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Genetic Screening: Marvel or Menace?

Peter T. Rowley

Is genetic screening a marvel about to free us from the scourge of genetic disease, or a menace about to invade our privacy and determine who may reproduce?

Genetic screening may be defined as a systematic search in a population for persons of certain genotypes. The usual purpose is to detect persons who themselves are at risk or whose offspring are at risk for genetic diseases or genetically determined susceptibilities to environmental agents (*1*). When an individual is diagnosed as having a genetic condition, the testing of relatives may be recommended. This "retrospective screening" differs from the screening of individuals without known affected relatives (prospective screening). Genetic screening may be undertaken also for research purposes unrelated to disease or the improvement of health. Retrospective screening and screening for research purposes will not be further considered here.

Genetic screening differs from nongenetic health screening in at least three important ways. First, whereas in both types of screening, identification of persons at risk may lead to the identification of others at risk, in the case of ordinary health screening the connection is often by physical proximity (contact) whereas in genetic screening it is by genetic proximity (kinship). Second, whereas in other forms of health screening the concern is about the subject being screened, in genetic screening the concern is often about the subject's offspring. Third, genetic screening carries an inherent risk of impairing self-image and perceived suitability as a marriage partner or parent.

Types of Genetic Screening

There are three principal types of genetic screening. Newborn screening seeks disease in the newborn. Fetal (prenatal) screening seeks disease in the fetus. Carrier screening seeks heterozygotes for genes for serious recessive disease. The three types have, respectively, a long established, a recently established, and a yet to be established place in health care.

Newborn Screening

Newborn screening has focused largely on the detection of inborn errors of metabolism. An inborn error of metabolism is an inherited biochemical defect, classically a deficiency of an intracellular enzyme. Such deficiencies cause disease due either to the accumulation of the enzyme's reactant or its metabolites or to a deficiency of the enzyme's product.

Phenylketonuria (PKU) was the first condition for which newborn screening was widely adopted (*2*). Mass screening was feasible, despite the disease's low incidence by public health standards (1 in 11,500) (*3*), because of the discovery, by Guthrie in 1961 (*4*), of a bacterial growth inhibition assay for measuring blood phenylalanine. Before a newborn is discharged from the hospital, a sample of its blood is spotted onto filter paper and mailed to a regional laboratory (*5*). Despite the fact that most states made newborn screening for PKU mandatory before methods for diagnosis and treatment of the disease were firmly established, newborn screening for PKU remains a major triumph of genetic screening (*6*). A low phenylalanine diet begun in the first few weeks of life prevents marked mental retardation in affected children.

Phenylketonuria, initially thought to be a single disease, illustrates the phenomenon of genetic heterogeneity. High concentrations of phenylalanine in the blood of a newborn may have multiple genetic and developmental causes. In

The author is professor of medicine, pediatrics, genetics, and microbiology at the University of Rochester, Rochester, New York 14642.

addition to classical PKU due to phenylalanine hydroxylase deficiency, there is a transient hyperphenylalaninemia due to hepatic immaturity. This abnormality disappears without treatment. More serious are some variant forms of PKU due to either a deficiency of dihydropteridine reductase or a defect in dihydrobiopterin synthesis (*2, 7*). These disorders require special procedures for diagnosis. Mental retardation is not prevented by phenylalanine restriction alone; a deficiency of monoamine neurotransmitters is also present. The efficacy of drug treatment for this deficiency is under study. At least eight causes for hyperphenylalaninemia in the newborn have been discovered (*7*), largely through newborn screening. In fact, any given clinical syndrome may have multiple genetic causes, each with its individual requirements for recognition and management. Such genetic heterogeneity, while providing valuable scientific insights into metabolic vagaries, makes genuine comprehensiveness of genetic screening programs an elusive goal.

