 'improve' complex human traits, each of which is coded by a large number of genes; for example, personality, intelligence, character, formation of body organs, and so on.

SOMATIC CELL GENE THERAPY

There are many examples of genes which, when defective, produce serious or lethal disease in a patient. Gene therapy should be beneficial primarily for the replacement of a defective or missing enzyme or protein that must function inside the cell that makes it, or of a deficient circulating protein whose level does not need to be exactly regulated (for example, blood clotting factor VIII which is deficient in hemophilia). Early attempts at gene therapy will almost certainly be done with genes for enzymes that have a simple 'always-on' type of regulation. (For a technical discussion of the state-of-the-art of somatic cell gene therapy, together with extensive references, see Anderson, 1984.)

Initial Candidates for Gene Therapy

The most likely genes to be used in the first experiments on human gene therapy are: hypoxanthine-guanine phosphoribosyl transferase (HPRT), the absence of which results in Lesch-Nyhan disease (a severe neurological disorder that includes uncontrollable self-mutilation); adenosine deaminase (ADA), the absence of which results in severe combined immunodeficiency disease (in which children have a greatly weakened resistance to infection and cannot survive the usual childhood diseases); and purine nucleoside phosphorylase (PNP), the absence of which results in another form of severe immunodeficiency disease. For all three, the clinical syndrome is profoundly debilitating. The disorder in each is found in the patient's bone marrow (although the severe central nervous system manifestations of Lesch-Nyhan disease are due to absence of HPRT in brain cells and probably cannot be corrected with current techniques). In all three, there is no, or minimal, detectable enzyme in marrow cells from patients who have no copies of the normal gene. In these patients, the production of a small percentage of the normal enzyme level should be beneficial and a mild overproduction of enzyme

should not be harmful. In addition, in the case of all three disorders, the normal gene has been cloned and is available.

Previously, clinical investigators thought that the human genetic diseases most likely to be the initial ones successfully treated by gene therapy would be the hemoglobin abnormalities (specifically, beta-thalassemia) because these disorders are the most obvious ones carried by blood cells, and bone marrow is the easiest tissue to manipulate outside the body. Regulation of globin synthesis, however, is unusually complicated. Not only are the embryonic, fetal, and adult globin chains carefully regulated during development, but also the subunits of the hemoglobin molecule are coded by genes on two different chromosomes. To understand the regulatory signals that control such a complicated system and to develop means for obtaining controlled expression of an exogenous (i.e., inserted by gene therapy) beta-globin gene will take considerably more research effort.

Severe combined immunodeficiency due to a defect in the ADA gene can be corrected by infusion of normal bone marrow cells from a histocompatible donor. Therefore, selective replication of the normal marrow cells appears to take place. This observation offers hope that defective bone marrow can be removed from a patient, the normal ADA gene inserted into a number of cells through gene therapy, and the treated marrow reimplanted into the patient where it may have a selective growth advantage. There is also evidence that marrow cells containing the normal gene for HPRT may have a selective advantage (in both mice and humans) over cells that do not. If selective growth occurs, elimination of the patient's own marrow would not be necessary. If, however, corrected marrow cells have no growth advantage over endogenous (i.e., the patient's own untreated) cells, then partial or complete marrow destruction (either by irradiation or by other means) may be required in order to allow the corrected marrow cells an environment favorable for expansion. The latter situation would require much greater confidence that the gene therapy procedure would work before a clinical trial should be undertaken.

Ethics

The ethics of gene therapy in humans has been discussed for many years and is being widely debated at present. John Fletcher (1985) has reviewed this area in detail in this issue. Essentially all observers have stated that they believe that it would be ethical to insert genetic material into a human being for the sole purpose of medically correcting a severe genetic defect in that patient, in other

words, somatic cell gene therapy. Attempts to correct a patient's reproductive cells (i.e., germ line gene therapy) or to alter or improve a 'normal' person by gene manipulation (i.e., enhancement or eugenic genetic engineering) are controversial areas. However, somatic cell gene therapy for a patient suffering a serious genetic disorder would be ethically acceptable if carried out under the same strict criteria that cover other new experimental medical procedures. The techniques now being developed by clinical investigators for human application are for somatic cell, not germ line, gene therapy.

