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Genomics and Medicine

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Ethics of Gene Therapy

Francis Crick once said, "We used to think that our fate was in our stars. Now we know that, in large measure, our fate is in our genes." Over 40 years ago, James Watson and Francis Crick discovered the structure of deoxyribonucleic acid (DNA). From this a new technique has evolved called gene therapy. Gene therapy is a technique which has developed in the wake of recombinant DNA (rDNA) technology. It is a process that results in the correction of a genetic disorder by the addition of a piece or fragment of DNA into the genetic material of a living, functioning cell. A mere forty years ago this concept belonged to the realm of the human imagination made manifest in the works of science fiction. Today it belongs to the realm of the human imagination made manifest in the works of science, period. It is mind boggling to try to comprehend the far reaching effects of gene therapy. How is it affecting society? Who will benefit from its use? Should it be used at all? Should research continue? How do we answer all of these questions? The answers are not readily available, nor are they black and white, but an attempt at finding some solutions must be made. Before exploring this line of thought further, a basic understanding of the technical aspects of gene therapy is essential.

The practice of gene therapy is related to two groups of cells - somatic cells and germ-line cells. A germ-line cell is a cell which, during the first few weeks after conception, is put aside in the embryonic sex organs to provide, possibly decades later,

ova or sperm. A somatic cell is any body cell except a germ-line cell. The genes carried by each of these two kinds of cell have distinct roles, and the distinction is very important. Genes that are carried by germ-line cells may be transmitted to offspring and successive generations. Genes that are carried by somatic cells have their role in the corporate life of those cells within the tissues and organs of the individual whom they endow. So far as is known, an alteration to the genes of somatic cells will affect only that individual, but an alteration to the genes of germ-line cells might affect offspring and successive generations.

Concerns with regard to somatic cell gene therapy are much the same as those regarding any novel form of medical practice or treatment. Somatic cell gene therapy impacts only on the individual subject of the gene therapy, and ethical concerns are centered around the risk to the participant or patient and the concomitant obligations of the investigator.

The ethics of gene therapy are largely dependent on its status either as medical practice or as research. While practice is undertaken with the primary intention of benefiting an individual patient, research is undertaken with the prime purpose of testing a hypothesis and permitting conclusions to be drawn, in the hope of contributing to general knowledge. At present, gene therapy has not yet been assimilated into mainstream medical practice. It is still perceived to be different, both in its nature and possible consequences, from any treatment used hitherto in medical practice. Thus, gene therapy should be considered to be in the research stages and subject, therefore, to those ethical considerations that currently govern genetic and medical research:

National guidelines for the conduct of human gene therapy are essential. These, with an expert national body to consider and approve proposals for such therapy, would ensure public confidence in the introduction of novel and sophisticated gene therapy practices. A regulatory system would go far in allaying public fears that gene therapy might be misused, or that it might be extended to enhancement uses beyond what is strictly medical therapy.

Somatic cell gene therapy takes multiple forms. In its simplest form, it entails supplementing or replacing dysfunctional or faulty genes with ones that are able to function correctly. Ideally, somatic cell gene therapy provides the correct genetic information in those cells which require it for their normal function. This form of therapy corrects or alleviates the genetic defect present in the individual alone, without impacting on the genetic information transmitted to any issue. It is argued that, in principle, somatic cell gene therapy is similar to current routine therapies such as organ transplantation, and therefore raises no new ethical issues. However, there is a greater danger present in gene therapy:

The correcting gene might be inserted into the wrong cell type, or be expressed inappropriately, either in the wrong amount or at the wrong time during development. The therapy might then do more harm than good. The gene might [also] be inserted in such a way as to cause a new mutation, by disrupting some other gene or its means of control. This might initiate a new genetic disease, or perhaps an uncontrollable multiplication of cells which could lead to cancer. These factors bear on the effectiveness, safety and risk of somatic cell gene therapy. Safety should be the

paramount factor when considering whether to conduct somatic cell gene therapy on a particular individual as a form of medical practice.

Different considerations apply in somatic cell gene therapy research. The Report of the Committee on the Ethics of Gene Therapy has set out the following conditions as prerequisites to gene therapy research:

a. There must be sufficient scientific and medical knowledge, together with knowledge of those proposing to undertake the research, to make sound judgements on:
i. the scientific merit of the research;
ii. its probable efficacy and safety;
iii. the competence of those who wish to undertake the research;
iv. the requirements for effective monitoring.

b. The clinical course of the disorder must be known sufficiently well for the investigators and those entrusted with counseling to:
i. give accurate information and advice;
ii. assess the outcomes of therapy.

Where are the boundaries for the practice of somatic cell gene therapy? It is arguable that current gene therapy should be directed to alleviating disease in individuals. However, gene therapy could have a wider application than the correction of single gene disorders. For example, it is being investigated as a possible new approach to the management of a wide spectrum of diseases, ranging from infections such as AIDS to cancer, and it is being studied as a means of strengthening the body's immune response to viral infections. Various approaches are being used which require the insertion of genes into particular cell populations in an attempt to counter some of the basic changes in cells which lead to them becoming cancerous. Gene therapy is also being explored for the management of chronic diseases such as diabetes.