With regard to classical PKU, questions remain. Must the diet be continued into adult life? A woman with undetected PKU and with unrestricted phenylalanine intake has a risk of producing children with severe mental and physical defects caused by high phenylalanine levels in the maternal blood (*8*). Although such women can have normal children if phenylalanine restriction is reinstituted prior to conception, their PKU may remain unknown to them or their physician. The Quebec Network of Genetic Medicine has instituted a register for all persons in Quebec Province known to have PKU (*9*). It contacts them on their 12th birthday to provide counseling about their reproductive options, that is, planned pregnancy with phenylalanine restriction, termination of an unplanned or untreated pregnancy, reliable birth control, sterilization, or adoption. This program illustrates how government can fulfill a need for long-term tracking that is difficult for private medicine because of the multiplicity of providers of care for one individual.

Other inborn errors frequently screened for at birth are galactosemia, branched-chain ketonuria (maple syrup urine disease), and homocystinuria. Like PKU, these inborn errors may cause severe mental retardation or death which may be preventable by promptly instituted dietary treatment. However, the benefit of screening is less clear-cut because of other features, such as rapidity of onset of symptoms, complexity of treatment, or rarity of the condition (*10*).

A major recent addition to newborn screening is testing for hypothyroidism (*11*). In most cases this is due to a multifactorial deficiency of thyroid tissue, rather than to an inborn metabolic error. Mental and physical retardation can be prevented by treatment, consisting of thyroid hormone replacement. No special diet is required. It is significantly more frequent (one in 4000) (*12*) than other conditions usually screened for at birth.

Summary. Genetic screening is a systematic search in the population for persons of certain genotypes. The usual purpose is to detect persons who themselves or whose offspring are at risk for genetic diseases or genetically determined susceptibilities to environmental agents. Is genetic screening a marvel about to free us from the scourge of genetic disease or a menace about to invade our privacy and determine who may reproduce? There are three different types of genetic screening. *Newborn screening* identifies serious genetic disease at birth, permitting prompt treatment to prevent mental and physical retardation. *Fetal screening* and prenatal diagnosis identify genetic disease in the fetus permitting selective termination of pregnancy and the opportunity to have children free of defects detectable in utero. *Carrier screening* identifies individuals heterozygous for a gene for a serious recessive disease who may be at risk for affected offspring. The challenge to society is to provide (by way of cost-effective programs) expert services, including genetic counseling and follow-up, to all who may benefit, to ensure confidentiality and freedom of choice, and to avoid misunderstanding and stigmatization. It is recommended that the objective of screening programs should be to maximize the options available to families at risk rather than to reduce the incidence of genetic diseases. Whenever possible, the providers of these services should be the providers of primary health care. Urgently needed are a greater awareness of avoidable genetic diseases on the part of primary care providers and efforts to familiarize the public with the basic concepts of human genetics through the public school system.

Of the various types of genetic screening, newborn screening is the most widely practiced. The great majority of infants born in the United States are tested for the above conditions resulting in a marked decrease in the number of symptomatic children. The cost of PKU screening is more than offset by the savings in health care required (usually institutionalization) without screening (*13*). Testing for other inborn errors on the same blood sample entails little additional cost. Newborn screening represents one form of genetic screening in which government has effectively participated. State health departments, which are responsible for the supervision of newborn screening, have effectively pooled resources on a regional basis for greater efficiency (for example, New England states, Northwestern states–Alaska).

Nevertheless, important issues remain (*14*). First, what additional diseases should be screened for? Several diseases proposed and some arguments made against them are adenosine deaminase deficiency (rare), tyrosinemia/tyrosinosis (rare except in certain populations), histidinemia (symptoms variable, treatment unproven), chromosomal disorders (*15*) (no intervention proposed), familial hypercholesterolemia (*16*) (treatment of unproven benefit), cystic fibrosis (treatment unsatisfactory), sickle cell disease (treatment unsatisfactory) (*17*), and Duchenne muscular dystrophy (treatment unsatisfactory) (*18*).

In the case of diseases for which treatment is ineffective, the argument has been made that neonatal diagnosis gives parents the opportunity to avoid the birth of a second affected child. However, the resulting decrease in incidence is small: assuming two-child families and abstinence from childbearing by all counseled couples, the reduction in incidence is only 1/8 (*19*). Second, should a second sample be obtained after hospital discharge because some cases may be missed by early discharge? Third, should states appropriate funds, not only for diagnosis but to ensure adequate treatment? Fourth, how can nongovernment laboratories which do the testing in some states be more effectively monitored? Fifth, should newborn screening be legally mandated or should informed consent be sought prior to testing, as in Maryland (*20*)?

