Medical Genetics and the Engineering of Man

Most technologies alter the conditions under which man lives–but biomedical technology can modify man himself

Recent advances in biology and medicine provide us with the power to modify and control the capacities and activities of men by direct intervention and manipulation of their minds and genes. Biologists and physicians disagree on the extent to which this "human engineering" is and will become a reality, but they agree that it is already beginning to have profound ethical and social consequences.

The impact these technologies will have on mankind is in part derived from the fact that they operate directly on man himself. The technologies of energy, transportation, communications, and food production admittedly alter the conditions under which man lives. In contrast, biomedical technology can modify the user himself; the engineer can for the first time engineer himself. The social and ethical questions thus created center about whether we should continue to develop and practice human engineering, what limitations we should impose, who should make these decisions, and what sets of values and other considerations should enter into them. The nature of these questions can be graphically illustrated by this case study:

A mongoloid with an intestinal obstruction was born to professional parents in Maryland. The parents refused permission for the surgery that would enable the infant to survive, deciding that it would be unfair to their two normal children to bring a mongoloid into the home. Doctors at Johns Hopkins Hospital in Baltimore sought help from the courts, which in Maryland have the power to appoint a guardian who will authorize necessary medical care for a child when parents refuse. A senior member of the judiciary advised the doctors that the courts would not force the parents—or society—to bear the burden of rearing such a child. Accordingly, the baby's bassinet was wheeled into a dark corner of the nursery where in 15 days the child became dehydrated enough to die a "natural" death.

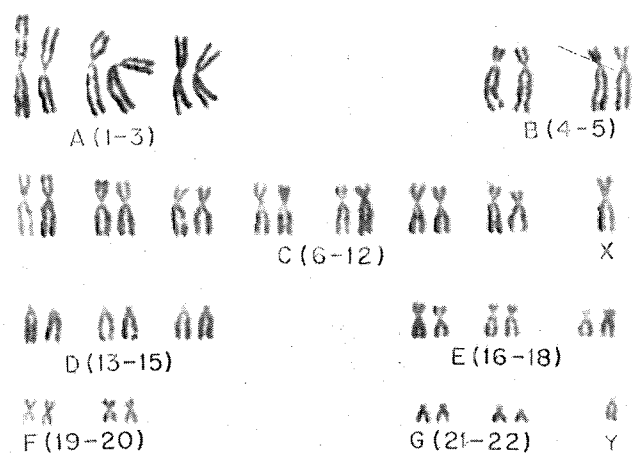
Modern medical technology has developed the life-saving operation for the removal of this intestinal obstruction in the last ten years. Prior to that time this infant would have died, and the life-or-death decision would not have arisen. Thus each advance in modern medical technology can present us with new and difficult social and ethical dilemmas.

This case and others like it raise a number of interrelated questions. Is the decision appropriate? Who should make these decisions? What is the process whereby these and similar decisions can be made?

Some aspects of modern medical genetics are of practical importance now (genetic counseling and genetic screening); others will gain importance in the future as new technologies are developed (*in vitro* fertilization and gene therapy). These technologies can alter the genetic fabric of society in two ways: First, certain constellations of favorable (or unfavorable) genes can be selectively expanded or deleted, thus altering the nature of the gene pool of the population as a whole. Second, in the future, man will develop the technology to alter his genes by direct modification. Either of these activities can have serious consequences for mankind and man's image of himself.

Human genetic disease

To appreciate the impact genetic technology can and will have on our lives, it is important to explain in general

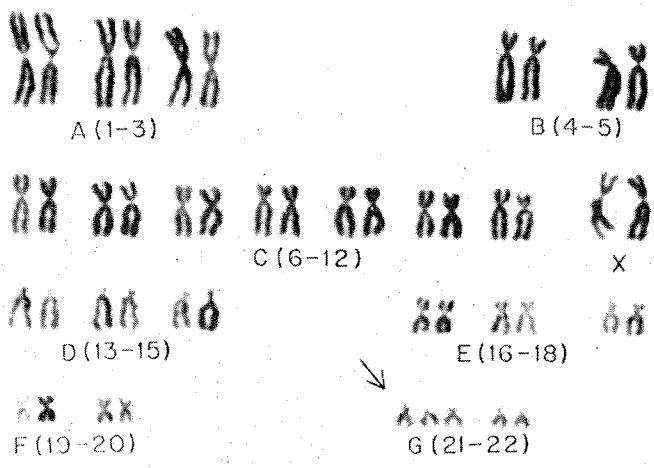


Normally, the 46 chromosomes of a human cell appear in random orientation in a microscopic slide, but in this display—called a karyotype analysis—they are organized into pairs numbered from 1 to 22, plus two single sex-determining chromosomes labeled X and Y. The pairs are collected into groups (lettered A through G) on the basis of size similarities. Because both an X and a Y chromosome are present, it is apparent that this karyotype is of a cell from a human male.

