Gene therapy for a particular disease like Parkinson's involves ethical principles worked out for other diseases. The major ethical issues for gene therapy (and the corresponding ethical principles) are safety (nonmaleficence), efficacy (beneficence), informed consent (autonomy), and allocation of resources (justice). Yet genetic engineering (germ-line interventions or interventions to enhance human potentialities) raises emotions and fears that might cause resistance to gene therapies. Looking at these technologies in a postmodern perspective helps one to appreciate the issues at stake in social and cultural change with a new technology such as gene therapy. While "modern" technology and ethics have focused on the autonomy of the individual, we are beginning to see a lessening of such emphasis on individualism and autonomy and more emphasis on the health of the population. Such a social change could cause technologies about which society may currently be cautious (such as human genetic interventions) to become more acceptable or even expected.

INTRODUCTION

One would like to think that there are constant ethical principles that might be used as points of reference in making decisions about novel medical therapies. Such principles have been articulated, but advances in technology as well as shifting social norms raise questions about how those principles might best be applied. The possibility of human genetic intervention is one such technology that raises fundamental questions about what it means to be a human being in a social system. It is in the context of such larger questions that the possibility of gene therapy for a particular illness such as Parkinson's disease must be considered (2–4, 16–18, 23).

The are four possible kinds of human genetic intervention as outlined in the following matrix (13):

<table>
<thead>
<tr>
<th>Human Genetic Intervention</th>
<th>Somatic</th>
<th>Germ-line</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cure or prevention of disease</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Enhancement of capabilities</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

1 = Gene therapy
2, 3, 4 = Genetic engineering

I identify cell 1 as gene therapy and distinguish it from cells 2, 3, and 4, which I consider genetic engineering. Gene therapy is conceptually easier to deal with because the principles that govern it are the familiar principles that govern medical therapeutics quite generally. Genetic engineering raises a host of perplexing questions, the emotions of which may influence the consideration of gene therapy.

Somatic cell gene therapy for the cure or prevention of disease does not constitute a major break with medical therapeutics or the ethical principles that govern it. The questions for gene therapy are similar to the questions for other medical therapy and involve specific attention to the safety and efficacy of the therapy and the information required for adequate consent. Larger social questions involve how the therapy will be made available and to whom, as well as the justice of allocation decisions.

THE EVOLUTION OF ETHICAL PRINCIPLES

The ethical principles that guide somatic cell gene therapy are articulated primarily as the principle of beneficence to the patient with its attendant cost-benefit analysis. Autonomy is a principle that is regularly applied in medical therapeutics: the right of the autonomous individual to self-determination. Nonmaleficence, or doing no harm, is a favorite principle of physicians based on the old Hippocratic adage "First do no harm," primum non nocere. Justice is increasingly being considered important, bringing the interests of a larger society into the doctor–patient relationship, particularly in terms of allocation of resources and the economics of medical therapeutics.

All of these principles have one feature in common: they are aspects of what may be recognized as "modern" society, involving certain assumptions about the relationship of members of society to one another. However, those assumptions could change, and indeed many are suggesting that the social order that we have understood as "modern" is giving way to social forms that are
being identified as "postmodern." This change is sometimes referred to as a shift in social paradigms, one feature of which is a loss of the social focus on the individual and more concern for the interests of the larger group or population. In the sense that genetic technology may impact future generations, it may be considered a postmodern technology.

One could say that the principles of beneficence, autonomy, nonmalefiance, and justice are the longstanding, enduring ethical norms that govern medical decision-making. However, it must be recognized that there has been a shifting of emphasis on these principles in recent years. Social forces have reshaped the emphasis on these principles. As we anticipate moving into another social era, we will want to keep a clear eye on the ethical principles that may influence the decision governing the behavior of physicians. Stemming from the Hippocratic tradition, the goodwill of the caring physician dominated medical ethical thinking. The Hippocratic Oath refers several times to the principle of patient benefit and justice, for example, in the third paragraph, "I will apply [treatment] for the benefit of the sick according to my ability and judgment; I will keep them from harm and injustice" (6). Similarly the sixth paragraph says, "Whatever houses I may visit I will come for the benefit of the sick, remaining free of all intentional injustice, of all mischief and in particular of sexual relations with both female and male persons, be they free or slave." Many of the conflicts a physician might face can be understood as internal conflicts to be resolved as matters of judgment for the physician.

Several things that happened in the 1960s began to change the way society thought about medical ethics. New technologies began to emerge, notably organ transplantation and the prospect of artificial organs, the possibility of genetic engineering, artificial life support, many surgical advances, and the development of sophisticated medical centers where research and therapy often went hand in hand. These advances offered many benefits, but certain risks. It could no longer be assumed that a patient would necessarily want what the doctor had to offer. Explicit informed consent was required as opposed to the implicit consent that might accompany the treatment of infections or palliative symptomatic treatment.

