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Impact of Genetic Manipulation on Society and Medicine

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Summary. Human beings have been manipulating the genetic characteristics of plants and animals since the introduction of agriculture. Indirect manipulation of human genes occurred with widespread use of public health and medical measures that preserve genes causing disease. The production of biologicals by DNA technology raises few ethical problems. Predictive medicine in which genetic markers (including DNA variants) are used for antenatal and preclinical diagnosis of genetic diseases and susceptibilities poses new questions of confidentiality, private versus societal goals, and self-determination. When normal DNA is used to treat the somatic cells of patients with hemoglobinopathies and other genetic diseases, no new ethical problems arise beyond those presented by any novel theory. In contrast, manipulation of DNA in human fertilized eggs would constitute a qualitative departure from previous therapies since this would affect future generations. In order to be able to make wise decisions on these matters the public must be well informed. Thus, formal and informal education in human biology and genetics must be improved at all levels.

The rapid development of molecular genetics and particularly the introduction of recombinant DNA technology have elicited much interest among scientists, physicians, and the public in general. The realization that scientists might be able to manipulate the heredity not only of lower organisms but also of our own species has led to much soul searching. Some observers maintain that mankind is at the threshold of new powers that are unlike any innovations ever faced before.

Where do we stand? Scientists and physicians need to be well informed about the current status of genetic manipulation so as to be able to inform the public regarding the scientific facts. Sometimes incomplete knowledge and lack of understanding of various issues in this rapidly evolving subject have led to unwarranted emotional reactions and ill-advised resolutions designed to block the progress of investigative activity.

Genetic Manipulation in the Past

Genetic manipulation is not a new development. For several thousand years, human beings have attempted to control their environment by influencing the genetic characteristics of other species. The domestication of wild plants and animals is an example of genetic manipulation with the aim of producing better and more food. Other examples include the improvement of egg and milk yields from domestic animals. The domestication of dogs shows that even behavior has been manipulated genetically. Hunting dogs, herding dogs, and watch dogs are only a few of the many kinds that were produced purposefully by breeding for specific behavioral characteristics—a form of genetic manipulation.

Genetic manipulation by design has rarely been practiced in our own species. However, unplanned genetic selection for intelligence probably occurs frequently. Marital partners resemble each other in intelligence (at least as measured by IQ tests) because of assortative mating for this trait (*1*). While the exact contribution of heredity to IQ remains unknown, most informed observers accept that genes contribute to the variability of IQ. Therefore, the elevated IQ levels observed on the average among offspring of intelligent parents are an example of genetic selection based on social customs. Such an assertion does not deny that there is a significant environmental component under these circumstances. However, even if the genetic contribution to intelligence is relatively small, assortative mating for IQ would be expected to concentrate high IQ genes among the offspring of gifted couples.

Human breeding by design for high intelligence was recently suggested by a California millionaire who arranged to use sperm from Nobel Prize winners in the sciences for artificial insemination of self-selected volunteer women. One would expect statistically that the offspring of such a procedure would be more intelligent than the average. No other predictions regarding future achievements could be made. Presumably, such voluntary private undertakings on a small scale would cause few social problems and would have no significant effects on the human gene pool. However, attempts by governments to control human breeding must be viewed with alarm—particularly since such efforts would interfere with civil liberties

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and democratic ideals. The attempt by the Nazi government in Germany to institute breeding centers for selected Aryan men and women illustrates an ill-conceived undertaking based on pseudoscientific standards of race ideology and retrogressive notions about individual rights and dignity.

Indirect Manipulation of Human Genes

Medical therapy and certain public health measures affect the human gene pool indirectly by preserving deleterious genes that would otherwise be eliminated. Thus, successful treatment of certain genetic diseases such as diabetes, hemophilia, immune deficiency, certain types of congenital heart disorders, and others, allows the bearers of defective genes to have children. Some biologists and geneticists have warned about the "dysgenic" effects of these practices, fearing serious contamination of the human gene pool with harmful genes that might necessitate a major expenditure by future societies on treatment of the genetically infirm.