terms the nature of genetic disease, of which modern medicine has defined close to 2,000 different kinds—most of them quite rare. But there is a genetic component in the diseases of 25 percent of the children who are currently hospitalized.

To understand the nature of genetic disease we must first consider the 23 pairs of chromosomes that are the blueprint repositories for all of the information necessary to construct the human organism. One chromosome from each pair is derived from the father and the second from the mother. There are two sex chromosomes, X and Y. A female has two X chromosomes whereas a male has an X and a Y chromosome. The information in each chromosome is subdivided into smaller units that are called genes. Each gene codes one unit of information. Genetic disease can, accordingly, be of more than one type.

First, there may be abnormalities of the chromosomes themselves—extra chromosomes, missing chromosomes, or detectably altered chromosomes. (The mongoloid child discussed earlier is one example of a chromosomal abnormality which is caused by the presence of one extra copy of a small chromosome). Chromosomal abnormalities nearly always lead to serious physical and mental derangement.



This karyotype differs in two important respects from the previous one. First, it shows two X and no Y chromosomes, indicating that the cell is derived from a female. Second, the arrow points to an extra chromosome in the G group, an abnormality that is the most frequent cause of mongolism.

A second type of genetic disease is caused by defects (mutations) in individual genes. An example is sickle cell disease, wherein a gene that codes for a component of the oxygen-carrying blood protein, hemoglobin, is defective. As a result, low oxygen levels cause the hemoglobin molecule to change its shape and this in turn causes the red blood cells to change their shape (to sickle), which leads to blocking of the small blood vessels and the pathologic manifestations of sickle cell disease.

If the defective gene is present as a single copy (e.g., a defective gene is present on the paternal chromosome but a good gene is contributed by the maternal chromosome), usually the individual is clinically normal. He has what is termed a *recessive* genetic disease. For example, an individual with a single copy of the sickle cell gene leads a nearly normal life, in contrast to the individual with sickle cell disease who has two bad hemoglobin genes. It has been estimated that each of us carries from three to eight lethal recessive genes; these are genes that would kill us if both of our copies were defective. The increased probability of producing offspring with two identical defective genes is, of course, one reason why it is undesirable for closely related individuals to have children.

There are other classes of genetic disease or diseases with a genetic component. *Dominant* genetic disease—for example, Huntington's chorea—produces anomalies even when only one bad gene is present. Several other of mankind's most widespread diseases have a genetic component (cancer, arteriosclerosis) but also have other contributing factors.

Prenatal diagnosis

Some of the most striking social and ethical dilemmas presented by modern genetics come from new techniques that permit genetic disease to be diagnosed at a point in fetal development where abortion of the defective fetus is a possibility. These new diagnostic techniques combine the ability to withdraw amniotic fluid from the membrane sac surrounding the newly developing fetus (amniocentesis), the ability to grow fetal cells in tissue culture outside the living organism, and the ability to detect genetic defects through biochemical or chromosome analysis of the fetal cells.

Amniocentesis can be performed as early as 12-16 weeks of gestation, and it can yield enough cells for subsequent biochemical analysis of gene defects or karyotype analysis

of chromosomal abnormalities. Once a particular diagnosis is made, the parents can decide whether or not to have the fetus aborted before 20 weeks of gestation.

Prenatal diagnosis can present parents and society with perplexing social and ethical dilemmas about whether or not to abort a genetically defective fetus. Gauge your reactions as a potential parent in the following cases which can be detected prenatally in adequate time for a safe abortion.

Would you abort these fetuses?

