

7.3.6 Research in Gene Therapy & Genetic Engineering

Gene therapy involves the replacement or modification of a genetic variant to restore or enhance cellular function or to improve response to nongenetic therapies. Genetic engineering involves the use of recombinant DNA techniques to introduce new characteristics or traits. In medicine, the goal of gene therapy and genetic engineering is to alleviate human suffering and disease. As with all therapies, this goal should be pursued only within the ethical traditions of the profession, which gives primacy to the welfare of the patient.

In general, genetic manipulation should be reserved for therapeutic purposes. Efforts to enhance “desirable” characteristics or to “improve” complex human traits are contrary to the ethical tradition of medicine. Because of the potential for abuse, genetic manipulation of nondisease traits or the eugenic development of offspring may never be justifiable.

Moreover, genetic manipulation can carry risks to both the individuals into whom modified genetic material is introduced and to future generations. Somatic cell gene therapy targets nongerm cells and thus does not carry risk to future generations. Germ-line therapy, in which a genetic modification is introduced into the genome of human gametes or their precursors, is intended to result in the expression of the modified gene in the recipient’s offspring and subsequent generations. Germ-line therapy thus may be associated with increased risk and the possibility of unpredictable and irreversible results that adversely affect the welfare of subsequent generations.

Thus in addition to fundamental ethical requirements for the appropriate conduct of research with human participants, research in gene therapy or genetic engineering must put in place additional safeguards to vigorously protect the safety and well-being of participants and future generations.

Physicians should not engage in research involving gene therapy or genetic engineering with human participants unless the following conditions are met:

- (a) Experience with animal studies is sufficient to assure that the experimental intervention will be safe and effective and its results predictable.
- (b) No other suitable, effective therapies are available.
- (c) Gene therapy is restricted to somatic cell interventions, in light of the far-reaching implications of germ-line interventions.
- (d) Evaluation of the effectiveness of the intervention includes determination of the natural history of the disease or condition under study and follow-up examination of the participants’ descendants.
- (e) The research minimizes risks to participants, including those from any viral vectors used.

- (f) Special attention is paid to the informed consent process to ensure that the prospective participant (or legally authorized representative) is fully informed about the distinctive risks of the research, including use of viral vectors to deliver the modified genetic material, possible implications for the participant's descendants, and the need for follow-up assessments.

Physicians should be aware that gene therapy or genetic engineering interventions may require additional scientific and ethical review, and regulatory oversight, before they are introduced into clinical practice.

Principles of Medical Ethics: I,V,VII

Background report(s):

CEJA Report 3-A-16 Modernized *Code of Medical Ethics* CEJA

Report D-I-92 Prenatal genetic screening

Report of the Judicial Council Dec 1983 Genetic counseling

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CEJA Report D – I-92 Prenatal Genetic Screening

BACKGROUND

The Human Genome Project

The Human Genome Project, begun recently, is part of an international effort to expand current genetic knowledge. According to James Watson, director of the National Center for Human Genome Research, the ultimate goal of the project is the construction of a detailed map of human chromosomes.¹ Each DNA base pair in the human genome would be identified and catalogued. Currently researchers are striving to improve DNA sequencing techniques and technologies to quicken achievement of this goal, which is estimated to take approximately 10-15 years and cost about 100 million dollars annually.^{1,2} The knowledge expected to be gained from the project could prove useful in at least two aspects: 1) it could aid in the identification and cure of disease at the genetic level, and 2) it could expand the understanding of genetic influences on human behavior.

Significantly, of the total funding for the project, a percentage has been designated for its ethical evaluation.⁴ Prominent among the ethical issues implied by the project is the appropriate use of new information about the genome and new procedures developed for genetic analysis and manipulation.^{2,5-7} Predictions vary about the amount of information that will be reaped from the project and the extent to which the new information will contribute to knowledge about disease and behavior. Some believe that the project will moderately improve the ability to diagnose and treat disease; others believe it will reduce miraculous solutions to longstanding medical and social problems.⁴ Already, a considerable number of commentators have offered their views on the Human Genome Project. It is clear that the Human Genome Project has the potential to alter radically concepts of human nature and relationships and to test society's commitment to egalitarian ideals.^{2,4}