Fetal Screening and Prenatal Diagnosis

Prenatal diagnosis of birth defects represents one of the most important practical advances in medical genetics in recent years. In most cases the fetal cells analyzed are obtained by amniocentesis, the removal of amniotic fluid containing

sloughed fetal skin cells at 14 to 20 weeks of pregnancy. The commonest indication for fetal screening is a maternal age of 35 or greater because of the increased risk for an offspring with a chromosomal anomaly. The most common of these is Down's syndrome; the abnormality is paternal in origin in 30 percent of cases (*21*). Prospective parents exposed to mutagenic agents such as chemicals and x-rays often seek prenatal diagnosis but are difficult to aid because most birth defects are not detectable by chromosomal analysis.

Prenatal diagnosis may also be indicated if a previous child has had a chromosome abnormality, if either parent is a carrier of a chromosomal anomaly (most commonly a balanced translocation), if a previous child or a close relative has had a neural tube defect, if the mother is a known or a presumed carrier of a serious X chromosome–linked recessive disorder (for example, hemophilia or Duchenne muscular dystrophy), or if both parents are known carriers of a gene for a significant autosomal recessive disorder detectable in utero (for example, Tay-Sachs disease).

Cytogenetic, biochemical, and developmental disorders involve different methods of analysis of the amniotic fluid cells obtained. In the case of neural tube defects, the commonly used biochemical marker is an increased concentration of α-fetoprotein, found where the fetus' spinal canal is in direct contact with the amniotic fluid ("open" cases).

The gene product can be directly measured in a large number of conditions (*22*), usually by assay of enzymatic activity (for example, in mucopolysaccharidoses). Less satisfactory is the prenatal diagnosis of X chromosome–linked conditions in which the biochemical defect is not known. In the case of Duchenne muscular dystrophy, a devastating disorder uniformly fatal in young adult life, parents at risk must decide whether to abort any male fetus even though there is only a 50 percent chance that a given male fetus has inherited the X chromosome bearing the Duchenne gene.

Recently, analysis of DNA from cells in the amniotic fluid has permitted prenatal diagnosis of hemoglobinopathies. Sickle cell anemia in the fetus can be diagnosed by restriction enzymes Dde I (*23*) and Mst II (*24*) because the nucleotide substitution in the sickle gene eliminates a restriction site for each enzyme. Various forms of thalassemia may be diagnosed by detection of the change in DNA that is causing the disease, for example, a deletion (*25*). Because of the multiplicity of mutations that cause thalassemia, however, analysis of genetic linkage between globin gene loci and polymorphic restriction sites is often necessary (*26*). Synthetic oligonucleotide probes specific for normal or mutant nucleotide sequences have also been used (*27*). Prenatal diagnosis based on linkage to polymorphic restriction sites is expected to become possible for any single-gene disorder (*28*).

Amniocentesis cannot be performed before the second trimester of pregnancy, and by the time results are available fetal movement may have been felt. Diagnosis during the first trimester would be preferable, both because of greater patient acceptance and because pregnancy termination would then be safer. An alternative method of diagnosis is to obtain, transvaginally at 6 to 10 weeks of pregnancy, samples of chorionic villi. These villi are of fetal origin and may be used for the prenatal diagnosis of hemoglobinopathies (*29*) and chromosome abnormalities.

Prenatal diagnostic methods have enabled many couples with a known genetic risk to have healthy children. As a result, the incidence of certain genetic diseases, for example, Tay-Sachs disease (*30*), Down's syndrome (*31*), and, in some regions, thalassemia major (Cooley's anemia) (*32*) has been markedly reduced. Fetal screening in cases of advanced maternal age has been widely adopted. An important factor has been extensive media coverage leading to a demand for services. Lawsuits, brought against obstetricians by parents of children with birth defects detectable but not detected by prenatal diagnosis because it was not offered, have educated obstetricians beyond the plaintiff.