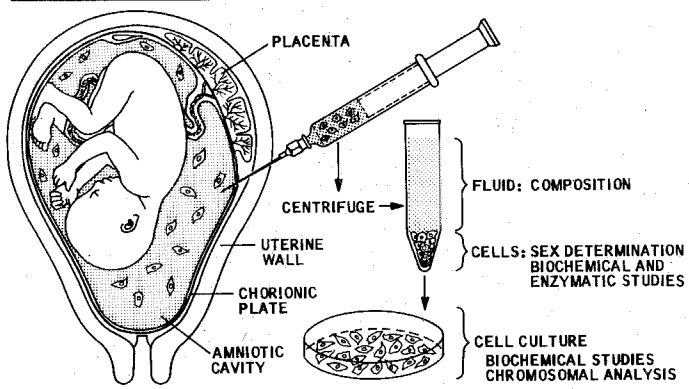
Case 1. Tay-Sachs disease is caused by a defective enzyme that leads to abnormal brain development. The child is born normal but quickly develops mental and physical abnormalities which rapidly progress and lead to the inevitable death of the child at 1 to 4 years of age. Obviously, the course of this disease is a traumatic experience from the viewpoint of a parent who sees an apparently healthy child deteriorate into a helpless vegetable, and finally die.

Case 2. Mongolism is a constellation of physical and mental abnormalities that is caused by the presence of an extra chromosome. Mongoloid children can have I.Q.'s that range from the low 20's up into the 70's. They are prone to a number of medical difficulties, such as repeated infections, and generally have a greatly shortened life span. Although many can learn simple tasks, mongoloids do not become independent members of society. These children generally have a happy disposition and are, some feel, quite loving.

Case 3. Another type of chromosomal abnormality consists of an extra male (Y) chromosome. The "XYY individual" has gained notoriety recently because certain studies on the inmates of penal-mental institutions have indicated their presence in such institutions at 50 times the frequency expected from their incidence in the general population. These statistics have led some investigators to infer that XYY individuals are prone to asocial behavior and as such are a destructive element in society. However, it must be stressed that this abnormality occurs at a frequency of about 1 per 1,000 births and, accordingly, there are many normal and functional members of society who are of this chromosomal constitution. Clearly the data on XYY individuals with regard to asocial behavior are very tentative and preliminary.

Case 4. Perhaps the most extreme possibility for abortion relates to the normal fetus that is aborted because of its sex. Suppose you are a parent with five girls and you want a boy. Prenatal diagnosis can establish the sex of a child in adequate time for a therapeutic abortion. Do you have the right to abort a normal female fetus in order to satisfy your desire for a boy?

The last two cases in particular illustrate the ever-present



Amniocentesis is one type of prenatal diagnosis. A sample of fluid surrounding the fetus is taken by inserting a sterile needle into the amniotic cavity and withdrawing a small amount. This fluid, derived mostly from fetal urine and secretions, contains fetal cells, and the sample is centrifuged to separate the cells and fluid. A variety of tests can then be made. For genetic diagnosis, the optimum time for an amniotic tap is about the 16th week of gestation.

conflict between individual needs and societal needs. Should society protect itself against XYY individuals by detecting them at birth and providing them with special attention or treatment? Or does an XYY have the right to attempt to lead a normal life without the stigma of a mandatory chromosome analysis? Do parents have the right to opt for abortion if their child has such a defect? Is an XYY individual responsible for criminal behavior if this behavior is caused by a chromosomal abnormality that is beyond his control? Several such cases have appeared before the courts. In the other instance, should society tolerate a change in the sex ratio of infants just to accommodate the desires of individual parents?

These four cases raise very clearly the general nature and range of the personal moral and ethical dilemmas posed by prenatal genetic diagnosis. If you agree in any one of these cases that abortion is acceptable (and most individuals agree that abortion is desirable for Tay-Sachs disease), then a series of questions arise. What are the boundaries or limits of acceptable indications for abortion? Who makes these decisions? How? What information is to be given to other members of the family who may be carrying defective genes?

Genetic counseling

Three points should be made about genetic counseling and the current process of decision making as it relates to genetic disease. First, genetic counselors, even if they try, cannot transmit value-free facts to their patients because they are very much constrained by their own background and philosophy. Studies have established that the predispositions of genetic counselors greatly influence their patients' decisions, even when the counselors insist that they are not being directive. For example, one genetic

counselor may be very concerned about the potential contamination by defective genes of the gene pool in the population as a whole. Thus he may inadvertently counsel in such a fashion that his patients generally choose to abort defective fetuses. Another genetic counselor may be more concerned about the emotional and psychological strengths and needs of the family and counsel accordingly.