What criteria should be satisfied prior to the time that somatic cell gene therapy is tested in a clinical trial? Three general requirements, first presented in 1980 (Anderson and Fletcher, 1980), are that it should be shown in animal studies that (i) the new gene can be put into the correct target cells and will remain there long enough to be effective; (ii) the new gene will be expressed in the cells at an appropriate level; and (iii) the new gene will not harm the cell or, by extension, the animal. These three requisites, summarized as delivery, expression, and safety, will each be examined in turn.

These criteria are very similar to those required prior to the use of any new drug, therapeutic procedure, or surgical operation. The requirements simply state that the new treatment should get to the area of disease, correct it, and do more good than harm. Some flexibility is necessary since the criteria might be altered for a critically ill patient for whom no further conventional therapy is available. The exact definitions of what is 'long enough to be effective', what level is 'an appropriate level', and how much harm is meant by 'harm', are questions for ongoing discussion as more is learned about gene therapy. Ultimately, local Institutional Review Boards and the National Institutes of Health (NIH), the latter through its newly created Working Group on Human Gene Therapy, must decide if a given protocol is ready for human application. Once the criteria are satisfied, that is, when the probable benefits for the patient are expected to exceed the possible risks, then attempts to cure human genetic disease by treatment with somatic cell gene therapy would be ethical. The goal of biomedical research is, and has always been, to alleviate human suffering. Gene therapy is a proper and logical part of that effort.

Delivery

At present, the only human tissue that can be used effectively for gene transfer is bone marrow. No other cells (except, perhaps, skin

cells) can be extracted from the body, grown in culture to allow insertion of exogenous genes, and then successfully reimplanted into the patient from whom the tissue was taken. In the future, as more is learned about how to package the DNA and to make it tissue-specific, the intravenous route would be the simplest and most desirable. However, attempting to give a foreign gene by injection directly into the bloodstream is not advisable with our present state of knowledge since the procedure would be enormously inefficient and there would be little control over the DNA's fate.

Studies are considerably more advanced with bone marrow than skin cells as a recipient tissue for gene transfer. Bone marrow consists of a heterogeneous population of cells, most of which are committed to differentiate into red blood cells, white blood cells, platelets, and so on. Only a small proportion (0.1 to 0.5 percent) of nucleated bone marrow cells are stem cells (that is, blood-forming cells that have not yet differentiated into specific cell types and which divide as needed to maintain the marrow population). In gene therapy, it would be these rare, unrecognizable stem cells that would be the primary target. Consequently, a delivery system useful for gene therapy must be efficient.

Several techniques for transferring cloned genes into cells have been developed (Anderson, 1984). Each procedure is valuable for certain types of experiments, but none can yet be used to insert a gene into a specific chromosomal site in a target cell. At present the most promising approach for use in humans employs retrovirus-based vectors carrying exogenous genes.

Vectors derived from retroviruses possess several advantages as a gene delivery system. First, up to 100 percent of cells can be infected and can express the integrated viral (and exogenous) genes. Second, as many cells as desired can be infected simultaneously; 10^6 to 10^7 is a convenient number for a simple protocol. Third, under appropriate conditions, the DNA can integrate as a single copy at a single, albeit random, site. Finally, the infection and long-term harboring of a retroviral vector usually does not harm cells. Several retroviral vector systems have been developed; those projected for human use at the present time are constructed from the Moloney murine (mouse) leukemia virus. Evidence obtained from studies with experimental animals and in tissue culture indicates that retroviruses can be used as a reasonably efficient delivery system.