Many issues remain to be resolved. Some of these are technical, for example, the need for safer methods to sample fetal blood, required at present for the diagnosis of hemophilia and currently carrying a 4 to 5 percent fetal mortality. One approach under investigation is the detection and sorting of fetal blood cells from the maternal circulation by means of flow cytometric methods. Other issues require more information to be resolved, for example, what should a physician tell parents about the phenotype of their child when fetal chromosome analysis reveals a previously undescribed karyotype? A major controversy is whether every pregnant woman should be screened for elevated concentrations of serum α-fetoprotein which can signal an increased risk of a neural tube defect in her fetus. Among the issues are the ability of providers to follow a complex sequence of diagnostic steps in following up elevated α-fetoprotein values, government regulation of reagent use, and whether benefits will outweigh costs [in view of the incidence of the defect in the United States (one in 590 births)] (*33*).

The overriding issue in the promulgation of prenatal diagnosis for birth defects is, of course, the controversy over abortion. Many parents who find abortion unacceptable in other circumstances do choose to terminate a pregnancy in which the fetus is proved to have a serious birth defect. In fact, prenatal diagnosis has had a "pro-life" effect for couples who previously avoided pregnancy because of a genetic risk but now willingly conceive (*34*). Further, some couples choose prenatal diagnosis with no thought of termination but rather to prepare for the birth of a child with special needs.

The lower socioeconomic groups are still underserved by this new technology. At least part of this underutilization is inadequate access to these services and insufficient understanding of their benefits (*35*).

Carrier Screening

Carrier screening is the identification of heterozygotes for an autosomal recessive or X-linked recessive disease. To many people, "genetic screening" brings to mind chiefly carrier screening because it is this form of screening that has frequently been carried out through public appeals, whereas newborn and prenatal screening have been carried out in the course of regular health care.

Many considerations should be weighed in establishing carrier screening programs (*36*). First, the disease in question should be serious. Second, the test to be performed on the population at risk should be simple, relatively inexpensive, and sensitive enough not to miss positive individuals. If the test itself is not specific, then a backup test of adequate specificity should be available. Third, the individual identified as positive should have some options. For example, married couples identified as being at risk for a recessive disease for which there is no prenatal diagnosis might choose to take the risk, undergo artificial insemination, or adopt a child and forgo pregnancy. But providing such information might not be a service since all of the options might be unattractive. Fourth, the costs avoided should exceed the costs incurred. A major determinant of the cost is the frequency of the disorder in the population screened.

Tay-Sachs disease was the first disorder for which large-scale carrier screening was done in the United States. Tay-Sachs disease meets most of the criteria

above. It is serious, being characterized by developmental delay, blindness, seizures, and paralysis; it is usually fatal by age 3; and it is without specific treatment. There is a satisfactory test for the carrier state. Prenatal diagnosis is available for the enzyme (hexosaminidase A) in amniotic fluid cells. The disease occurs predominantly in the Ashkenazi Jewish population. Kaback directed a program in the Washington/Baltimore area in the early 1970's with excellent results (*37*), and since then similar programs have been initiated in most large U.S. cities and many cities abroad. The relative incidence of Tay-Sachs disease has been significantly reduced by such programs (as well as by exogamy) and couples at risk have been able to have only healthy children.

In contrast to this generally successful experience with Tay-Sachs screening was the experience with sickle cell screening in the early 1970's. Some of the screening programs were politically motivated and lacked sufficient expertise, confidentiality, and provision for the counseling of subjects identified as positive. Positive individuals often suffered a decreased self-image (*38*). Positive children were often overprotected by parents. Individuals were sometimes discriminated against for purposes of marriage, employment, or insurance. A revealing study of a sickle screening program was conducted in Orchomenos, a Greek village where marriages were frequently arranged by parents, a conceivably ideal arrangement to take into account genetic knowledge. Nevertheless carriers were stigmatized as undesirable marriage partners, not only for other carriers, but for everyone (*39*). Another adverse result of the U.S. screening program was the exposure of nonpaternity, that is, the fathering of a child by someone other than the presumed father. Many states passed laws requiring sickle testing at birth, at school entry, or prior to marriage, laws leading to charges by blacks of attempted genocide.