In this report, the Council will consider ethical issues related to prenatal genetic screening, the examination of the genetic makeup of a fetus or pre-embryo. Currently, prenatal screening is performed through amniocentesis or chorionic villi sampling during fetal gestation, or through examination of a pre-embryo at the pre-implantation state of artificial reproductive techniques. If a genetic defect is discovered, it cannot be corrected; the parents can avoid the defect only by aborting the fetus or discarding the pre-embryo. In the future, other methods for prenatal genetic screening may develop, and it may be possible to correct genetic defects through manipulation. As much as possible, this report concentrates on the ethical dimensions of existing genetic screening practices. However, genetic technologies are developing at a rapid rate, and will in all likelihood develop even faster as the human Genome Project progresses. As technology advances, scientists hope to examine and understand the human genome in ever increasing clarity and detail. Many commentators recognize a possibility that increased understanding of the genetic component of human characteristics may one day make it possible to alter human traits through manipulations at the genetic level. Clearly, future developments in genetic technologies will require close scrutiny to assess their potential social impact and ensure their ethical use. It is in recognition of this need for scrutiny that the Council, in addition to examining current practices, also explores some of the possible future uses of current and emerging genetic technologies, particularly those that relate to genetic manipulation.

Prenatal genetic screening is still an emerging technique. Even though the Council offers this report to inform physicians about the ethical dimensions of prenatal genetic screening, its recommendations on future practices must be seen as only preliminary. No one can predict with certainty the results of scientific research, particularly in a relatively young field like human genetics. As genetic technologies

advance in the coming years, further consideration of the ethical application of those technologies will inevitably be warranted.

Current Abilities to Select or Manipulate for Genetic Disorders and Traits

When couples suspect they are at high risk for having a child with a genetic disease, they may respond to the risk in one of four ways. They may choose not to reproduce at all, to accept the risk and reproduce anyway, to undergo prenatal diagnosis for detectable disorders and possibly abort an affected fetus, or to reproduce with the aid of artificial reproductive technologies.⁸

When artificial reproductive technologies are used, an affected child can be avoided in a number of ways. A couple may use artificial insemination or surrogacy in order to have a child which is biologically related to one parent but would not inherit the undesired gene from the other parent.^{9,10} Couples may undergo in vitro fertilization, or make use of other reproductive technologies where the gametes or zygotes may be examined in vitro, and discard the gametes or zygotes which would result in a child with a genetic disorder.¹¹

Generally, the ability to detect a genetic abnormality precedes the ability to correct the abnormality. Consequently, when a fetus or pre-embryo is found to have a genetic abnormality, abortion or rejection may be required to avoid having an affected child. Genetic selection is a term commonly used to refer to abortion of the fetus or, in the case of in vitro fertilization (IVF) procedures, rejection of preimplanted embryos.

Currently, selection is used for control of a number of genetic diseases, including Down's syndrome and Tay-Sachs disease. The possibility of selecting for benign (i.e., non-disease-related) genetic traits is more hypothetical and is currently limited essentially to sex selection.¹¹⁻¹⁴ Both prenatal diagnosis and in vitro analysis identify the sex of the fetus in most cases, thus creating the possibility of aborting fetuses of the undesired sex. In some cases, sex selection is performed to be able to avoid the birth of a male infant with an X-linked disorder.¹⁵ However, the ability to select for sex also allows for the possibility of doing so for non therapeutic reasons.

Genetic manipulation, the alteration of genetic material through gene therapy or other means, is in the early stages of investigation.³⁻⁵ Gene therapy is the replacement or repair of an undesired gene with a desired gene,¹⁶ and may provide a promising treatment for genetic disorders resulting from a single gene defect.^{16,17} Gene therapy has been attempted with encouraging results for few disorders, such as cystic fibrosis, adenosine deaminase deficiency and advanced, melanoma.^{18,19} It is also theoretically possible at the pre-embryo level.^{11,20} In addition, although resources have been focused on the diagnosis and cure of genetic diseases, gene therapy could potentially be used to alter benign genetic traits.

Fundamental Ethical Issues

Since physicians will lay a critical part in the future application of reproductive genetic technology, it is important for the medical profession to define its role in the overall process. It is also important for the profession to consider the potential social effects of genetic technology when defining its role; genetic technology will have a major impact on all of society. Several ethical issues present themselves.

The Role of Parental Choice

One underlying ethic I issue is how to balance the rights of individuals to make choices about the health and characteristics of their children against social values and needs which may be in conflict with individual preferences.²¹ Traditionally, parents have been given great (but not unlimited) latitude in

making decisions regarding their children. In some cases, individuals may make choices for their children which others may regard as wrong, but which are not prohibited because of the larger interest in preserving choice in general. The dilemma posed by new genetic technologies is the question of how far parents' authority over their children should extend, and in particular as to how completely parents should be able to control the genetic composition of their child.