Second, the emotional trauma of having a defective child (or fetus) very often places the parents in such a state of emotional shock that education about the defect and subsequent rational decisions about a course of action are often impossible—sometimes for extended periods of time.

Finally, the genetic counselor often consciously plays a major, if not determinative, role in this decision-making process. Many feel this is justified by the frequent inability of parents to cope rationally with the problem or by their desire to relieve parents of the guilt feelings the decision may produce.

Clearly, certain of these decisions should rest with well-informed and thoughtful individuals who are themselves directly affected, and not with a single group in society—such as the medical profession. The critical question is, of course, how to determine when social rights have precedence over individual rights or desires. These decisions will affect the very nature of the gene pool that is passed on to future generations. A great deal of thought must be given to the consequences of various alternative courses of action and to the process whereby these decisions are made.

It is important to stress that the prenatal diagnosis of genetic disease may be made even more routine and inexpensive in the future. Effective new techniques such as the staining of chromosomes with fluorescent dyes generate complex and characteristic banding patterns for each chromosome, which will permit a much more refined analysis of its structure. New devices are being developed—at Caltech's Jet Propulsion Laboratory and elsewhere—for the automatic and computer-aided analysis of large numbers of chromosomal karyotypes. And, finally, it may be possible that amniocentesis can some day be replaced by a simpler test of a small amount of the mother's blood. This possibility is based on the recent development of a device that can apparently separate a small number of fetal cells normally present in the maternal circulation from their maternal counterparts, for culturing and subsequent biochemical and karyotype analysis.

As these developments make prenatal genetic analysis increasingly simple and inexpensive, more and more widespread prenatal screening becomes a tempting option. New classes of questions emerge as screening programs begin to involve large segments of the population.

Genetic screening programs

Current genetic screening programs are designed to test large groups of individuals with special predilections for the presence of one (or two) defective copies of particular genes. The screening program for Tay-Sachs disease that has recently been carried out in the Baltimore area and is now being started in Los Angeles is an example of a useful application of this procedure. The defective gene for Tay-Sachs disease occurs ten times more frequently in certain Jewish populations (where 1 in 30 individuals carries the defective gene) than in other population groups. This defect can be detected in individuals with a single bad gene (carriers) by a simple biochemical test made on a small blood sample. It is useful to identify normal-appearing carriers of this disease because when two such individuals marry, the chances are one in four that an offspring will carry the two defective genes causing Tay-Sachs disease. Thus the pregnancies in any such marriage can be monitored by amniocentesis and afflicted fetuses aborted, if desired.

In contrast, the many recently initiated sickle cell screening programs are of questionable usefulness and, indeed, appear to invite some very dangerous consequences. This genetic disease occurs almost exclusively in one group, the blacks; there, one individual in ten carries a sickle cell gene. This sickle cell carrier (said to have "sickle cell trait") can readily be detected, once again, by a simple biochemical test of the blood. Although it is a matter of some current controversy, the carrier appears to be an essentially normal individual. The individual with sickle cell disease (two bad gene copies) is detected early in life through repeated sickle cell crises. This is an extremely debilitating disease, and afflicted individuals rarely live beyond their twenties.

Since sickle cell disease cannot be detected by prenatal diagnosis, and since there is currently no effective treatment for this disease, the usefulness of this screening program is not apparent. While it appears that few, if any, positive medical benefits accrue from this screening program (except for appropriate counseling regarding the marriage of two carriers), there are a number of dangerous side effects. Many states now require sickle cell screening to be carried out on all blacks by the time they are of school age, and this brings about two types of difficulties. First, it is hard to explain to the public at large the difference between sickle cell *disease* and sickle cell *trait*. Children with the trait, who can lead perfectly normal lives, are often categorized by parents and friends as sick, and these children rapidly become psychological cripples. Second, insurance companies and employers have on occasion obtained these genetic records and used them to the detriment of both those with sickle cell trait and those with sickle cell disease.