In theory, it should be easy to avert some of these unfortunate results by providing accurate testing, adequate counseling, and strict confidentiality. These goals are difficult to achieve in public programs. A major reason is the regrettable fact that the average citizen lacks the background in biology and genetics to comprehend the significance of the carrier state.

Few diseases are common enough in the general population to merit carrier screening. Many genetic diseases have an especially high incidence in a particular ethnic, racial, or religious group (*40*). Screening only members of such a group involves difficulty in determining who is a member of that group and risks charges of discrimination. A group to be screened should have a partnership role in planning any screening effort. The most common serious autosomal recessive disease in Caucasians is cystic fibrosis, but at present there is no satisfactory test for the heterozygote.

The best age for carrier screening is arguable. The newborn identified as having sickle trait is not likely to benefit directly since reproduction is remote. However, if the parents are screened and found to be at risk for a child with sickle cell anemia, the information may be a significant benefit to the family unit, particularly now that prenatal diagnosis of sickle cell anemia by DNA analysis is safe and accurate.

A major issue in genetic screening is whether it should be legally mandated or voluntary. Arguments made for mandatory screening are higher compliance rates, lower unit cost, timely execution, and facilitation of record-keeping of incidence and outcome. However, voluntary screening is more in keeping with the American tradition. It recognizes the fact that not all citizens will benefit equally, for example, those who do not condone termination of pregnancy may not view prenatal diagnosis as a benefit. Voluntary screening may also reduce the likelihood of adverse psychological effects if the screening is preceded by appropriate education about the benefits and risks of testing and if consent for testing is truly informed. Whereas in most states newborn screening is legally mandated, carrier screening is generally voluntary. A National Academy of Sciences Committee has condemned mandatory carrier screening (*41*).

A quite separate issue is whether genetic carrier screening should be a public or private matter. The Tay-Sachs and sickle cell screening programs described above were conducted publicly and involved temples, churches, fraternal organizations, and in some cases announcement by the media. Advantages of such sponsorship include the assistance of the voluntary organization in enlisting screenees in a group educational program prior to screening and voluntary personnel who may donate time and provide support for those found to be positive. However, an equally good case can be made for incorporation of certain types of screening into primary health care (*42*). For all its success the Tay-Sachs programs have screened only 10 percent of the adult target population in 10 years (*43*). Public screening efforts may involve subtle forms of coercion, for example, among members of an extended family, and may risk stigmatizing carriers (*44*). A regular health setting is more likely to provide confidentiality and needed follow-up and to avoid duplication of testing. Voluntary groups may operate only intermittently and for some populations there may be no suitable organization. The success of the Tay-Sachs effort has been due in no small part to the high educational attainment of this population group and, to the extent that this characteristic does not apply to other population groups, other screening efforts may be less successful. Rosenstock (*45*) has observed that "systematic efforts to develop rational screening programs on a regional level are likely to pay greater health dividends than a series of unrelated opportunistic programs."

To claim that genetic screening is ideally provided by the primary health care sector is not to claim that this sector is now ideally equipped to shoulder the task. First of all, the poor integration among health care providers in the United States compared to most Western countries causes duplication of effort and lack of follow-up (*46*). Second, most medical practitioners, excepting family practitioners, are oriented to the care of the individual rather than to the care of the family as a unit. Much primary medical care today is rendered by the specialist. The pediatrician may make a genetic diagnosis but leave reproductive counseling to the obstetrician who may fail to take a family history. Preventive medicine as a whole has taken a rather slower hold on the practice of medicine than might be desired. For the most part, adult medical care still waits for the individual to appear with a "chief complaint."

Genetic knowledge among medical practitioners is deficient (*47*). A survey of pediatricians, obstetricians, and family practitioners in 1974 found that nearly three-quarters reported that no course in genetics had been available during their medical training and that, as a whole, these physicians were not ready to accept genetic screening (*48*). Although the percentage of medical schools with a formal course in genetics increased from 8.6 percent in 1955 to 75 percent in 1978, teaching is still primarily in the first 2 years of medical school and lacks adequate integration into clinical training (*49*).