An ideal delivery system would be tissue-specific. When a genetic disorder is in the blood cells, the isolated bone marrow can be

treated. But no other tissue (except skin cells) can be removed, treated, and replaced at present. Since many viruses are known to infect only specific tissues (that is, to bind to receptors that are present only on certain cell types), a retroviral particle containing a coat that recognizes only human blood-forming cells would permit the retroviral vector to be given intravenously with little danger that cells other than those in the marrow would be infected. In the future, such specificity could permit the liver and brain, for example, to be treated individually. In addition, the danger of inadvertently infecting germ cells could be eliminated. One problem, however, is that cell replication appears to be necessary for retrovirus integration. It would not be possible to infect nondividing brain cells, for example, so far as we now know.

The optimal system not only would deliver the vector specifically into the cell type of choice, but would also direct the vector to a predetermined chromosomal site. Specific insertion into a selected site on a chromosome can be achieved in lower organisms but has not yet been possible in mammals.

Expression

In order for gene therapy to be successful, there must be appropriate expression of the new gene in the target cells. Even when a delivery system can transport an exogenous gene into the DNA of the correct cells of an organism, it has been a major problem to get the integrated DNA to function. A vast array of cloned genes have been introduced into a wide range of cells by several gene transfer techniques. 'Normal' expression of exogenous genes is the exception rather than the rule.

Expression of exogenous genes carried by retroviral vectors into intact animals via treated bone marrow cells has been reported by three laboratories. Two studies demonstrated the expression of an antibiotic resistance gene in mice (Joyner *et al.*, 1983; Williams *et al.*, 1984). The most extensive data, however, are from studies with the enzyme HPRT (Miller *et al.*, 1984; Willis *et al.*, 1984). A homozygous Lesch-Nyhan (LN) lymphoblast (white blood cell) line, which lacks a functional HPRT gene, was used to demonstrate that an $HPRT^-$ human blood-forming cell could be corrected by a retroviral vector containing an active HPRT gene. In a corollary study, viral particles containing the HPRT-vector were used to infect mouse bone marrow cells that were then injected into lethally irradiated mice. Both human HPRT protein and chronic production of HPRT-vector particles were detected in the blood-forming tissues of the mice. These

data provide hope that vectors can eventually be built with all the regulatory signals necessary to produce correctly controlled expression of exogenous genes in target cells.

Safety

Finally, a human gene therapy protocol must be safe. Although retroviruses have many advantages for gene transfer, they also have disadvantages. One problem is that they can rearrange their own structure, as well as exchange sequences with other retroviruses. In the future it might be possible to modify non-infectious retroviral vectors in such a way that they remain stable. At present, however, there is the possibility that a retroviral vector might recombine with an endogenous viral sequence to produce an infectious recombinant virus. Properties that such a recombinant would have are unknown, but there is a potential homology between retroviral vectors and human T-cell leukemia viruses so that the formation of a recombinant that could produce a malignancy is a possibility. There is, however, a built-in safety feature with the mouse retroviral vectors now in use. These mouse structures have a very different sequence from known primate retroviruses, and there appears to be little or no homology between the two. Therefore, it should be possible, with continuing research, to build a safe retroviral vector.

With the present constructs, three types of experiments ought to be carried out before any retrovirus-treated bone marrow is injected into a patient. These protocols, designed to test the safety of the delivery-expression system, are necessary since once treated bone marrow is reinserted into a patient, it and all retroviruses that it contains are irretrievable.

First, studies with human bone marrow in tissue culture are needed. Marrow cultures infected with the therapeutic vector should be tested for a period of time for the production of recombinant viruses. Any infectious virus isolated should be studied for possible pathogenicity.

Second, studies *in vivo* with mice are needed. Treated animals should be followed to determine if genomic rearrangement or the site of chromosomal integration of the retroviral vector has resulted in any pathologic manifestations or the production of any infectious viruses.

Third, studies *in vivo* with primates are needed. A protocol similar to the one planned for human application should be carried out in primates, not just mice, because the endogenous viral sequences in

primate, including human, DNA are different from those in mouse DNA. Therefore, the nature of any viral recombinants would be different. Treated bone marrow should be reimplanted into primates, the successful transfer of intact vector DNA into blood-forming cells demonstrated, the expression of at least small amounts of gene product verified, and the existence of infectious recombinant viruses sought.