There are other non-disease-related uses to which genetic manipulation could be put. The current limits placed on the use of gene modification, however, curtail its use for the enhancement or change of human traits not associated with disease. Somatic cell gene therapy will be a new kind of treatment, but it does not represent a major departure from established medical practice; nor does it, in our view, pose new ethical challenges.

It will, of course, raise familiar issues, which attend any new medical procedure. However, there are public concerns about a medical intervention that may be perceived, understandably, as different from any used hitherto. In addition, because of the special qualities of an individual's genetic make-up and the complex nature of genetic disorders, the issues will assume greater prominence. They are:

i. questions of safety, which are heightened by the possibility of inadvertent and unpredictable consequences of gene therapy to the patient, and the possible long-term consequences;
ii. the need for long-term surveillance and follow-up;
iii. the matter of consent
iv. the probability that children will be among the first candidates for therapy;
v. confidentiality, and disclosure of genetic information important to kindred.

It is essential to ensure that these issues are properly considered, and to demonstrate satisfactorily that this has been done.

While the safety and effectiveness of somatic cell gene therapy remain uncertain, this new treatment, as with any other treatment, should be limited to patients in whom the potential for benefit is greatest in relation to possible inadvertent harm. It is therefore recommend that the first candidates for gene therapy should be patients:

i. in whom the disorder is life threatening or causes serious handicap;
ii. for whom treatment is at present unavailable or is unsatisfactory but for whom treatment may be beneficial.

Gene therapy should be directed to alleviating disease in individual patients, although wider applications may soon call for attention. In the present state of knowledge, any attempt by gene modification to change human traits not associated with disease would be unacceptable. The insertion of genes into fertilized eggs or very early embryos is fundamentally different because these genes would be passed on to the offspring in subsequent generations. Germ-line therapy should not be contemplated.

This line of thinking is, fundamentally, the point of departure for most commentators on the ethics of gene therapy. It is also a simplistic response to a complex ethical issue. The predominant feature of germ-line therapy which posits the greatest ethical dilemmas is also its greatest advantage. Gene modification at an early stage of embryonic development, before differentiation of the germ line, might be a way of correcting gene defects in both the germ line and somatic cells.

It is fundamental to separate the various ethical issues surrounding germ-line gene therapy. There are at least three aspects to the ethical concerns raised. First, that relating to the research of germ-line gene therapy; second, that of the safety of the procedure and its impact on the patient; third, the public policy issues relating to the practice of germ-line gene therapy. The first two questions pose no new ethical concerns. It is the public policy questions regarding the use and misuse of germ-line therapy, both in medical practice and outside of the practice of medicine, with which these guidelines are most concerned.

There are no simple solutions to the dilemmas presented by the practice of germ-

line gene therapy. On one hand, germ-line gene therapy may lead to the eradication of genetic disorders in the human genome; on the other, the line between the elimination of genetic disorders and the genetic enhancement of normal human traits becomes blurred. It is with germ-line therapy that the question of boundaries is most starkly confronted. Once sufficient knowledge has been attained to evaluate the risks to future generations, the question of limitation becomes central. It is in this context that ethics becomes paramount.

Eugenics is widely defined. It accepts within its confines both the enhancement of certain human traits and the reduction of the incidence of certain severe hereditary diseases. It is seen to be either a private issue or a matter for State intervention. A universal response to eugenics in this sense is one of opposition. This is an approach to which people around the world object, because it denies human freedom, devalues some human beings, and falsely elevates the reproductive status of others. In undertaking genetic programs such as carrier screening or biochemical screening in pregnancy, the primary goal must be the welfare of the individuals/couples, not the welfare of the State, future generations or the gene pool.

Eugenics, better termed genetic enhancement, has dogged our history. Nazi Germany is only one example of the pursuit of eugenic goals. There are many current examples, and two are cited below. The government of Singapore instituted a policy of providing financial incentives to 'smart' people to have more babies. The California-based Repository for Germinal Choice, known more colloquially as the Nobel Prize sperm bank, has assigned itself the mission of seeking out and storing gametes from men

selected for their scientific, athletic or entrepreneurial acumen. Their sperm is made available to women of high intelligence for the express purpose of creating genetically superior children who can improve the long-term happiness and stability of human society.

Criticism of genetic enhancement is not invalid. There are many ethical dangers in pursuing genetic enhancement, including increased social inequality and a lowered tolerance for human diversity. Enhancement creates inequality in the competition for social goods such as wealth, status or power in a meritocracy and violates the goals of medicine. In this context genetic enhancement is seen to be a misallocation of scarce resources that would be better placed in serving medical practices. However, it begs the question to state that gene therapy should be limited to medical practices. What are the boundaries of a medical practice? One method of differentiating between genetic enhancement and medical practice lies in the definition of disease, and yet, how does one assess the significance between difference and abnormality?