Just as laymen have played a role in educating obstetricians about the benefits of prenatal diagnosis, so laymen must ultimately educate physicians as a whole about their desires for genetic screening. An important contribution toward this end has been made by Scriver

and his colleagues who developed a genetics curriculum for Montreal high school students. In the context of learning about genetic differences among normal individuals, high school students had a 75 percent acceptance rate of carrier (Tay-Sachs) testing compared to a 10 percent acceptance rate among adults (*50*). Conducting genetic screening in public schools requires parental permission in most U.S. communities and can be criticized as risking coercion through peer pressure. However, public schools are ideal for educating the public about genetics. If citizens learn simple genetic principles as part of their high school education, they can better understand the significance of genetic tests offered later and help health care policy-makers decide what information will be useful. Childs and Hickman (*51*) have outlined how genetics could serve as a focal point for the teaching of human biology throughout elementary and secondary school years.

Informed consent is generally stated to be a requirement for genetic screening. This is abrogated by most states in the case of newborn screening where it is generally felt that the stakes are too high and time too short to make it voluntary (*20*). In favor of informed consent for most types of genetic screening is the recognition that genetic information is psychologically different from other health information in that it refers to an immutable part of oneself which may complicate marital and reproductive plans. Nevertheless, it is common for parents of a child born with a preventable birth defect to ask, "Why didn't you doctors tells us this could happen? We would never willingly have had a child like this!" The problem with requiring informed consent in the primary health care setting is the fact that it can be argued that as much time must be spent in obtaining informed consent as in educating the individual found to be positive about the significance of the result. Consequently, a case can be made for including appropriate genetic screening as a part of multiphasic health screening. The person to be screened could be informed as to purpose by means of fact sheets provided in advance and giving the person the opportunity to decline. Such a procedure is feasible only if adequate provision is made for counseling subjects found to be positive. Videotapes supplemented by written material to take home may reduce the total professional time required. A medical genetic paraprofessional, or "genetic associate," can be of enormous value in answering the many questions that genetic screening programs elicit (*52*).

The National Genetic Diseases Act of 1976 has provided federal money to 34 states to support genetic testing and counseling services, much of which has provided salary support for genetic associates (*53*). Since 1981, however, federal administrative changes and funding cuts have threatened the continuation of these programs.

In many cases reluctance to undergo genetic screening is the result of considering only the short-term risk of anxiety related to the testing procedure rather than the long-term risk of anxiety associated with the birth of a child with a serious genetic defect. In so far as this reluctance represents a lack of awareness, more attention might be devoted to persuading individuals to find out what they need to know about their genetic constitution. Such educational programs deserve as much effort and imagination as are now invested in persuading people to choose a given antacid.

Occupational Screening

Genetic screening in industry has two different rationales. The first is the identification of individuals at greater risk than the average worker for suffering adverse effects from industrial exposures. The second is the use of genetic tests (for example, chromosome analysis) to detect actual or potential genetic damage to the genetically normal worker.

Omenn (*54*) has listed criteria for traits for which occupational testing might be justifiable: (i) a sufficiently high prevalence of the trait in the worker population; (ii) a significant increase in the risk of morbidity in workers with the trait compared to those without it; (iii) the availability of a test to detect the trait which is reliable and inexpensive; and (iv) a clear understanding between management and labor about what action might be taken on the basis of test results and who would have access to this information. Omenn (*54*) has also listed traits known to be genetically polymorphic and which, if deficient, might predispose an individual to occupational morbidity upon exposure to chemical agents (*N*-acetyltransferase, plasma pseudocholinesterase, glucose-6-phosphate dehydrogenase, and methemoglobin reductase deficiency) and to inhaled pollutants (α_1-antitrypsin, arylhydrocarbon hydroxylase inducibility, metabolic conversion of nicotine, and plasma paraoxonase).

It was recently reported that 59 major corporations were considering adopting some kind of genetic testing of employees (*55*). Labor leaders and toxicologists have expressed concern that industry is putting a bigger emphasis on "weeding out the susceptibles" than on cleaning up the workplace.