While there is some formal merit in such arguments, it is important to distinguish the human from other species (*2*). Human beings have a unique brain that allows "cultural inheritance," which, with the rapid dissemination of ideas, has facilitated our adaptation to a variety of environments. From a strictly biologic viewpoint, the necessity for humans to wear clothes is a deleterious trait, in that we lost the genes for hairiness that protected us against the elements. Development of the human brain enabled our ancestors to devise the necessary protection by the fabrication of clothes from animal skins first, from agricultural products later, and from synthetic fibers more recently. Cloth making and cloth wearing is a valuable part of human culture in all but the most primitive human societies and therefore cannot be considered a harmful trait in the human context.

What about wearing eyeglasses? In developed countries the wearing of eyeglasses because of genetically conditioned myopia or other refractive error is not particularly harmful except in limited occupational settings. The relatively high frequency of myopia and the need to wear eyeglasses represents loss of an adaptive biologic trait among civilized populations. Yet, in the absence of a nuclear holocaust that would relegate humans to a hunting and gathering existence, myopia is a trait that can be well supported by modern societies. Indeed, the existence of myopia and other refractive errors has created an industry of ophthalmologists, opticians, and spectacle frame makers. Analogously, in the distant future human beings might require injections and pills for a variety of genetic infirmities—a development that we currently view as unhealthy. However, our descendants might consider this state of affairs to be as "normal" as we consider the wearing of clothing or eyeglasses today. Thus, the characterization of human genetic traits as beneficial or harmful depends entirely on the environment in which the trait or traits operate.

The "New" Genetics

DNA has come to be recognized as the genetic material in organisms as far apart as viruses and humans. The basis of life on this planet is unitary and founded on the DNA genetic code. The "dictionary" of this genetic code is well worked out. Human hemoglobins have been useful for showing the effect of DNA mutations on gene function (*3*). Study of various genes has shown that the coding sequences in the DNA (exons) are interrupted by intervening sequences (introns) with yet unknown function. Before gene transcripts consisting of RNA can be translated into proteins according to the genetic specification laid down by DNA, these introns need to be spliced out. Mutations affecting the coding sequences as well as the splicing mechanism can give rise to genetic diseases (*3, 4*).

The discovery of restriction enzymes that cut DNA at specific base sequences has been a major development (*5*). Many different restriction enzymes—each splitting DNA at different specific sites—have been discovered. DNA that has been split by a given restriction enzyme can combine with any other DNA molecule cut by the same enzyme. It is therefore possible to join DNA molecules from different sources to produce so-called "recombinant DNA" consisting of parts of DNA from different species. Species barriers can therefore be crossed.

The technology necessary to determine the sequence of the component bases of DNA molecules has developed rapidly (*6*). Other methodologic advances have made it possible to sequence the amino acids in proteins with very small quantities of material (*7*). "Gene machines" that synthesize portions of genes or even whole genes already exist (*8*). Such synthesized partial genes can be used as probes to isolate genes of biologic interest (*9*).

What are the applications of the new biology and what problems do they raise?

Production of Enzymes and Protein by DNA Technology

Human genes that specify the synthesis of biologically important substances can be inserted into the DNA of microbiologic vectors, such as the intestinal bacterium *Escherichia coli*, where the human DNA becomes integrated. The small quantities of genetic material thus introduced can be amplified by growing the "engineered" microorganisms in culture (*10*). The gene products manufactured by the manipulated human genes in the microorganism can be collected. Human insulin already has been produced in this manner and has been safely used in diabetes therapy. Other polypeptides such as human growth hormone and interferon are under production. Various laboratories and companies plan to use DNA technology to manufacture vaccines and many other therapeutic and diagnostic agents. In principle, any polypeptide gene product could be synthesized by these new methods.

What are the ethical problems?