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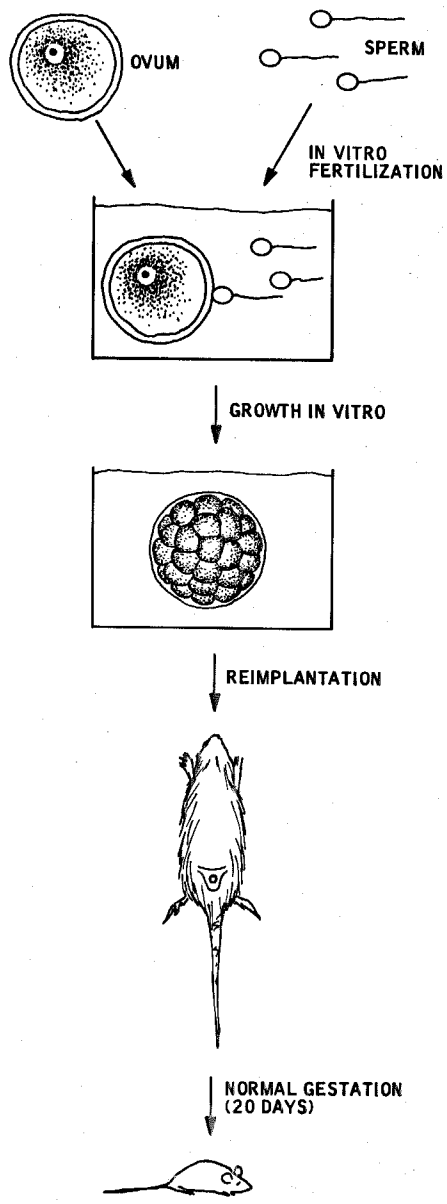
Thorny questions arise concerning any genetic screening program. Should a screening program be carried out if there is neither treatment for the disease nor any possibility of prenatal diagnosis? If the screening program is desirable for medical reasons, how should the information be stored and who should have access to it? Insurance companies? Employees? Interested private individuals?

In the future two other techniques now in the developmental stages will also afford man opportunities to manipulate his gene pool (*in vitro* or test tube fertilization and reimplantation) or to alter his own genes directly (gene therapy).

Test Tube fertilization

It is now possible to combine mouse sperm and ovum outside the mother's body to produce a normal fertilized zygote which can be grown in tissue culture to the 16- or 32-cell stage (blastocyst stage). At this stage of development, if the zygote is implanted in the uterus of an appropriately prepared female, in more than 50 percent of the cases normal infant mice will be produced after an appropriate gestational period. *In vitro* fertilization has also been accomplished with human sperm and ova. Reimplantation of the fertilized zygote in female humans should be possible within a very few years. These procedures could permit many thousands of couples who are infertile due to blockage of the uterine tubes to have their own children.

Obviously this procedure raises its own interesting questions. Can one be assured that the offspring from such a procedure will be normal infants? (In mice the abnormal offspring appear to abort early, and most of the fetuses surviving through to birth appear perfectly normal.) The procedure of ovum extraction from the mother generally yields multiple ova. If only a single ovum is necessary for fertilization, how will the remaining ova be used? The



Manipulating the gene pool in mice is now possible with *in vitro* fertilization and reimplantation. Ova and sperm from mice can be mixed in a test tube to yield a fertilized egg (zygote). After the egg grows in the test tube to the blastocyst stage, it can then be reimplanted in an appropriately prepared female. After a normal gestation period, normal mice are born.

fertilized egg can be transplanted into any female uterus. Could a single set of parents hire wombs (i.e., "wombs for rent") to produce many of their own progeny? Artificial wombs seem to be a very distant possibility at this time, and Aldous Huxley's test-tube factory for babies appears remote.

These studies also set the stage for advances in yet another area which, for human beings, is currently placed in the realm of science fiction—cloning. Frogs and carrots, however, have been successfully cloned. In the case of a frog, a nucleus is removed from one of the cells that line the intestinal wall, and it is reimplanted in an ovum that has had its own nucleus removed. This "manufactured" zygote (i.e., fertilized egg) apparently initiates the normal developmental programs, which thereby induce the growth of a normal frog with a genetic constitution identical to the parent from whom the intestinal nucleus was removed (i.e., a clone).

Two major difficulties arise in carrying out such a procedure in mammals. First, mammalian ova are extremely small and, accordingly, difficult to manipulate with the microsurgical techniques required for the transplantation of a new nucleus. Second, mammalian eggs, unlike their amphibian counterparts, develop in the mother's body rather than in pond water. In theory the first difficulty can be circumvented by an important new technique of cell biology—cell fusion, which makes it possible to fuse together any two cells (even those from different species). Using this technique, it should be possible to destroy the nucleus in a human ovum (with a laser beam, for example) and then to fuse this enucleated egg to a normal human cell from the same or a different individual. Presumably this egg with a single nucleus could be induced to start the normal developmental program, and at an appropriate stage the "clone" could be implanted in the uterus of a surrogate mother.