Selective Abortion

A second issue is the appropriate role of selective abortion. Several genetic disorders can be detected *in utero* but do not have satisfactory treatment or cures. Presently, the detection and elimination of genetic disorders generally relies on a combination of prenatal diagnosis plus abortion of an affected fetus. Many individuals, regardless of their views regarding abortion, consider prenatal diagnosis plus abortion a less than optimal solution to the problem of genetic disease.²²⁻²⁷

Modifying the Human Genome

Even if abortion (or rejection of pre-embryos) is not used to avoid disease, many ethical questions remain about the use of genetic technologies to modify the genes of a fetus or pre-embryo.^{2,27-31} Genetic manipulation introduces larger questions about the potential effects of genetic technologies on human relationships, questions that also exist with abortion or rejection of pre-embryos.

Uncertain Future Developments

A final issue is the difficulty inherent in providing ethical guidelines for use of a technology which is still in its rudimentary stages. The depth of information which will come out of the Human Genome Project is uncertain, as well as the extent to which it can be applied to select for and manipulate human genes.⁴ There is little direct empirical evidence to predict how genetic technology will be used, complicating attempts to formulate ethical guidelines for its use.

DEFENSES OF THE USE OF GENETIC REPRODUCTIVE TECHNOLOGIES FOR SELECTION AND MANIPULATION

Elimination of Disease

A primary goal of genetic selection and manipulation is to increase the capacity to diagnose, treat, and eliminate disorders which are genetically caused.^{2,3} Of the 4000 known genetic disorders,³ several already can be detected through prenatal testing and others may be identified through analysis of pre-embryos.³² Genetically detectable disorders include Tay-Sachs disease, cystic fibrosis, Duchenne muscular dystrophy, Lesch-Nyhan syndrome, Down's syndrome, and sickle cell anemia.^{11,33,34} Some of these disorders involve substantial functional abnormality, suffering, and early death. Being able to avoid or effectively to treat such disorders would of course be highly desirable.

Improvement of Individual

It may be possible to enhance a person's intellectual or physical abilities through genetic manipulation. While such a use of genetics would be highly problematic, some view it as a natural extension of nongenetic efforts to improve personal capacities. Society considers it acceptable to improve individual abilities through behavioral modification, instruction in the schools, and other approaches; genetic manipulation might be a more effective way to accomplish the same goals. In addition, it is argued, if it is permissible to use genetic technologies to improve intelligence by avoiding mental retardation, then it should be permissible to improve intelligence to achieve wisdom.

Reproductive Choice

Increased ability to understand the genetic causes of diseases and traits may also enhance reproductive choice. Many couples at high risk for having a child with a genetic disorder previously might have foregone reproduction due to the risks. Now they may be willing to have children.³⁵ Also, for a large number of women, the actual likelihood of having a child with a genetic disorder is relatively small, and the results of prenatal genetic testing could provide reassurance for them.³⁵ Furthermore, increasing abilities to select or manipulate for specific diseases or traits may expand parents' potential control over the health, appearance, or talents of the child.

Early Detection

Early detection of genetic disorders gives parents the time to prepare for the birth of an affected child, both emotionally and in terms of the medical, financial, and other resources needed.

OBJECTIONS TO THE USE OF GENETIC REPRODUCTIVE TECHNOLOGIES FOR SELECTION AND MANIPULATION

Judicious Use of Societal Resources to Improve Health

Most objections or warnings against using reproductive genetic technology to improve overall health anticipate the misuse of genetic technology. However, apart from the issue of misuse, expenditures on new genetic technologies may be an inefficient use of scarce societal resources.^{4,23,27,28} Currently, use of genetic technology is expensive and is unlikely to become easily affordable in the foreseeable future. The ethical principle of justice requires that the distribution of benefits and burdens be done in a fair manner. Under the current system of access to genetic technology, the benefits will primarily accrue to a relatively small number of people.² It may not be justifiable to concentrate resources on a technology which will benefit few if it is at the expense of resources which would provide a more general benefit to health if concentrate elsewhere.²

This consideration becomes more serious in light of uncertainty regarding the possibility of ultimately curing or eradicating genetic disease.^{3,4} Development of genetic technology is likely to be time-consuming, and may not result in optimal or even significant reduction of disease. Some disorders are likely to remain extremely difficult to treat or cure.³ It may not be appropriate to devote resources to speculative improvements in overall health when other solutions are known but lack sufficient resources.