Conclusion

It now appears that effective delivery-expression systems are becoming available that will allow reasonable attempts at somatic cell gene therapy. The first clinical trials will probably be carried out within the next year. The initial protocols will be based on treatment of bone marrow cells with retroviral vectors carrying a normal gene. The safety of the procedures is the remaining major issue. Patients severely debilitated by having no normal copies of the gene that produces the enzyme HPRT, ADA, or PNP are the most likely first candidates for gene therapy.

It is unrealistic to expect a complete cure from the initial attempts at gene therapy. Many patients who suffer from severe genetic diseases, as well as their families, are eager to participate in early clinical trials even if the likelihood is low that the original experiments will alleviate symptoms. However, for the protection of the patients (particularly since those with the most severe diseases and, therefore, the most ethically justifiable first candidates are children), gene therapy trials should not be attempted until there are good animal data to suggest that some amelioration of the biochemical defect is likely. Then it would be necessary to weigh the potential risks to the patient, including the possibility of producing a pathologic virus or a malignancy, against the anticipated benefits to be gained from the functional gene. This risk to benefit determination, a standard procedure for all clinical research protocols, would need to be carried out for each patient.

In summary, Institutional Review Boards and the NIH 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, even if small, for the patient, and that safety protocols have demonstrated that the probability is low for the production of either a malignant cell or a harmful infectious retrovirus. Once these criteria are met, I maintain that it would be unethical to delay human trials.

Patients with serious genetic diseases have little other hope at present for alleviation of their medical problems. Arguments that genetic engineering might someday 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.

GERM LINE GENE THERAPY

The second level of genetic engineering, gene therapy of germ line cells, would require a major advance in our present state of knowledge. It would require that we learn how to insert a gene not only into the appropriate cells of the patient's body, but also how to introduce it into the germ line of the patient in such a way that it would be transmitted to offspring and would be functional in the correct way in the correct cells in the offspring. Based on the small amount of information now available from animal studies, the step from correction of a disorder in somatic cells to correction of the germ line would be difficult.

Germ Line Therapy in Animals

Germ line transmission and expression of inserted genes in mice has been obtained by several laboratories but with a technique that is not acceptable for use in human patients, namely, the physical microinjection of fertilized eggs. Microinjection into tissue culture cells has been used for a number of years and has the advantage of high efficiency (up to one cell in five injected can be permanently transfected). However, the distinct disadvantage is that only one cell at a time can be injected. Transfection of a large number (like 10^6) of blood-forming stem cells is not feasible.

Microinjection has been used with considerable success in transferring genes into mouse zygotes. DNA can be microinjected into one of the two pronuclei of a recently fertilized mouse egg. This egg can then be placed into the oviduct of a pseudopregnant female where it can develop into a normal mouse carrying the exogenous DNA in every cell of its body including its germ cells. Consequently, the injected DNA can be transmitted to offspring in a normal Mendelian manner. Mice carrying an exogenous gene in their genome are called 'transgenic'.

It is this technique that was used to partially correct a mouse with a defect in its growth hormone production (Hammer *et al.*, 1984).

By attaching a rat growth hormone gene to an active regulatory sequence (specifically, the promoter that normally directs the synthesis of metallothionein messenger RNA in mice), researchers obtained a recombinant DNA construct that actively produces growth hormone in the genetically defective mouse and in a number of its offspring. Although the level of growth hormone production was inappropriately controlled (that is, influence by signals that normally regulate metallothionein synthesis), these experiments did show that microinjection can be used as a delivery system that can put a gene into every cell of an animal's body, that a genetic disorder can, as a result, be corrected, and that the correction can be passed on to the next generation of animals.