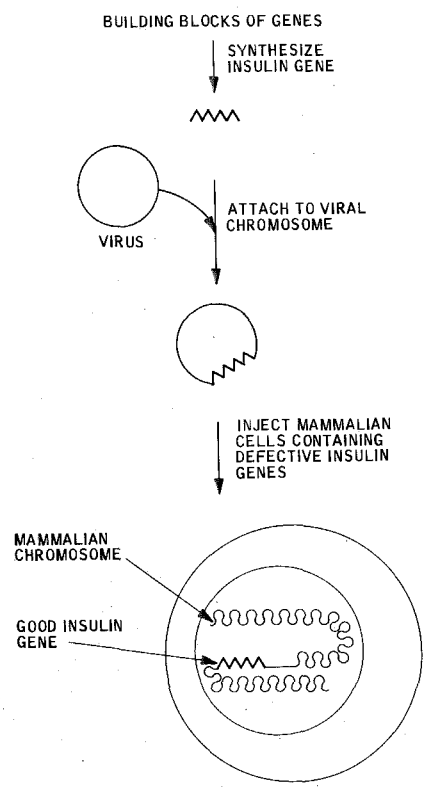
Most of the theoretical barriers to cloning have been circumvented by various techniques of modern science. A number of technical details have yet to be mastered, but within 10 to 15 years cloning is likely to be a reality. Then, of course, another host of questions will be raised. Should only individuals with unusual traits or abilities (such as music, mathematics, art) be cloned, or should any individual who can afford the procedure be permitted to generate copies of himself?

The potential use (or abuse) of cloning will be limited by the necessity of providing a surrogate mother for each clone. Thus a single individual could be cloned only to the extent that surrogate mothers could be found. When and if Aldous Huxley's vision of fetal development in an artificial womb becomes a reality, a new dimension of cloning possibilities will arise.

Gene therapy

Gene therapy, or "genetic engineering" as it is often called, might take many forms. Perhaps the simplest to envision is the use of modified viruses to replace defective genes. For example, certain simple genes have already been synthesized in the test tube, and in theory, the gene coding for the hormone insulin could be synthesized. This gene could then be attached to the chromosome of an appropriate virus. Certain viruses have the ability to insert or attach their chromosomes into those of their mammalian hosts. Thus, in principle, an individual with a defective insulin gene could be infected with a virus carrying a good insulin gene, which in turn could lead to the integration of a good insulin gene into one (or more) of the human chromosomes in the defective cells. Presumably the good gene could then supply the missing hormone and thus correct the genetic defect.

It must be stressed that many theoretical and practical difficulties remain before this form of gene therapy, or any other for that matter, becomes a reality. How can the defective gene be identified and isolated for chemical analysis? Must the gene be inserted into a single correct position in a particular mammalian chromosome? Will the complex control systems for the genes of mammals operate appropriately on such an inserted gene? Can we be assured that the virus vector will not cause cancer in the host? These are only a few of the questions that render the possibility of gene therapy unlikely for many years—but the eventuality will come to pass, perhaps much sooner than the always conservative estimates of medical scientists.



Theoretically, gene therapy could be accomplished by replacing defective genes with modified viruses. For example, a human insulin gene could be synthesized and attached to a viral chromosome. The modified virus could then be used to infect human cells that have a defective insulin gene by integrating the good insulin gene into one or more human chromosomes. The good gene could supply the insulin that defective cells are otherwise unable to synthesize.

Two points should be made with regard to gene therapy. First, it will be utilized for treating single-gene defects. Most of the human qualities that we attribute to man, such as intelligence, emotions, and physical appearance, are controlled by many different genes in the human chromosomes—that is, they are polygenic traits. It appears unlikely that man will soon be able to alter polygenic traits because this would require an understanding of complex multigenic interactions as well as the actual identification of all of the genes involved. Thus gene therapy will be directed at diseases that are caused by single defective genes (such as phenylketonuria and galactosemia). Second, genetic engineering will provide man with the opportunity to alter either the genes in the organs and tissues that constitute most of his own body (somatic cells) or those in his sex cells. In the first case the gene correction will be confined to the individual himself and will not be passed on to his progeny. In the second case, man will alter the genes to be passed on to future generations and in doing so will start to play an active role in guiding, consciously or unconsciously, the evolution of the human race.