Potential for Exacerbation of Discriminatory Practices

Potential for misuse of genetic technology for discriminatory purposes comes from several sources. One is misinterpretation of data, particularly if the misinterpreted results are used as a reason to punish individuals or eliminate them from the gene pool. An example of this danger is seen in the early interpretation of the significance of an XYY chromosome.^{2,36} Early investigation of XYY males seemed to show that they were more prone to criminal behavior than XY males. For several years, the public and some physicians eagerly embraced the idea that some violent behavior could be avoided by identifying males with XYY chromosomes and trying to alter their behavior. For a brief time, a legal defense to criminal behavior, the xyy defense, was formulated in the hope that it would mitigate the penalties for violent behavior.³⁶ Eventually, the connection between xyy chromosomes and behavior was found to be too tenuous to withstand scrutiny as a legal defense or to justify screening programs or reeducation efforts.

A second potential source of discrimination is genetic selection and manipulation in favor of characteristics which should be irrelevant in an egalitarian society. Most immediately problematic are choices or preferences that reinforce invidious discriminatory practices (e.g., choices based on beauty or height).

Sex selection is the most evident example of the discriminatory potential of selection for benign genetic traits. Despite increasing societal equality of men and women, even recent studies show a marked preference for male children in general and especially for male first-born children.³⁷⁻⁴² Sex selection is problematic for several reasons: it implicitly fosters the value of one sex over the other; it confirms that sex is a governing factor in how humans behave; and it treats gender, a genetic trait, as a disease.^{43,44} Sex selection might result in significant disruption of usual social relationships, and discrimination and violence against women might increase.^{37,45} It may be true that not every instance of non therapeutic sex selection would be sexist.⁴⁶ Some sex selection may be motivated by a desire to have children of both sexes, each valued equally. Still, sex selection must be considered a dangerous practice both because of the possible negative social impact on women's status and because of arbitrary and ethically unacceptable motivations.

Even when genetic selection is appropriate, it may have some adverse discriminatory consequences. Selection on the basis of genetic disease could increase negative attitudes toward the disabled in a manner similar to attitudes toward women under sex selection. The number of disabled individuals may decrease to levels where the needs of those remaining are not given attention or sufficient priority in resource allocation.^{2,23,27} Some commentators have observed that active elimination of all genetic disorders from populations sends a profoundly devaluing message to individuals who have the diseases which are being eliminated.^{2,23} It may be difficult to maintain a general social structure in which people are valued on an individual basis, for their potential and achievements, while some people have disorders which are being eradicated from the gene pool. Also, the range of general diversity of genetic characteristics may be limited to the critical point where appreciation of similarity overpowers the appreciation of difference and fuels further discrimination.

Eugenics

Many discussions about the future of genetic technologies include consideration of human eugenics, the improvement of hereditary qualities or traits through genetic selection and manipulation. The immediate concern for most is not that the advancement of genetic technology would necessarily lead to compulsory eugenic programs, although some fear that may be an ultimate result.^{27,31} Rather, most fear a subtle or passive eugenics brought about through a combination of social pressures. These social pressures could include disapproval or shame for parents who have an affected child or who fail to maximize their child's genetic capacities.^{27,31} In addition, lack of social and economic support for the disabled might dissuade parents who would otherwise bear and raise an affected child from choosing to reproduce.

With existing technologies for selection, it is already true that decisions about life and an individual's worth are made on the basis of genetic factors. This may constitute extremely dilute but acceptable form of eugenic selection. However, even is limited selection, usually based on eliminating the most severe genetic diseases, makes many individuals uncomfortable. This discomfort probably reflects the belief that eugenics may be inherently an unacceptable philosophy, even if pursued voluntarily. Some fear that genetic selection and manipulation may set us on a slippery slope in which genetic intervention, once begun, would eventually lead to the alteration of humanity itself through maximization of select genetic traits.⁴⁷ Given the lack of empirical evidence of how people would deal with advancing genetic technologies, it is difficult to evaluate such speculations. Still, the fact that present practices can be seen as precursors to more extreme scenarios indicates that the possibility of voluntary or passive eugenics should be included in evaluations of genetic reproductive technology.