There was anxiety initially that genetic manipulation of *E. coli* could result in the creation of pathogenic bacterial strains that might cause mass epidemics (*11, 12*). Similarly, it was feared that genetic manipulation of certain human cell lines might cause the spread of cancer (*11, 12*). Scientists shared these fears with the public and there was much alarm. It was soon shown, however, that genetic exchange between microorganisms was not new and had occurred all along in evolution. Furthermore, it was demonstrated that the *E. coli* strains created by the genetic engineers are so enfeebled that they represent no danger in outgrowing *E. coli* organisms. Much additional experimentation over the last few years has suggested no unusual dangers of the new DNA technology. The initial anxiety regarding the safety of genetic manipulation has therefore receded, but it is important to understand that the rather remote potential dangers were first described by highly reputable scientists.

When the potential dangers of recombinant DNA were first discussed, medical microbiologists who were experienced in working with highly lethal hu-

man microorganisms had not been fully consulted by the molecular biologists who were not accustomed to strict microbial containment in their work. It is unlikely that medical microbiologists would have raised the kind of fears suggested by the molecular biologists. Similarly, cancer epidemiologists had not been fully consulted in the early stages of safety discussions about recombinant DNA. Some scientists now question whether hypothetical, frightening scenarios that appear farfetched in retrospect should have been shared publicly. Most observers agree that scientists should not make important decisions that affect the public without full disclosure. Although the DNA safety issue, because it dealt with the "stuff of life," was alarming to many people, it stimulated the interest of the public who therefore became better informed.

The new genetic technology has raised problems of corporate control. The involvement by university scientists in industry may lead to less open exchange as scientists try to capitalize financially on their findings. Secrecy may be necessary to allow a company a commercial advantage in bringing a certain product to market, but in basic science departments this could throttle the open communication that led to those very developments that can now be commercially exploited. The availability of ready money for commercially valuable research also may distort research objectives, leading to possible neglect of basic research. University administrators are eager to attract funds from industry at a time of decline in governmental grant support. Such problems are not entirely new, having been faced by faculties of chemistry, pharmacy, engineering, and electronics in the past. However, the engagement of basic biologists in industrial applications is rather novel, since previously applied scientists usually had been involved with industry.

An ethical issue faced in relation to the pharmaceutical industry is the understandable interest in manufacturing products with a potentially large market. Drugs or biologicals for treating rare diseases are less likely to be developed than those agents that will have a wide sale because of their effect on common diseases such as cancer and hypertension. Profits derived from vaccines against tropical diseases prevalent in Third World countries are likely to be much smaller than those obtained from widely sold products in developed countries. Developing countries cannot afford expensive biologicals. Such financial issues distort the priorities of product development in the commercial sector and require enlightened governmental financial aid.

Genetic Techniques in Diagnosis of Hereditary Disease

The new DNA technology has shown that differences in DNA sequences affecting the noncoding areas as well as differences in the intervening sequences (introns) are common among individuals (*13*). DNA variants of either type have no known functional consequences in the expressed phenotype of the organism, but affect the length of DNA fragments defined by a given restriction enzyme. These variants are inherited by Mendelian segregation and can be traced through families. Their laboratory determination is not excessively difficult (*13–15*). If such a DNA variant is located close to a defective gene and if the defective gene cannot be tested for directly, the DNA variant may be used as a marker to infer the presence of the linked gene that causes disease. It has been calculated that the visualization of 150 to 300 different DNA markers of this type randomly distributed over the 23 pairs of human chromosomes would yield a sufficient number of specific landmarks on each chromosome to allow detection of any disease-producing gene (*13, 16*). Diagnosis by DNA markers usually requires study of the parents and of other affected and unaffected family members. With this information it is possible to assign the relationship of the DNA marker gene to the disease gene by using the principles of conventional genetic linkage analysis. In a few cases, such as in sickle cell anemia, where the specific mutation in the DNA is already known, certain restriction enzymes that recognize the abnormal DNA sequence at the mutant site can be used to demonstrate the mutation directly without family study (*17*). Gene deletions that occur in some other hemoglobinopathies may also be recognized directly by using the appropriate probes without family study (*18*).