Today, many people believe that the statement made by Cooper (*56*) a decade ago still applies:

> What is the current state of tests of hypersusceptibility? There is insufficient epidemiologic evidence to support the use of any of them as a criterion for employability without many qualifications. On the other hand, there is ample scientific evidence to support wider testing. Premature assumptions as to the necessity for such tests or overoptimistic claims for the benefits can actually impede testing. On the basis of what we now know, no employers should be regarded as liable or derelict for not choosing to screen his employees. If he screens all employees, he would have to consider whether he would be regarded as liable to criticism for using a positive test to deny employment, or conversely, for jeopardizing the health of an individual permitted to work with a positive test. If it is clearly understood that the appropriate application of tests of hypersusceptibility is still on trial, then progress can be made in studying them.

The workplace is only one example of an environment that may reveal genetically determined differences in susceptibilities among individuals. The morbidity to be reduced by genetic screening is thus not due to genetic factors exclusively, but rather due to an interaction between specific genetic and specific environmental factors. Childs (*57*) has deplored the tendency to categorize a disease as due exclusively to heredity *or* to the environment. He has emphasized that each patient presentation calls for assessing the separate contributions of genetic and environmental factors.

Screening Donors for Artificial Insemination

It is possible for a woman whose mate has a dominant gene for a serious genetic disease, or who shares with her mate a gene for a serious autosomal recessive disease, or who has no male partner, to bear a healthy child by means of artificial insemination. It is the responsibility of the physician performing artificial insemination to maximize the probability that the resulting child will be born healthy. Hence the genetic screening of the sperm donor should be particularly comprehensive. Such screening should include a complete medical history with information on any exposure to radiation or mutagenic drugs, a reproductive as well as family history, Rh typing if the recipient is Rh-negative, and testing for any heterozygous state commonly found in his or the recipient's ethnic group (*58*).

Population Aspects of Genetic Screening

Hohenemser *et al.* (*59*) have suggested a method for constructing, for any technological innovation, a profile of hazardousness. This profile reflects both hazards (threats to humans and what they value) and risks (quantitative measures of hazard consequences that can be expressed as conditional probabilities of experiencing harm). Since genetic screening can affect the genetic structure of offspring, the effects of such screening may be long lasting. However, unless choices were to be mandated on a large scale, no significant alteration in the genetic structure of populations would be likely. Hence, ensuring the availability of free choice should ensure continued genetic diversity of the population.

Limitations of Screening Capabilities

It has been estimated that, of every 200 newborns, approximately two will have a significant single-gene disorder, one will have a chromosome disorder, eight will have a significant congenital malformation, two to four will have idiopathic mental retardation, and nine will have a multifactorial (partly genetic) disorder of later onset (for example, diabetes, coronary heart disease, psychoses) (*60*). Genetic screening can identify the risk of many monogenic disorders by study of the prospective parents and can identify chromosomal disorders and additional monogenic disorders from study of the fetus. But such screening prenatally cannot readily identify multifactorial disorders, including most instances of idiopathic mental retardation and congenital malformations.

In addition to the genetic factors transmitted from parents to child, the occurrence of new mutations must also be considered. New dominant mutations may cause genetic disease regardless of the screening of prospective parents. Methods to monitor human mutation rates are urgently needed because of increased environmental exposure to mutagenic agents.

Psychological Aspects of Genetic Screening

Discussions of genetic screening often refer to reproductive decision-making as though reproduction were necessarily preceded by deliberation. In fact, even for couples at genetic risk, many conceptions are not planned, others represent attempts to compensate for a deceased or defective child, still others constitute efforts, often unconscious, to demonstrate ability to bear a normal child. The average couple has difficulty with the concept of probability and may, while ignoring the actual risk of its occurrence (*61*), convert a statement of risk (for example, a 1 percent chance of having a child with a chromosome abnormality) into a binary statement (either it will or it will not happen). They then may visualize the worst outcome and judge whether or not they could cope with it (*62*). Additional information on the process of genetic counseling is provided elsewhere (*63*). Achieving the full benefits of genetic screening will require better methods for communicating risk information based upon a better understanding of how individuals deal with probabilities of adverse reproductive outcomes.