Evolution of Ethical Priorities:

<table>
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<tr>
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<tbody>
<tr>
<td>Beneficence</td>
<td>Autonomy</td>
<td>Social justice</td>
</tr>
<tr>
<td>Autonomy</td>
<td>Beneficence</td>
<td>Autonomy</td>
</tr>
<tr>
<td>Social justice</td>
<td>Beneficence</td>
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</tr>
</tbody>
</table>

Prior to the mid-1960s with the upswing in interest in medical ethics, later to be called bioethics, the principle of beneficence was the primary ethical prin...
The rationale for informed consent was the right to self-determination of the autonomous person; hence, autonomy came to the forefront as the primary principle to be considered. Autonomy became important not only in medicine, but also as part of a much larger social shift occurring at that time with the emergence of the consumer movement and the civil rights movement. The beneficence of the physician, recently a hallmark of medical virtue, came to be seen by many as paternalistic. Medicine (or more inclusively, health care) was rapidly becoming a commodity.

Issues of social justice were rarely considered, although the cost of high-technology medicine made the allocation of scarce resources an increasingly important issue. The hope of maintaining high-quality, high-technology health care for all gradually began to fade. The allocation questions began to be formulated as questions of distributive justice.

The other ethical principle that has received attention has been the principle of nonmaleficaence. It is essentially a derivative of the Hippocratic slogan, primum non nocere, "First do no harm." It merits consideration because it is so deeply ingrained in the medical culture and so often serves as a reference for physician decision-making in morally ambiguous situations.

WHEN IS IT ETHICAL TO BEGIN GENE THERAPY?

Novel therapy involves a calculation that the expected benefits outweigh the possible risks. Since such a calculation can never be precisely quantified, certain judgments must be made at a number of levels. Most immediately the appropriate Institutional Review Board must review the protocol and the written consent. Next the subject of the investigation must review the consent to determine that his or her wants and interests are likely to be met. Beyond the formal requirements, the investigator must ensure as a matter of conscience that adequate information is provided for the subject to make an informed, voluntary, and competent decision.

Beginning with the Nuremberg Code (20), attempts have been made to systematically articulate the ethical principles and constraints involved for investigators doing research with human subjects. Rule 3 of the Nuremberg Code articulates the important principle that human experimentation must be preceded by appropriate animal trials.

The experiment should be so designed and based on the results of animal experimentation and a knowledge of the natural history of the disease or other problem under study that the anticipated results will justify the performance of the experiment.

Anderson and Fletcher (3) have delineated three minimum ethical requirements that must be met in animal studies before gene therapy might be under- taken in humans: First, the new gene should be put into the proper target cells and should remain there. Should the gene enter other cells, it should be shown that its presence (or the presence of a gene product) does not damage the nontarget cell.

Second, the new gene should be regulated appropriately in the target cells. The gene’s product should be made in amounts that are sufficient to correct the genetic defect but not so large as to have a detrimental effect.

Third, the presence of the new gene should not harm the cell. Inserted genetic material should not produce mutations in the organism, interfere with regulatory pathways with the cell, or otherwise adversely affect critical cell functions.

It should be noted that exceptions to these principles may be permissible for critically ill subjects. Yet it is precisely those patients with lethal or extremely serious genetic diseases that may lead investigators to be tempted to undertake promising, but not fully tested, new regimens.

THE UNIQUENESS OF ETHICAL CONSIDERATIONS INVOLVING HUMAN GENETIC INTERVENTION

Gene therapy may be conceptualized as similar to other medical interventions and thus involves no unfamiliar ethical considerations. Genetic engineering raises the specter of altering the species and hence raises certain anxieties about irreversible changes, crossing a threshold that admits no return. Such nodal points are often considered slippery slopes, a metaphor that does not deter the intrepid, but does signal caution for those of a mind to be cautious (8, 14).

In the remarks that follow, I examine the nodal point of the first genetic interventions to try to bring into focus the values that may be at stake in crossing the boundary. At present, social consensus would suggest a green light for gene therapy of somatic cells on the basis of ethical principles that have received careful consideration in recent decades. It appears that there is no such social consensus at this time for genetic engineering, whether of somatic cells or germ cells. Indeed much the opposite is the case. There is much opposition to the idea of genetic engineering.

Social consensus being what it is, i.e., political and subject to change, I try to bring the issues into focus by considering what might change the red light to a green light, what might bring about a change from prohibited to permissible or even expected. As a useful example of what a genetically engineered world might look like, I cite a fascinating article by J. Hughes called “Embracing Change with All Four Arms: A Post-humanist Defense of Genetic Engineering” published on the home page of MacLean Center for Clinical Medical Ethics on the Internet (11). Hughes juxtaposes the alarmist attack of the coming gene age as represented by Jeremy Rifkin (“Once we decide to begin the process of human
ANTICIPATING THE POSTMODERN FUTURE

Medical technology brings medicine to the crossroads of the physician's ambition and ethical obligations to alleviate human suffering and the technological, even narcissistic, society's ambition for human perfection. At the least the physician works to alleviate suffering within an ethical tradition. But at the same time there are many possibilities for the physician to become merely a technician dispensing goods and services in the marketplace. Even worse is the possibility of an authoritarian society allowing or requiring those technologies to be used for political ends.