It may thus be possible, by means of these innovations in DNA technology as well as by other advances in biochemical genetics, to detect susceptibility to and provide early diagnoses of a variety of hereditary diseases that currently cannot be detected until they are clinically manifest. Certain hemoglobinopathies can already be diagnosed prenatally by using amniotic fluid cells aspirated by amniocentesis (*19*). Parents have the choice of abortion of fetuses affected with the genetic disease and may thus avoid the birth of an affected child. Although this option is favored by many couples, it is not acceptable to others for religious or other reasons.

If a predictive test is available, should it be applied to detect all family members that might be affected by a hereditary disease? For example, an appropriate test might be developed for detecting individuals at risk for Huntington's disease. This neurologic disease does not usually become manifest until middle age. If a test were available, it would be possible to assure one-half of the children of an affected parent that they would never be affected. My general philosophy in such situations is to strongly urge patients to be tested if the condition can be prevented or treated. In situations where a positive test would only provide knowledge but no further options for medical or reproductive management it may not be appropriate to insist on testing. Huntington's disease is such an example. Some medical geneticists, however, feel that if a reliable test is available it should be used to identify all members of a kindred who are at risk for developing the disease. Thus, individuals destined to get sick at a later date can order their lives and make appropriate reproductive decisions, while those free of the disease can continue their lives without undue anxiety. Rationally, such an approach makes good sense, but not every person wants to know. Should we not respect the right of the people to privacy and their desire to remain uncertain about their future health? If a testing program has been recommended, does a family member have the right to stop the program and thus prevent someone else in the kindred from knowing his or her susceptibility?

The clinical investigator and affected families might face a dilemma if a test for an untreatable, late-manifesting disease appeared promising. If, additionally, preventive management of such a disease became feasible, investigations of those who might later be affected would be required. The selection of such persons for study would then require the disclosure of information about which at least some individuals might rather have remained ignorant.

"Labeling" of individuals as carriers for genetic disease occurred in the United States when genetic screening for the sickling trait was introduced (*20*). Carriers of the trait who never develop any clinical problems were considered as

mildly affected by the public or even by physicians who were unaware of the harmlessness of the carrier state for sickle hemoglobin. "Labeling" may be particularly serious if a given genetic trait sometimes, but not always, has undesirable consequences. Acrimonious discussions took place when studies of newborns were initiated to follow the developmental and psychologic consequences of sex chromosome aberrations such as XYY [for references, see (*21*)]. Critics of these studies raised the specter of "self-fulfilling prophecies" in view of early suggestions that the XYY state might always be associated with criminal behavior—a concept that turned out to be false.

Occupational restriction might be instituted for genetic reasons. Certain individuals may be at higher risk to toxic damage from specific chemicals because of inherited enzyme variations. Genetic testing in industry has already been discussed [see (*22*)]. Trade unions have criticized the introduction of such testing because management might use the testing as a pretext to avoid cleaning up unhealthy industrial conditions. It is cheaper to exclude workers than to provide healthy working conditions for everyone. In a related problem, an executive might be passed up for promotion if it became known that he carried the gene for familial hypercholesterolemia with its high risk of premature heart attacks. Could one blame an industrial company for such action? Do individuals who know they carry such a gene have the right to withhold such information from employers?

"Predictive medicine," that is, the early detection of individuals at risk for a specific disease, will become increasingly possible with the new developments in DNA and genetic marker technology (*22, 23*). As public bodies assume a more direct role in the health system in many countries, confidentiality may become eroded and genetic information may be used by social and health planners to assign individuals their niche in society. As long as such knowledge only concerns genes affecting variables of physical health and as long as testing remains voluntary, society might be able to cope. But when we learn more about the genetics of personality and mental traits (*21, 24*), new problems could arise. At present, there are few clearcut genetic data in human behavioral genetics and there is no way to apply this knowledge in the foreseeable future. However, the recent claim that cognitive intelligence might be predicted by evoked auditory or visual responses (*25*) (that is, by presenting auditory or visual stimuli to an individual and measuring certain brainwave responses) suggests that advances in this area may soon bring new problems.