Why is the technique of microinjecting a fertilized egg not acceptable for use for human gene therapy at the present time? First, the procedure has a high failure rate; second, it can produce a deleterious result; and third, it would have limited usefulness. Microinjection has a high failure rate because the majority of eggs are so damaged by the microinjection and transfer procedures that they do not develop into live offspring. In one recent experiment (Brinster *et al.*, 1983) involving microinjection of an immunoglobulin gene into mouse eggs, 300 eggs were injected, 192 (64 percent) were judged sufficiently healthy to be transferred to surrogate mothers, only 11 (3.7 percent) proceeded to live birth, and just 6 (2 percent) carried the gene. These results are from a highly experienced laboratory in which thousands of identical eggs from the same hybrid cross of inbred mice have been injected over several years. The mice were chosen precisely because they gave the best results for gene transfer by microinjection. Attempts to microinject functional growth hormone genes into livestock eggs met with several major biological and technical problems before being accomplished. Successful gene transfer by microinjection of human eggs, without a long period of trial and error experimentation, is extremely unlikely.

Second, microinjection of eggs can produce deleterious results because there is no control over where the injected DNA will integrate in the genome. For example, the integration of an exogenous rabbit beta-globin gene in transgenic mice can sometimes occur at a chromosomal location that results in expression of the beta-globin gene in an inappropriate tissue, viz., muscle or testis (Lacy *et al.*, 1983). There have also been several cases reported where integration of microinjected DNA has resulted in a pathological condition. Although there is no control over where exogenous DNA will integrate

in any gene transfer procedure, the damaging effect caused by a harmful insertion site could be great when it occurs in the egg but may be negligible when it occurs in one or a few of a large number of bone marrow cells.

The third objection to microinjection of eggs is limited usefulness. Not only is it ethically questionable to experiment on human eggs because of the expected losses, but even if 'success' were obtained, it would be applicable primarily when both patients are homozygous for the defect. When the parents are both carriers of a recessive trait, only one fertilized egg out of four would result in an affected child. Since a homozygous defect cannot yet be recognized in early embryos, and since the procedure itself carries such a high risk, it would be improper to attempt any manipulation in this situation. Furthermore, most of the very serious genetic disorders result in infertility (or death before reproductive age) in homozygous patients. Consequently, there would be little use for the procedure even if it were feasible.

Ethics

Even when the technical capability becomes available to attempt germ line gene therapy in humans, there are major medical and ethical concerns to consider. The medical issues center primarily around the question: will the transmitted gene itself, or any side effects caused by its presence, adversely affect the immediate offspring or their descendants? Since in this case one must study several generations of progeny to obtain answers, it will clearly take longer to gain knowledge from animal studies on the long-term safety of germ line gene therapy than on somatic cell gene therapy.

Germ line therapy deserves careful ethical consideration well in advance of the time when the technical capability for carrying it out arrives. The critical ethical question is: should a treatment which produces an inherited change, and could therefore perpetuate in future generations any mistake or unanticipated problems resulting from the therapy, ever be undertaken?

What criteria would be needed to justify the use of this unique type of therapy? At least three conditions should be met prior to the time that germ line gene therapy is attempted in human beings.

First, there should be considerable previous experience with somatic cell gene therapy that clearly establishes the effectiveness and safety of treatment of somatic cells. There is a wide range of biological variability among humans. Even if the first few patients treated

by somatic cell therapy are helped, the next ones may not be, or may even be harmed. Therefore, extensive experience with many patients over a number of years will be necessary before somatic cell therapy can properly be judged to be safe and effective. If somatic cell therapy has not become highly efficient with very minimal risks, germ line gene therapy should not be considered.

Second, there should be adequate animal studies that establish the reproducibility, reliability, and safety of germ line therapy, using the same vectors and procedures that would be used in humans. Of greatest importance would be the demonstration 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. It should be remembered that gene therapy does not remove or correct the defective genes in the recipient; it only adds a normal gene into the genome. It is not now known what the influence of this combination of defective and normal genes may be on the developing embryo. Might the regulatory signals still associated with the non-functional genes adversely affect the regulation of the exogenous gene during development?