There is also the prospect of a more limited eugenic tendency based on class or cultural factors. If access to genetic technologies is dependent on individual wealth, then the more well-off financially could also become the more healthy overall. Also, individuals from different cultural backgrounds, regardless of economic class, have different definitions of health, sickness, and treatment. Some cultural groups may not consider genetic origins of disease to be important. Concern has been expressed that certain classes or groups may be excluded from the health benefits accruing to others, relegated to the fringes of society, and consequently made more vulnerable to elimination through eugenics.

Treating Children as Products: A Consumeristic View of Reproduction

In general, children are regarded and valued as autonomous beings, subject to the limitations of their particular developmental and cognitive capacities. Wide leeway is given to parents concerning child-raising because it is believed that they are in the best position to assess and act on the needs and best interests of the child. However, parental control is subject to limitations. Children are legally subject to parental authority only until the age of majority, children must be given an education, and the state can intervene to protect children in a variety of situations. For instance, a parent cannot refuse a life-saving care or intervention for a child based on the parent's own religious beliefs.⁴⁸

New genetic technologies suggest the possibility that parents will one day be able to control many aspects of their child's genetic makeup. If parents use genetic technologies of selection and manipulation to affect benign traits, such as sex or height, it is not clear that they are acting in the best interests of their future child.⁴³ Although it is reasonable to assume that children would prefer to be free of disease, persons' preferences concerning benign traits or characteristics will depend on their own particular values. Consequently, decisions about traits or characteristics may not always be best left to parents.

A further consequence of using selection and manipulation to enhance benign traits is that it may dehumanize the reproductive process by treating fetuses as products rather than as potentially autonomous human beings.^{28,30} Subjecting a child's core physical appearance and potential talents to the whims of its parents impinges on the child's ability to develop an autonomous self. Allowing parents to manipulate a child's most basic characteristics fosters a consumeristic attitude toward a child's development and personatilty.^{2,5,24,28,30,43}

The Voluntary Nature of Prenatal Selection

Despite common perc ptions to the contrary, new reproductive genetic technologies may not chance the voluntariness of reproductive choices.^{21,27,28} Even without formal coercion through government mandates to participate in selection technology or to make particular choices, other influences and pressures can make some options much more difficult to choose than others. While a couple may not believe in genetic manipulation or abortion and therefore prefer to raise a child with a genetic disability, social constraints such a societal, familial, and peer pressure may deter them from exercising their own preferences.^{23,27,31} Furthermore, the development of genetic technology may increase parents' feelings of guilt or responsibility for bearing an affected child.^{22,27,31,43} Some commentators have suggested that parents should not be able to attempt reproduction if there is a risk of genetic disease in offspring, and that the parents be held liable if they do produce a child with a genetic disorder.^{49,50}

ROLE OF MEDICINE IN APPLICATION OF REPRODUCTIVE GENETIC TECHNOLOGIES

Participation in some aspects of genetic technologies for selection and manipulation is antithetic to the professional role of the physician as care giver and provider of therapeutic benefit. In addition to

undermining this traditional role, this practice can also lead to social harm, primarily in the form of discrimination based on gender or other characteristics.

Definition of Physician's Role

The provision of therapeutic benefit lies at the core of the physician's professional role. Although the physician may typically perform auxiliary functions during the course of the physician-patient relationship, these functions are secondary to the primary goal of preventing or treating disease. It is the presence of or potential for a disease state which generates this relationship. It is specifically in response to the illness that the physician reacts, striving to reduce harm and suffering while also trying to restore the patient to a state of both psychological and physiological health. Technology often serves as the physician's assistant in performing the central aspects of the professional role, providing medical benefit.

In recent years, there has been a broadening of the physician's professional role with greater recognition of the factors that can affect a person's sense of well-being. For example, physicians employ cosmetic surgery to improve a person's psychological health. As the physician's role extends beyond traditional concepts of disease, great care must be taken to ensure that the practice of medicine is not misused.

Genetic Selection and Prenatal Diagnosis

Given the therapeutic focus of the physician's role, it is inappropriate for physicians to participate in nonmedical uses of information gleaned from prenatal testing. The use of genetic technology to avoid the birth of a child with a genetic disorder is in accordance with the ethical principles associated with physicians' therapeutic role. However, selection for non-disease-related traits would be inappropriate. Selective practices, such as sex selection, may result in lasting social harms, such as the exacerbation of discrimination, a tendency to view children as products, and eugenics. Recognizing the potential for social harms, the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research strongly discouraged the use of prenatal diagnosis for sex selection, stressing the need to confine prenatal diagnosis to "seeking genetic information in order to correct or avoid unambiguous disabilities or to improve the well-being of the fetus."⁴³(p.58)