Ethical Aspects of Genetic Screening

Genetic screening programs, existing and proposed, have sparked many ethical debates over the past decade (*64*). The President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research has recently issued a report on the ethical, social, and legal implications of genetic screening, counseling, and education programs (*53*). The Commission enunciates five principles and makes some recommendations. Excerpts are:

1) *Confidentiality*. "Genetic information should not be given to unrelated third parties. . . ." However, adoption laws should be changed so that information about serious genetic risks can be conveyed to adoptees or their biological families without betraying anonymity.

2) *Autonomy*. "Mandatory genetic screening programs are only justified when voluntary testing proves inadequate to prevent serious harm to the defenseless, such as children, that could be avoided were screening performed. . . . The value of the information provided by genetic screening and counseling would be diminished if available reproductive choices were to be restricted. (This is a factual conclusion that is not intended to involve the Commission in a national debate over abortion.)"

3) *Knowledge*. "Decisions regarding the release of incidental findings (such as nonpaternity) or sensitive findings (such as diagnosis of an XY female) should begin with the presumption in favor of disclosure. . . ." An informed public requires, not just extensive genetic counseling services, but more intensive exposure to genetic principles in public schools.

4) *Well-being*. "Screening programs should not be undertaken until the [screening] test has first demonstrated its value in well-conducted, large-scale pilot studies. . . . A full range of prescreening and followup services for the population to be screened should be available before a program is introduced."

5) *Equity*. "Access to screening may take account of the incidence of genetic disease in various racial or ethnic groups within the population without violating the principles of equity, justice, and fairness."

The above precepts are concerned primarily with protecting the individual from undesirable effects of genetic screening. Such effects will be minimized if screening programs adopt the specific goal, not of reducing the incidence of a disease, but of maximizing options available to couples at risk for an affected child.

The larger ethical issues in genetic screening concern whether the benefits of a proposed screening program will outweigh the burdens, and, if this is judged to be likely, what priority to assign the program in competition for limited resources with other desirable programs of health care. As in other fields of medicine, a case-by-case analysis, as advocated by Toulmin (*65*), may be more helpful than abstract principles.

Legal Aspects of Genetic Screening

If a family had an undesirable reproductive outcome, such as the birth of a defective child, and there was reason to identify the family as at increased risk for such an outcome, and yet the physician did not inform them of their options (for example, prenatal diagnosis), then the family may decide to bring suit against the physician (*66*). Other examples of legal liability in the provision of genetic services include intervention which proves harmful, for example, artificial insemination resulting in the birth of a child with Tay-Sachs disease (*67*), or breach of confidentiality occurring when a physician notifies relatives of their genetic risk without the permission of the patient (*68*).

Conclusions

Genetic screening thus represents neither a panacea nor an anathema. Among its past accomplishments are reduction in the incidence of symptomatic inborn errors through newborn screening and, for many couples at risk for a child with a serious birth defect, provision of the

option to avoid having a child with a defect that could have been detected. Still uncertain is the advantage to be gained by optimal provision of carrier testing. Individual differences in receptivity to genetic information and in reproductive preferences complicate policy-making.

If the promise of genetic screening is to be fulfilled, certain needs for the future are evident. First, research must be conducted on the best delivery mechanism for technologies already at hand. For example, now that it is possible for a couple at risk to avoid the birth of a first child with sickle cell anemia or Cooley's anemia by analyzing fetal DNA, what kind of screening program should be used to identify such couples? Comparisons are needed between various methods of delivery of genetic services (*69*). The roles of the health care provider, the voluntary organization, and local, state, and federal governments should be clarified and integrated (*70*). Legislative and executive branches need the advice of commissions which include medical geneticists to prevent hasty legislation and to provide for timely updating of health policy without requiring legislative revision, such as provided in Maryland by the Commission on Hereditary Disorders (*71*).

Kaback has distinguished three approaches to the control of genetic disease: cure, effective therapy, and prevention (*72*). Cure—that is, the correction of the intrinsic defect in germ line DNA—is not in the immediate future, despite the success of certain recent gene transfer experiments with the use of somatic cells in vitro. Prevention is a high priority primarily because truly effective therapy is not available for most genetic diseases.

The scientific community bears a responsibility, not only to expand knowledge but also to educate the public. Scientists must assist their fellow citizens in understanding the true promise of science, including what science cannot provide. Science provides options but individuals must choose among them.

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