Third, there should be public awareness and approval of the procedure. New drugs, medical regimens, and surgical techniques certainly do not require individual public approval prior to their initiation. There are already regulatory processes in place that insure the protection of human subjects (this issue has been addressed in a previous publication (Anderson and Fletcher, 1980)). Somatic cell gene therapy is receiving widespread public attention, but prior public approval is not being specifically sought. Germ line gene therapy, however, is a different and unique form of treatment. It will affect unborn generations and has, therefore, 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. Since germ line therapy will affect the gene pool, the public should have a thorough understanding of the implications of this form of treatment. Only when an informed public has indicated its support, by the various avenues open for society to express its views, should clinical trials begin. *In vitro* fertilization, surrogate motherhood, animal organ transplants into humans, holistic treatment of cancer, and other controversial medical procedures can take place based on the decision of the patient (with his/her doctor and/or family) whether society as a whole approves or not. But the decision to initiate germ line gene therapy demands assent from more than the

individual involved, since the effects go beyond that individual. If and when germ line therapy is approved by society for clinical trials, then the decision to apply it in any individual case again should be made privately by the patient with his/her doctor.

In conclusion, my position is that germ line therapy, since it is the correction of a genetic defect (albeit in the future), would be ethical and appropriate if the three conditions discussed above were met.

ENHANCEMENT GENETIC ENGINEERING

The third level of genetic engineering, enhancement genetic engineering, is considerably different in principle from the first two. This is no longer therapy of a genetic disorder; it is the insertion of an additional normal gene (or a gene modified in a specific way) to produce a change in some characteristic that the individual wants. Enhancement would involve the insertion of a single gene, or a small number of genes, that code for a product (or products) that would produce the desired effect – for example, greater size through the insertion of an additional growth hormone gene into the cells of an infant. Enhancement genetic engineering presents a major additional scientific hurdle, as well as serious new ethical issues. Except under very specific circumstances as detailed below, genetic engineering should not be used for enhancement purposes.

Scientific and Ethical Concerns

The scientific hurdle to be overcome is a formidable one. Until now, we have considered the correction of a defect, of a 'broken part', if you will. Fix the broken part and the human machine should operate correctly again. Replacing a faulty part is different from trying to add something new to a normally functioning system. To insert a gene in the hope of improving or selectively altering a characteristic might endanger the overall metabolic balance of the individual cells as well as of the entire body. Medicine is a very inexact science. Every year new hormones, new regulators, and new pathways are discovered. There are clearly many more to be discovered. Most impressive is the enormously intricate way that each cell coordinates within itself all of its thousands of pathways. Likewise, the body as a whole carefully monitors and balances a multitude of physiological systems. Much additional research will be required to elucidate the effects of altering one or more major pathways in a cell. To correct a faulty gene is probably not going to be dangerous, but intentionally

to insert a gene to make more of one product might adversely affect numerous other biochemical pathways.

We possess insufficient information at present to understand the effects of attempts to alter the genetic machinery of a human. Is it wise, safe, or ethical for parents to give, for example, growth hormone (now that it is available in large amounts) to their normal sons in order to produce very large football or basketball players? Unfortunately, this practice now takes place in this country. But even worse, why would anyone want to insert a growth hormone *gene* into a normal child? Once it is in, there is no way to get it back out. The child's reflexes, coordination, and balance might all be grossly affected. In addition, even more serious questions can be asked: might one alter the regulatory pathways of cells, inadvertently affecting cell division or other properties? In short, we know too little about the human body to chance inserting a gene designed for 'improvement' into a normal healthy person.