In summary, medical genetics has given (or will give) man the opportunity to engineer his own genes, either by expansion or elimination of selected genotypes or individuals through genetic counseling, genetic screening, and *in vitro* fertilization followed by reimplantation, or by direct alteration of his genes through gene therapy. Critical questions arise with regard to determining how these techniques should be applied, who should make these decisions, and how they should be enforced. These questions are, of course, made even more pressing because they raise issues concerning the nature and essence of man himself, which he can and probably will change. We are dealing with an intensely personal dilemma. How will the decisions be made?

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Why not stop research in medical genetics?

One conceptual solution to many of these dilemmas is to stop all genetic research, but this appears unlikely. On the one hand, many of these genetic studies are important to areas of medicine other than "human engineering." Cell fusion studies, for example, may lead to important clues about the nature of cancer, as may studies on the insertion of viral chromosomes into mammalian chromosomes. In addition, studies in all areas of medical genetics are being carried on everywhere. A moratorium on genetic studies in any one country would probably have only a modest effect on the rate at which these various genetic techniques are being developed elsewhere. Accordingly, any solutions to the social and ethical dilemmas of modern genetics must be approached from an international point of view.

Two legitimate points, however, should be raised with regard to a consideration of controls over genetic research. First, society's resources are finite and priorities must be assigned for their deployment. How should we balance efforts in biology and medicine against efforts to eliminate poverty, pollution, urban decay, discrimination, and poor education? What are the social consequences of seducing many of our brightest young people into spending their lives in science while other more immediate and possibly more serious problems go begging? Second, are the biomedical sciences justified because they are directed toward the "betterment of mankind"? Perhaps it is time to explore what we mean by this phrase. What ends should these new technologies serve? What values should guide society's adjustments? Man must assess his goals, his values, and his needs.

The public's role

It is clear that an informed and thoughtful public should play a decisive role in formulating these decisions. The critical point is how to inform the lay public of the present and future possibilities of genetics and of their social and ethical implications. The mass media have so far not accomplished these ends in that their programs on medical genetics, even when carefully done, have focused mainly upon the medical advances themselves and not on the resulting social and ethical dilemmas. Scientists and physicians have done little better—partly out of indifference, sometimes from the erroneous belief that science is too complex to transmit to the public, or indeed, from the conviction that the moral and ethical implications of medical research should not be aired for fear of jeopardizing the funding of medical research itself.

At this pivotal point, our future directions should reflect the applied wisdom of the many–not of a few

Perhaps the most difficult aspect of the social and ethical dilemmas of modern genetics to convey to the public is the realization that the solutions are not single-valued; that is, different people will arrive at different, but equally valid, solutions to these dilemmas. For some families a mongoloid child could be a devastating experience; for others it could be inspirational. To account for the vast spectrum of different value systems, legislation resulting from public consideration of these matters must be appropriately flexible. The social and ethical implications of medical genetics are a paradigm for those presented by many other areas of medical science.

Future directions

If man can develop effective processes for dealing with the dilemmas of medical genetics, there is hope that these processes can provide a model for similarly coping with new developments in other areas of biology and medicine.

First, the armamentarium of modern medicine and its ability to maintain the human organism after the loss of varying degrees of brain function has raised thorny questions about euthanasia.

Second, B. F. Skinner, a behavioral psychologist at Harvard, has developed effective means of changing man's behavior without his conscious knowledge of what is happening. These methods are being employed experimentally in some penal and mental institutes throughout the country as well as in a variety of institutions that deal with ordinary individuals.

Third, effective drugs and chemicals are being developed for altering man's moods. These agents are already widely used in the treatment of certain mental diseases.

Finally, psychosurgery involves techniques which will alter certain types of behavior, presumably in an irreversible fashion. It has been advocated that these techniques be used to control socially undesirable behavior such as violence.

Each of these developments gives rise to a parallel set of questions. When, if ever, should these techniques be applied? Who should decide, and how should the decisions be enforced? In each case these techniques can be used for mankind's benefit or to his detriment. We have before us one glaring example of man's failure to deal with a problem posing comparable ethical and social dilemmas—the development of atomic weapons. Decisions will be made on these critical issues, whether or not the lay public contributes in an informed and thoughtful fashion. We stand at a pivotal point in man's history. Let us hope that our future directions will reflect the applied wisdom of the many, and not of a few. □