Gene Therapy

The replacement of a defective gene with its normal counterpart, if it were possible, would be applicable only in monogenic diseases where abnormal function of a major single gene is the principal cause of the disease. These diseases, while numerous, are individually quite rare. It should be emphasized, however, that the technical problems allowing the practical use of gene therapy have not yet been overcome. Gene therapy or gene manipulation could probably not be carried out in complex traits where many genes are involved in phenotypic determination. Thus, genetic manipulation would not be possible for traits such as skin color, hair shape, personality, or intelligence. However, if one or several major genes were the principal contributors to the variation of these traits, it might theoretically be feasible to manipulate them genetically. Currently, the nature and location of most genes affecting normal variation of body structure and function are unknown.

The procedure used to replace a defective gene is likely to be as follows. The normal gene to be used for gene therapy will first be isolated. After a small portion of the diseased tissue, such as bone marrow cells, are removed from the patient, the normal gene will be introduced into the patient's cells containing the defective genes. The nuclei of the target marrow cells will be induced to take up the normal gene by means of a variety of techniques. The genetically manipulated cells will then be reintroduced into the patient. It is postulated that the manipulated cells would have an advantage over the genetically defective cells which they would perhaps ultimately replace, thereby curing the patient. Before any such therapy could be successful, however, several conditions would have to be fulfilled (*26*). The transplanted gene would have to be taken up by the abnormal target cell and integrated into its nucleus, where it would have to remain and function normally. The expression of the introduced gene would have to be regulated to produce appropriate amounts of gene product. The engineered cells as well as the total organisms would have to be unharmed by the procedure (*26, 27*).

This scenario for gene replacement represents a new approach to somatic therapy in that the procedure will not affect genes in the germ cells of the ovaries or testes of the patient, but will affect only the somatic cells that have been manipulated. Patients whose cells have been engineered in this manner still will carry the abnormal gene in their gonads and, if they are able to reproduce, will transmit the defective gene to some of their descendants according to Mendelian principles.

Gene therapy of this type is therefore conceptually no different from any therapy in medicine that attempts to improve the health of a sick patient. The only difference is that DNA, rather than other biologicals, drugs, or surgery is used as the therapeutic modality. This point is important because some critics claim that gene replacement represents a revolutionary departure in medical treatment. In fact, gene therapy for diseased tissues is no different from any other therapy. No change in the genes of the reproductive organs is attempted.

What is the current status of gene therapy?

The best understood genetic system in humans is the hemoglobin gene complex, and the most common monogenic genetic disorders affect hemoglobin structure and function (*3, 4*). Sickle cell anemia and the various thalassemias cause severe anemia (*3*). It is now technically feasible to produce normal or abnormal human hemoglobin genes in the laboratory. Since hemoglobin is produced by certain bone marrow cells (that can easily be aspirated in a routine manner), normal isolated hemoglobin genes in the form of DNA can be added to the patient's abnormal erythropoietic marrow cells. After the normal hemoglobin DNA has been taken up, the manipulated marrow cells can be returned to the patient where they are expected to proliferate and produce normal hemoglobin. A cure, or at least a partial cure, by DNA therapy might therefore ensue.

How does this mode of therapy conceptually compare with other new and old treatments of the hemoglobinopathies?

Treatment of anemia by transfusion of red cells is a well-recognized form of therapy. Transfusion historically was the first successful type of transplantation in medicine, and few ethical arguments have been raised against blood transfusions. A new type of experimental therapy is bone marrow transplantation (*28*). When the hemoglobin-producing cells of the bone marrow are genetically defective, marrow of appropriate tissue type (so as to minimize cell rejection) from a normal sib can be transplanted into the

patient with hemoglobinopathy. It is hoped that the transplanted marrow cells will proliferate normally and synthesize the hemoglobin that the patient is not making properly. At least one case of thalassemia has already been successfully treated in this way (*29*).