An Acceptable Use

There is, however, a set of circumstances under which enhancement genetic engineering may be ethical. This is when it could be justified on grounds of preventive medicine. For example, it is well established that heart attacks and stroke are a direct result of atherosclerosis (i.e., hardening of the arteries). The rate of development of atherosclerosis appears to correlate directly with elevated levels of cholesterol in the blood. The level of blood cholesterol is regulated, at least in part, by its rate of clearance from the blood by the low density lipoprotein (LDL) receptors on body cells (Goldstein and Brown, 1983). LDL is the major cholesterol-transport protein in human plasma. If further research should verify that an increased number of LDL receptors on cells would result in lower blood cholesterol levels and, consequently, in a decreased incidence of heart attacks and strokes, then the insertion of an additional LDL receptor gene in 'normal' individuals could significantly decrease the morbidity and mortality caused by atherosclerosis. In this type of situation, the purpose of the intervention would be the prevention of disease, not simply the personal desire of an individual for an altered characteristic. The concerns expressed above about disrupting the regulatory pathways in the body still should be considered, of course. However, since there is a range for the number of receptors on a cell's surface, shifting a person with a "low normal" number of receptors to a "high normal" number may not be disruptive to other physiological or biochemical pathways.

EUGENIC GENETIC ENGINEERING

The fourth level is 'eugenic' genetic engineering. This area has received considerable attention in the popular press, with the result that at times unjustified fears have been produced because of claims that scientists might soon be able to re-make human beings. In fact, however, such traits as personality, character, formation of body organs, fertility, intelligence, physical, mental, and emotional characteristics, etc., are enormously complex. Dozens, perhaps hundreds, of unknown genes that interact in totally unknown ways probably contribute to each such trait. Environmental influences also interact with these genetic backgrounds in poorly understood ways. With time, as more is learned about each of these complex traits, individual genes will be discovered that play specific roles. Undoubtedly, disorders will be recognized that are caused by defects in these genes. Then, somatic cell gene therapy could be employed to correct the defect. But the concept of 're-making a human' (i.e., eugenic genetic engineering) is not realistic at present.

Complex polygenic traits may never be influenced in a predictable manner by genetic engineering, but, at a minimum, developing the techniques for producing such changes will take many years. Therefore, there is no point to a scientific discussion of eugenic genetic engineering at present – there is simply no science to discuss. But from a philosophical standpoint, a discussion of the ethics of eugenic genetic engineering is very important. After all, what is it that makes us human? Why are we what we are? Are there genes which are indeed 'human' genes? If we were to alter one of these genes, would we be other than human? These are important questions for us to think about and discuss.

If eugenic genetic engineering were possible today, I would be strongly opposed to its use on philosophical and ethical grounds. Our knowledge of how the human body works is still elementary. Our understanding of how the mind, both conscious and subconscious, functions is even more rudimentary. The genetic basis for instinctual behavior is largely unknown. Our disagreements about what constitutes 'humanhood' are notorious. And our insight into what, and to what extent, genetic components might play a role in what we comprehend as our 'spiritual' side is almost non-existent. We simply should not meddle in areas where we are so ignorant. Regardless of how fast our technological abilities increase, there should

be no attempt to manipulate, for other than therapeutic reasons, the genetic framework (i.e., the genome) of human beings.

CONCLUSION

In summary, somatic cell gene therapy for human genetic disease should be possible in the very near future. The scientific basis on which this new therapeutic approach is founded has been thoroughly documented in a number of publications, as has the ethical justification for its use. Germ line gene therapy is still in the future, but the technical ability to carry it out will almost certainly be developed. Society must determine if this therapeutic option should be used. Enhancement genetic engineering should also be possible and its medical and disturbing ethical implications need continuing discussion. Eugenic genetic engineering, on the other hand, is purely theoretical and will, from a practical standpoint, be impossible for the foreseeable future. The topic is valuable for reflective thinking but not for scientific discussion.

Many of the fears generated by some articles in the popular press that discuss 'gene therapy' or 'genetic engineering' are simply unfounded. Insertion of single functional genes should soon become possible, but claims that new organs, designed personalities, master races, or Frankenstein monsters will be created can be given no credence in the light of what is presently known. Even so, we should be concerned about the possibility that genetic engineering might be misused in the future. The best insurance against possible abuse is a well-informed public. Gene therapy has the potential for producing tremendous good by reducing the suffering and death caused by genetic diseases. We can look forward to the day when, with proper safeguards imposed by society, this powerful new therapeutic procedure is available.

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