Both advances in medical technology and changes in societal forms (such as proliferation of visual images in the media or anonymous communication on the Internet) have the potential for changing the assumptions about what it means to be human and how humans do or should interact with one another. As the 20th century draws to a close, social commentators (7, 9, 12, 15) are identifying new social paradigms. These are variously identified as "postmodern," an historical epoch observing itself in the process of change.

What the postmodern future will hold has yet to be determined. In fact, there are several postmodernisms so far identified. For some, postmodernism is a liberation from restraints of tradition, an opportunity to start over, a shattering of old conventions, of form, of language, and of epistemology, particularly the epistemology of objectivist science.

For others postmodernism is a more humanistic reconnection with the traditions of the past, a linkage with the human forms and styles that prevailed before the more sterile mechanisms of the modern era. The disciplines of art and architecture help us appreciate this linkage most clearly. Premodern buildings were human in scale and served human functions. Windows and doors were in human proportion. Buildings were ornamented as the human body might be adorned. Large buildings, such as the medieval cathedrals, brought communities together and emphasized the relationship between man and God, earth and the above. Modern architecture stripped buildings of their ornamentation, emphasized their function, and often forced the humans who occupied them (small and impersonal) to adapt to the mechanism. Postmodern architecture, recognizable in every urban landscape, brings back the ornamentation of old, often in an exaggerated scale through the use of oversize arches and pediments, and attempts to find a place for human interaction through interior courtyards and alcoves.

Postmodern art follows a similar progression. The human themes of classical art disappeared in modern art. Abstract expressionism involved color and form, but not human representation, which was to be reintroduced in postmodern art.

One of the features of postmodern architecture is the relationship of one building to its environment, the "conversation" with what has preceded it and what surrounds it. Perhaps one of the most exciting postmodern solutions is the new Sainsbury Wing of Britain's National Gallery in Trafalgar Square designed by Philadelphia architects Robert Venturi and Denise Scott Brown. The original National Gallery is in the classical style with a facade much like the Parthenon. Proposals for a modern wing drew huge protest, quotable from Prince Charles himself who called one proposal "a carbuncle on the face of a much beloved friend." The Venturi–Scott Brown design (to the left of the main gallery in Fig. 1) harmonizes respectfully, but whimsically, with its classical, premodern neighbor. It has Corinthian columns for ornamentation, but not for support. It has pediments, arches, and window frames, humanly scaled, even where there are no windows.
So the future is very much up for grabs, but it can be said that the modern age has certain recognizable features and that the modern age is historical; i.e., it has ended or at least is drawing to a close. If that assumption is correct, it is worth looking at what those features were, why they might have been important to us, and what we might wish to preserve or discard. If the postmodern future is yet to be determined, we should make some decisions about what is at stake and how we might like to influence the direction in which things are moving.

One of the things that can be said about modern medical ethics is that it is focused on the individual. The centrality of autonomy in bioethics is a reflection of the importance modern (Western) civilization has placed on the individual. One of the things we might anticipate changing is that individualism. We might become, for example, more concerned with the health of the population (public health) than the health of the individual. This change could be economic and probably will be economic. For example, genetic alteration might be given strong economic incentive if the cost of treating a genetic anomaly (let us imagine addictive propensities) outweighed the cost to society of altering such traits genetically.

Such a shift in focus could very well change the social consensus about gene therapy, not only somatic cell gene therapy for the cure or prevention of disease, but most especially germ-line therapies or manipulations. And if gene therapies were technologies whose distribution were to be determined by market forces, the logic and rhetoric of which so often drive the distribution of medical services in this era, then we would be talking about the distribution of technologies according to desirable traits, i.e., genetic engineering for the enhancement of capabilities.

The possibility of genetic therapy and engineering brings us face to face with ourselves as individuals and as a culture in terms of how we value technology and the value we place on human life. Or to say the same thing another way: our relationship to technology—positive or negative—including genetic technology—defines how we value humanness. The prospect of genetic engineering helps put the relationship between our humanness and our technology in perspective. In genetic engineering, the machine that is engineered is the engineer. Mankind or potentially personhood is what is changed. And with that change goes the possibility of revaluing the ambiguities of humanness. Cultural values and cultural consensus could change—or should we say have changed—with those new realities.

It is the prospect of genetic engineering that helps us appreciate what it means to be human: It means to be mortal, to be imperfect, to be flawed. It also means to wish to be better.

REFERENCES