No special ethical arguments are raised against bone marrow transplantation except those that apply to all of human therapeutic experimentation. A further logical step in the treatment of hemoglobinopathies, that is, the use of isolated normal hemoglobin genes rather than of entire donor cells to improve function of a patient's abnormal marrow cells, is conceptually no different from bone marrow transplantation. Gene therapy is therefore a natural therapeutic development that evolves from increasing understanding of disease mechanisms. Public unease about gene therapy can therefore be lessened by explaining that the nature of such therapy is not a radical departure from previous medical intervention. Gene therapy can be considered as a form of "euphenics" rather than the practice of "eugenics." The phenotype may be altered but not the genotype. Medicine has been proceeding in this manner since its beginnings.

Although the use of DNA in such projected therapy causes no new ethical problems, many problems are raised as with other types of innovative therapy. First, extensive animal experimentation is required to work out the details and to ensure safety of the proposed treatment. The severity of a disease is an important criterion in deciding when to introduce a new therapy. With mildly affected patients one would hesitate to initiate a completely new therapy that might have unanticipated side effects. However, with life-threatening diseases, one might be less hesitant to use new treatments, particularly if the patient is in the end stages of the disease and no alternative treatments are available. For example, for a patient with a terminal malignancy a new treatment based on rational principles that has not been worked out in all details in animals might be acceptable.

The timing of the introduction of a new therapeutic modality depends on many factors. Observers with different medical or scientific backgrounds might have different views. The recent controversy about the use of DNA therapy for two patients with thalassemia major in Italy and Israel is illustrative (*30*). Many scientists felt that these attempts were premature in the absence of full animal experimentation. The U.S. investigator who attempted the therapy was a medically qualified scientist who maintained that the patients had a life-threatening disease and that no meaningful alternative treatment was available. This incident was further beclouded by long delays in decision-making by a human experimentation committee in the United States that was considering the appropriateness of the planned treatment. Before obtaining a ruling from this committee, the investigator decided to carry out the experimental treatment in other countries. Permission by ethics committees abroad was obtained more rapidly, but, since recombinant DNA (rather than a nonrecombinant DNA technique as specified in the application) was used, further problems arose (*31*). The investigator lost grant support from the National Institutes of Health for transgressing the relevant regulations. The patients apparently were neither helped nor harmed by the procedure, but a full account has not yet been published. The case attracted much public attention because it represented the first attempted use of gene therapy in humans.

Medical pioneers in the past, such as Jenner and Pasteur, performed their respective studies on smallpox and rabies prevention on a single human subject without the safeguards we demand today. They were successful and established immunization schemes that wiped out dangerous and lethal diseases and saved many lives. In retrospect we honor their achievements, but there was no assurance at the time that the first vaccinated subjects would not suffer serious side effects or even contract the fatal diseases meant to be prevented. Current attitudes regarding human experimentation are more in keeping with our respect for human autonomy and dignity. It is conceivable, however, that the ethics committees that are now required to approve proposed experimental treatments in humans might be unduly cautious or conservative and might defer or prevent the introduction of innovative treatments with great potential impact. Since human subjects in the past have sometimes been abused by medical experimenters, our current system of safeguarding human subjects is clearly desirable. But let us hope that this system will not inhibit imaginative new approaches in the prevention or treatment of human disease.

Genetic Manipulation of Fertilized Eggs

Some recent technical developments may allow genetic manipulation of germ cells (*32–38*). In several experiments, isolated genes were introduced into mouse eggs shortly after fertilization when the male's genetic contribution was still present as a distinctive pronucleus. When rabbit or human DNA coding for hemoglobin or some other protein from a different species was injected into the mouse pronucleii, the foreign DNA could in some instances be detected in the mouse offspring that developed from the fusion of the manipulated pronucleus and the egg's pronucleus. Some mice actually synthesized the protein coded by the DNA of the donor species. In these cases, the transferred DNA functioned actively in cells that had differentiated after genetic manipulation of the fertilized egg. Furthermore, in some cases, the foreign genes had become incorporated into germ cells, since the specific protein synthesized under the signal of the transferred gene could be detected in offspring of the next generation and was again transmitted to the third generation. Means of overcoming the low efficiency of integrating foreign DNA are still needed, and ways must be found to target genes to the appropriate chromosomes. Reliable, time-specific expression is likely to depend on correct integration. While much remains to be done, these experiments show that genetic manipulation of germ cells is a distinct possibility.