Selection to avoid genetic disorders would not always be appropriate. Abortion because of genetic disease is most understandable when the disease would have serious manifestations, such as with Tay-Sachs disease, Down's syndrome or Huntington's disease. Conversely, selection becomes more problematic as the effects of the disease become milder and as they become manifest later in life.⁵¹ For example, the justification for abortion would be weaker if the purpose is to avoid a disorder which does not prevent a full life span and for which medical therapy can achieve good control of complications until late in life. It is not possible to indicate precisely when a disease would not be serious enough to justify prenatal selection. Any such situations are only hypothetical at this time, and other factors would affect the acceptability of selection. For instance, over the next several years, it may become possible to make prenatal genetic diagnoses earlier during gestation.⁵² Just as the justification for abortion weakens as the disease to be avoided becomes milder, the objection to abortion becomes weaker the earlier during the pregnancy that it occurs. Abortion at the pre-embryo stage of development is less problematic than abortion after viability.⁵³ In deciding whether genetic selection is acceptable, then, a number of factors need to be considered: the severity of the disease, the probability of its occurrence, the age at onset, and the time of gestation at which selection would occur.

The potential use of prenatal diagnosis for the purposes of selection urges caution to physicians practicing in that area. In counseling women or couples about prenatal diagnosis, physicians should discuss the ethical issues involved and indicate when and for what purposes it is appropriate to employ prenatal

diagnosis. Physicians should make clear to patients their opposition to benign trait selection and discourage testing of fetuses when it is clear that inappropriate selection is the sole motive for the testing request.

There are limits to how far physicians' counseling efforts can go in discouraging inappropriate selection. Physicians cannot always be certain about parents' motives, and excessive second-guessing of parents' wishes could jeopardize the trust so crucial to the physician-patient relationship. Physicians' efforts alone can not ensure that inappropriate selection will never take place. Rather, prevention of inappropriate selection ultimately depends on societal educative efforts that promote appreciation of genetic diversity as an important component of egalitarian ideals.

Some observers believe that, aside from misuse of prenatal diagnosis findings, overuse of prenatal diagnosis presents dangers of its own. Reasons include possible risks to the fetus from invasive testing techniques, a reduction in women's reproductive freedom as a result of increased professional or societal "management" of pregnancies, and the imposition of unwarranted levels of stress and anxiety on pregnant women who do not have an elevated risk of passing on a genetic disorder. In cases involving couples whose medical histories and family backgrounds do not indicate an elevated risk of fetal genetic disorders, performance of prenatal diagnosis may not be desirable. The physician should inform such couples of their statistical probability of having an affected fetus, and warn them of the chances of damage to the fetus or spontaneous abortion. Women without an elevated risk of genetic disease can legitimately request prenatal diagnosis, provided they understand and accept the risks involved.

If prenatal diagnosis is performed, the principle of patient autonomy requires that all medically relevant information generated from fetal tests be passed along to the parent or parents. While the physician should generally discourage requests for information about benign genetic traits, the physician may not ethically refuse to pass along any requested information in his or her possession. The final decision as to what information is deemed appropriate for disclosure can only fall to the parents, informed by the facts and recommendations presented to them by their physician.

Genetic Manipulation

At the present time, selection through abortion or discard of preimplanted embryos is the only way to avoid the effects of an undesired gene that has been detected through prenatal diagnosis. In the future, however, genetic manipulation may allow correction of an undesired gene without the need for abortion or discard.

Treatment of Genetic Disease

The use of genetic manipulation to avoid disease is consistent with ethical principles. The tools of medicine are designed to prevent functional abnormalities, such as occur in Tay-Sachs disease, Down's syndrome or cystic fibrosis, and the fact that genetics are used, rather than surgery or antibiotics, does not make the treatment unacceptable. Genetic manipulation in this instance would be a legitimate extension of the physician's preexisting and fundamental duty to combat disease.