The question of disease as currently assessed in the realm of clinical genetics is not entirely a hypothetical one. After all, counselors and clinicians have been treating patients for genetic diseases for decades. It is instructive to look and see how they currently define disease and health. Initially scientists took a restrictive view of what constituted a genetic disease. This was expressed in the view that the simplest, most straightforward definition of a genetic disease was a single locus defect, with a 100% heritability. This definition evolved over the years to encompass polygenic traits with less than 100% heritability. The definition evolved further to encompass complex behavioural

traits where the evidence for heritability was less clear. The expanded definition no longer assumes the heritability of the trait. This is easily explained from a scientific basis but from an ethical perspective it may not be advisable to adopt such a broad definition of genetic disease. This definition does not distinguish between medical and non-medical gene therapy.

The purpose of defining disease in the ethical context is to draw a distinction between acceptable and unacceptable gene therapy practices, those practices designed to prevent, correct or alleviate disease being acceptable while all other forms of gene therapy are not acceptable. However, it is not sufficient to delineate health as the basis for distinction. Health, like disease, is not readily ascertainable without reference to an individual opinion. The distinction between 'health' and 'defect' is particularly dangerous when applied to mental or intellectual capacities and behavioral traits - the ideal of a norm 'healthy', against which 'defect' is judged, cannot find a valid place in an eclectic society where diversity of opinion is protected by the most powerful law of the land. There must be other factors that can be used as indicators of what constitutes acceptable gene therapy.

It is recommended that further investigation of the distinction between medical and non-medical therapy be undertaken before gene therapy is considered. It is indisputable that prior to being introduced into medical practice, gene therapy must be ethically acceptable. To find a position which commands acceptance, requires wide consultation. In the interim, germ-line gene therapy should not be contemplated on human subjects. However, we have concluded that the development of safe and effective

means of gene modification, for the purpose of alleviating disease in individual patients, is a proper goal for medical science.

Continuing supervision of gene therapy is necessary. No existing body is constituted for this task. The supervisory body should be of sufficient standing to command the confidence of existing Research Ethics Committees and of the public, the professions and Parliament. It should have a responsibility for:

i. advising on the content of proposals, including the details of protocols, for therapeutic research in somatic cell gene modification;
ii. advising on the design and conduct of the research;
iii. advising on the facilities and service arrangements necessary for the proper conduct of the research;
iv. advising on the arrangements necessary for the long-term surveillance and follow-up of treated patients;
v. receiving proposals from clinicians who wish to conduct gene therapy in individual patients, and making an assessment of:
a. the clinical status of the patient;
b. the scientific quality of the proposal, with particular regard to the technical competence and scientific requirements for achieving therapy effectively and safely;
c. whether the clinical course of the particular disorder is known sufficiently well
▪ for sound information, counseling and advice to be given to the patient (or those acting on behalf of the patient)
▪ for the outcomes of therapy to be assessable;
d. the potential benefits and risks for the patient of what is proposed;
e. the ethical acceptability of the proposal; and
f. the informed consent documents

In the light of this assessment the expert supervisory body should make a recommendation on whether the proposal should be approved, and if so on what, if any, conditions. The supervisory body should also have a responsibility for:

i. acting in co-ordination with existing Research Ethics Committees;
ii. acting as a repository of up-to-date information on research in gene therapy internationally;
iii. setting up and maintaining a confidential register of patients who have been the subjects of gene therapy;
iv. oversight and monitoring of the research; and

v. providing advice to Health Ministers, on scientific and medical developments which bear on the safety and efficacy of human gene modification.

At first, and probably for several years, gene therapy will be applicable to a small number of uncommon disorders and be confined to a few patients. As with other new, specialized medical interventions, it is recommended that it be confined to a small number of centers while experience is gained.

References

Biotechnology Industry Organization. "Biotechnology's Impact on Society." Obtained from the WWW: http://www.gene.com/ae/AB/IE/Biotechnologys_Impact.html

Blowers, Jay. "Scientist Returns Research Grant to Show Concern about Dangers of Genetically Engineered Organisms." Obtained from the WWW: http://www.gene.com/ae/AB/IE/Scientists_Protest.html

Kennedy, Dr. Donald. "Challenges to Public Policy." Obtained from the WWW: http://www.gene.com/ae/AB/IE/Challenges_Policy.html

Kevles, Daniel J. and Leroy Hood, ed. The Code of Codes. Cambridge and London: Harvard University Press, 1993.

Tanouye, Elyse. "Efforts to Repair Fetal Genes Spark Debatre aover Risks, Ethics." The Wall Street Journal 2 April 1996: B1, col 3.

U.S. Department of Agriculture. "To Regulate or Not to Regulate." Obtained from the WWW: http://www.gene.com/ae/AB/IE/To_Regulate_or_Not.html

Wadman, Meredith. "Hyping Results 'Could Damage' Gene Therapy." Nature 14 Dec. 1995: 655.

Ward, Darrell E. "Gene Therapy: the Splice of Life." USA Today Jan. 1993: pp63-66.