Techniques for the manipulation of germ cells are currently used by investigators studying gene regulation who attempt to understand how genes are turned "on" and "off." Practical applications for such techniques may come in agriculture, since commercially useful traits, such as faster growth and higher milk yields, might be introduced into animal stocks by genetic manipulation of fertilized eggs. However, most of the valuable traits in livestock are polygenic, so that conventional breeding techniques would have the same end result. If genes such as those for growth hormone or prolactin have a major effect on normal growth or milk yield, respectively, it might be possible to obtain the desired results by injection of the appropriate genes into fertilized eggs rather than by the usual breeding techniques. It is difficult to visualize human applications of such techniques, since the genetic manipulation of human eggs would require prior knowledge of the genotypes of both the egg and the pronucleus of the sperm. Such genetic typing of germ cells is not possible with current technology. Nevertheless, the animal studies raise the possibility of future genetic manipulation in humans. Unlike the somatic therapy with DNA discussed earlier, use of such technology would constitute a definitive qualitative departure from other thera-

pies since it would affect future generations. Extensive safeguards and public discussion would therefore be needed before these techniques were ever applied in humans.

Other Forms of Reproductive Engineering

Sex selection by physicochemical or immunologic separation of sperm carrying X or Y chromosomes has been discussed for many years but has not yet been achieved. When such techniques do become successful, they will be used initially for sex choice in animal breeding. Application to humans might also be relatively simple, and the possibility that the sex ratio of the population might become distorted has been discussed (*39*).

Human fertilization in vitro to bypass blocked Fallopian tubes has been achieved several times but is technically difficult (*40*). When the procedure was first introduced, there was much discussion about possible misuse of the technique since any sperm and any egg might be used for fertilization. It was feared that some women might hire themselves out as host mothers to bear embryos from other couples, that is, they would provide "wombs for rent" (*41*). I consider it unlikely that widespread abuse will develop and the method does permit infertile couples to have their own children.

"Cloning" has been widely discussed in the past (*42*) and was achieved in frogs some time ago. In this procedure, the nucleus of a somatic cell is transplanted into an enucleated egg thereby allowing the exact reproduction of the genes of the individual from whom the transplanted nucleus was obtained. Recent developments suggest that a similar approach, with nuclei being transplanted from embryonic mouse cells, might be used to clone mice (*43*). Even if cloning of humans with nuclei from adult cells ever became possible it is unlikely that the procedure would be widely used. The occasional utilization of cloning of humans would be both startling and of some scientific interest since pairs of "identical twins" of different ages could be produced. While this procedure has occasionally raised emotionally charged reactions I do not believe that cloning in humans will cause grave societal problems in the future.

General Comments

There is agreement in most societies that medical practices that depart from current therapeutic modes or that introduce completely novel reproductive procedures require public discussion. Scientists should be accountable to the public before they utilize such innovations. To be able to make wise and informed decisions in these matters, people must have some knowledge of human biology, including genetics. This means that science education at all levels from elementary schools through college needs to be strengthened. Teachers must be trained to offer exciting and attractive courses in human genetics and biology. Nontechnical science courses in colleges need to be emphasized. The media can play an important part in this endeavor by explaining and reporting responsibly on new developments. Uninformed decision-making can lead to prohibition of laudable but not particularly dangerous innovations.

The new biologic revolution based on DNA has been with us for only one generation and genetic manipulation by gene splicing was developed less than 10 years ago. Neither scientists nor the public in general have absorbed the full impact of these developments. As more is learned about DNA and human genetics more problems are certain to arise. Nevertheless, well-informed human beings in enlightened democratic societies should foster the use of the new DNA technology in a responsible manner that will lead to better health and welfare for all.

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