Debate continues over whether only somatic-cell gene therapy should be used to combat disease, or whether germ-line therapy could also be used. In somatic-cell therapy genetic alterations affect only the fetus at hand; in germ-line therapy, alterations would be inherited by the fetus' future offspring as well. At least two reasons initially suggest that genetic manipulation should be limited to somatic cells only. First, the profound impact of germ-line manipulations in future generations requires that we proceed with extreme caution. Until all the effects of a genetic manipulation, both long and short-term, are completely certain, germ-line manipulations should not be attempted. Second, germ-line manipulations give parents

unprecedented control over the lives of multiple generations of descendants. Such far-reaching control would curtail the autonomy of future generations, limiting their control over their own lives and restricting the decisions they can make about their own children. Parents' ability to extend authority beyond their own immediate offspring is already restricted in property law, in which individuals are prevented from dictating the fate of their estate in perpetuity. If society has an interest in protecting future generations' autonomy in property matters, it may very well have an even stronger interest in protecting that autonomy in matters of genetic control over offspring. Initially, then, it would seem appropriate to limit genetic intervention to somatic cells only, though further consideration of this issue may be advisable in the future.

There may be exceptional situations in which genetic manipulation would not be appropriate to treat or cure disease. Occasionally genetic manipulation might harm the fetus in some way, even if it were successful in treating the targeted disease. For instance, the manipulation might damage or interfere with other genes, which in turn could cause increased susceptibility to a serious illness, impairment of mental or physical faculties, or other adverse effects. At some point, the potential adverse effects would be so serious that it would no longer be appropriate to assume that the future child would prefer the intervention.

Benign Trait Manipulation

When genetic technology would be used to change characteristics that are not disease-causing, the dangers of abuse discussed in this report require that extreme caution be exercised. In general, it would not be appropriate to use genetic technology to manipulate a fetus' or pre-embryo's traits or characteristics. Such manipulation risks the severe adverse consequences discussed earlier: exacerbation of discriminatory practices, the commoditization of children, and the prospects of repugnant eugenic practices. These considerations counsel against genetic manipulation of benign characteristics.

Nevertheless, there may be some very exceptional circumstances in which genetic manipulation would be reasonable. Society already employs a number of strategies to improve the abilities or characteristics of its citizens. For example, the education system generally aims at improving the lives of citizens by making them more intelligent and more socially responsible. Parental choices of schools and extracurricular activities are often designed to maximize the capacities and life chances of their children. Individual self-improvement of all kind is generally viewed as both laudable and one of the distinguishing capacities of human beings. These considerations suggest that, under certain circumstances, genetic manipulation could be justified as an extension of society's, parents', and individuals' continuing efforts to enhance the capacities and improve the lives of citizens.

It is difficult to say whether in fact genetic manipulations can be justified as extensions of current practices. Such manipulations are still speculative, and the mechanism by which they would be performed are unknown. Since there is still much to learn about the possibilities of genetic manipulation, a total ban on manipulation would be premature. However, because of the potentially grave dangers and drawbacks of manipulation, genetic interventions to enhance traits should be considered permissible only in severely restricted situations. The kinds of criteria that would have to be satisfied include the following.

First, there would have to be a clear and meaningful benefit for the fetus or the child that will be born. This criterion would ensure that parents do not impose their own idiosyncratic values on their children, but only engage in genetic manipulation when there would be an important improvement for the child.

Second, there would have to be no trade-off with other characteristics or traits. A genetic manipulation would be permissible only if the benefit could be gained without a change in some other characteristic or trait. Whether a gain in one area is worth a loss in another area is a choice that depends upon subjective values. Consequently, only the individual who would experience the consequences of the trade-off

should be able to decide whether the trade-off should be made. There also would have to be clear evidence that no trade-off will occur. It would not be sufficient to show merely that no trade-off was known, since adverse effects often are unanticipated. Instead, the mechanisms of genetic manipulation would have to be understood in enough detail to ensure certainty that trade-offs would not occur.

Third, there would have to be equal access to genetic technologies, irrespective of income or other socioeconomic characteristics. If access depended on wealth, social divisions would widen, and the promise of equal opportunity for all citizens would quickly become an illusion.

These potential criteria should be viewed as a minimal, not an exhaustive, test of the ethic propriety of non-disease-related genetic intervention. As genetic technology and knowledge of the human genome develop further, additional restrictions or guidelines may be required.

CONCLUSIONS

Physicians should promote informed reproductive choices by counseling prospective parents on the availability and role of prenatal genetic screening. Counseling should include reasons for and against screening as well discussion of inappropriate uses of genetic testing. Prenatal genetic screening is most appropriate for women or couples whose medical histories or family backgrounds indicate an elevated risk of fetal genetic disorders. Physicians should inform women or couples without an elevated risk of the reasons why prenatal diagnosis may not be desirable in their case. Women or couples without an elevated risk of genetic disease can legitimately request prenatal diagnosis, provided they understand and accept the risks involved.

Currently, prenatal genetic screening is available for serious disorders like Tay-Sachs disease, Down's syndrome and cystic fibrosis. In the future, genetic screening may become available for milder genetic disorders. As the ability to screen for genetic disorders increases, the possibility of genetic selection will also increase. It is not possible to give precise guidelines on when prenatal genetic selection would be ethically acceptable. Many situations in which selection would be possible are only hypothetical at this time, and other factors would affect the acceptability of selection. Nevertheless it is important to begin discussion of the issue now to ensure that appropriate ethical guidelines are in place when new applications become available. In general, it would be ethically permissible for physicians to participate in genetic selection to prevent, cure, or treat genetic disease. Selection to avoid genetic disease would not always be appropriate in some cases, the disease would have such mild manifestations that prenatal selection would not be justified. In deciding whether genetic selection is acceptable, a number of factors need to be considered: the severity of the disease, the probability of its occurrence, the age at onset, and the time of gestation at which selection would occur. It would not be ethical to engage in selection on the basis of non-disease-causing characteristics or traits.

As genetic understanding and technology continues to develop, prenatal manipulation of genetic material may become possible. As with genetic selection, the hypothetical nature of manipulation precludes precise guidelines at this time, but it is nevertheless important to begin discussion of genetic manipulation now to ensure that appropriate guidelines are developed in a timely fashion. In general, it would be ethically acceptable for physicians to participate in the manipulation of genetic material in order to prevent, cure, or treat genetic disease. There might be exceptional situations in which genetic manipulation would not be appropriate to treat or cure disease, such as when manipulation would cause serious adverse side effects.

Manipulation of genetic material to alter benign characteristics or traits should be approached with extreme reservation. In general, such manipulation is inappropriate, and its use should be strongly discouraged. There may be exceptional circumstances in which genetic manipulation to alter traits or

characteristics would be acceptable. At a minimum, three criteria would have to be satisfied: (a) there would have to be a clear and meaningful benefit for the child, (b) there would have to be no trade-off with other characteristics or traits, and (c) all citizens would have to have equal access to the genetic technology, irrespective of income or other socioeconomic characteristics.

Currently, when prenatal genetic screening is performed for Down's syndrome or other disorders, the sex of the fetus is an incidental finding. In the future, prenatal genetic screening may yield other, more varied, incidental findings. If that occurs, incidental findings relative to the health of the fetus should be given to parents. Whether incidental findings related to genetic characteristics should be released is a more complicated issue and would depend upon whether it would be acceptable to engage in genetic manipulation of the characteristics. If it would be permissible to manipulate the characteristics, then the incidental findings should be released to allow the parents to decide whether to seek manipulation. No information should be withheld when requested, but it may be appropriate to discuss with parents their motivation for wanting to know the child's characteristics.

The ability to treat genetic diseases through prenatal genetic manipulation should not divert attention from efforts to find postnatal treatment or cures for those diseases.

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GENETIC COUNSELING

Two primary areas of genetic diagnosis are: (1) screening or evaluating prospective parents before conception for genetic disease to predict the likelihood of conceiving an affected child, and (2) in utero testing after conception, such as ultrasonography, amniocentesis, and fetoscopy, to determine the condition of the fetus. Physicians engaged in genetic counseling are ethically obligated to provide prospective parents with the basis for an informed decision for childbearing. In providing information to couples who choose to reproduce, physicians should adhere to the Principles of Medical Ethics and standards of medical practice.

Technological developments in the accuracy of predicting and detecting genetic disorders have created a dilemma for the physician who for personal reasons opposes contraception, sterilization or abortion. The physician should be aware that where a genetic defect is found in the fetus, prospective parents may request or refuse an abortion. A dilemma may also exist for physicians who do not oppose the provision of these services (contraception, sterilization or abortion).

Physicians who consider the legal and ethical requirements applicable to genetic counseling to be in conflict with their moral values and conscience may choose to limit such services to preconception diagnosis and advice or not provide any genetic services. However, there are circumstances in which the physician who is so disposed is nevertheless obligated to alert prospective parents that a potential genetic problem does exist, that the physician does not offer genetic services, and that the patient should seek medical genetic counseling from another qualified specialist.

Physicians whether they oppose or do not oppose contraception, sterilization or abortion may decide that they can engage in genetic counseling and screening but should avoid the imposition of their personal moral values and the substitution of their own moral judgment for that of the prospective parents.