Current Comments

Medical Genetics: The New Preventive Medicine

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Recently, I published an essay describing the current state of preventive medicine and the impressive efforts being made by the Centers for Disease Control (CDC) to incorporate this philosophy into standard medical practice.[1] Shortly after that essay was published, I received a letter from cytogeneticist D. Soudek, Kingston Psychiatric Hospital, Kingston, Ontario, pointing out I had failed to discuss a very important aspect of preventive medicine—medical genetics.[2] In fact, I was somewhat stunned by this important reminder as I had been planning an essay on medical genetics for some time. Considering ISI®'s early work in developing a citation index to the genetics literature, it is somewhat disconcerting to realize how little editorial attention I've devoted to any aspect of genetics. Soudek's letter merely emphasizes that even knowledgeable people do not automatically think of medical genetics as an important part of preventive medicine—if not now, certainly in the future.

Until recently, physician involvement in what is now being called medical genetics was largely confined to discussing the recurrence of genetic disorders and explaining the limited number of options available for preventing the birth of a child with these disorders. Since, for many years, most genetic diseases could only be detected after the birth of a child, medical genetics was mainly the province of physicians and researchers investigating "esoteric" diseases known to have a genetic component. One exception to this generalization was the discovery that different Rh blood groups in parents can pose a threat to their offspring. Blood tests to detect this hereditary incompatibility have been available for many years.

In the past 20 years, new and more accurate methods of diagnosing hereditary disease have been developed. Researchers have also recognized that many diseases that occur later in life are genetically influenced. As a result, physicians and basic research scientists alike have increasingly focused their attention on the genetic basis for disease. In addition, each year thousands of persons are requesting amniocentesis and other medical techniques which can detect specific diseases in the fetus. People are requesting these tests because they have a family history of hereditary diseases, are concerned about having a defective child, or are concerned about having a child with chromosomal abnormalities related to the parent's advanced age.

More than 3,000 diseases are known to have a genetic component, and 150 new ones are being recognized each year, according to James R. McBee, director, National Clearinghouse for Human Genetic Disease, which provides information on genetic screening and treatment programs.[3] So the preventive

value of recognizing the presence of, or susceptibility to, genetic disease can be far-reaching.

Methods for prenatally diagnosing genetic disease have helped to diminish the fears of people who might not have chosen to become parents without the knowledge now available. In a similar vein, individuals with a hereditary susceptibility to certain diseases can now take steps to moderate the disease or begin treatment in its early stages.

While knowledge of inherited factors in disease has been available since the early 1900s, it generally was not applied to clinical practice until the 1950s.[4] Part of this delay can be attributed to the early affiliations of some medical "hygienists"[4] with the already well-established eugenics movement. Scientists in Europe and the US were doing research on the hereditary transmission of human traits prior to the twentieth century, but institutions devoted to predicting the recurrence of inherited human diseases originated in the US and UK. As is well-known, in Germany—where eugenics research and publication were quite active around the turn of the century—eugenics became a political issue, despite the best intentions of many geneticists.

Two of the major institutions in the US and UK where genetics was first applied to human health were also associated with the controversial field of applied eugenics. The Laboratory of National Eugenics, established in London in 1907, was closely aligned with the beliefs of its founder, Francis Galton.[5,6] He is well-known for his advocacy of selective human breeding.

Charles B. Davenport, who established the first institute for human genetics in the US, tried to show that criminality and insanity represented simple Mendelian traits.[7] The Eugenics Records Office was founded by Davenport in Cold Spring Harbor, New York, in 1910.[6] This was only ten years after the rediscovery of the work of Gregor Johann Mendel, the nineteenth-century monk who elucidated the first laws of heredity. Mendel theorized that the traits observed in pea plants occurred through generations because of paired elementary units of heredity. These were later to be called genes. He worked out the statistical occurrence of these traits and, although further refinements and elaborations to his laws have been made, they still form the foundation of modern genetics. There is a considerable mythology about the long delay in the acceptance of his ideas.[8,9]

In the early 1900s, then, human genetics was often treated as that part of eugenics "concerned with the acquisition of knowledge of human heredity."[6] In many cases, this happened because both subjects were taught by the same person at universities and colleges.

Although many geneticists did not investigate medical genetics because of its association with eugenics, an even more important factor was the difficulty of studying the hereditary transmission of diseases and traits in humans. As is so often the case, scientists who were interested in human genetics did not have the technical methodology to study hereditary disease in man.

While the eugenics movement and methodological limitations may explain a general lack of interest in medical genetics among genetics researchers, it does not explain why physicians took so long to adopt Mendelian thinking into their practice and research. The reason for this is the same as for their lack of interest in preventive medicine. According to A. Caplan, Hastings Center, Hastings-on-Hudson, New York, they simply were not aware of its relevance. During the early part of this century, physicians infrequently came across diseases that showed Mendelian inheritance patterns. And diseases which showed such patterns were frequently untreatable.

Consequently, physicians didn't believe they were worth studying.[10] Additionally, doctors and researchers were "busily extending their new etiologic model of disease."[10] Medical attention at this point was focused on microbial sources of disease and infection.

As a result of these factors, genetics remained primarily the territory of zoologists and botanists until the 1950s. At this point, the control of nongenetic diseases—those caused by infection and nutritional deficiency—was advancing, so that attention could focus more on genetic disease.[4] The number of diseases recognized as displaying Mendelian inheritance patterns also began to increase. Medical geneticists were now able to make estimates of the risks of recurrence of hereditary disease.

According to F. Clark Fraser, McGill University, the next major "boost" to medical genetics came with advances in molecular and biochemical genetics, which led to the identification of "inborn errors of metabolism."[4] This term was first introduced by A.E. Garrod, Oxford University, who was also the first to describe Mendelian inheritance in human disease.[11,12] The term "inborn error of metabolism" is now used to describe any genetically determined biochemical disorder in which enzymatic defects produce problems of metabolism. The discovery that one such enzyme deficiency, which results in mental retardation (phenylketonuria), could be successfully treated had major ramifications.[4] Infants in most states of the US and in the UK are now regularly screened for this defect[13] and for congenital hypothyroidism.[3]

During the 1950s, a number of major discoveries further advanced our understanding of medical genetics. In 1956, J.H. Tjio, Experimental Station of Aula, Zaragoza, Spain, and A. Levan, Institute of Genetics, Lund, Sweden;[14] and C.E. Ford and J.L. Hamerton, Medical Research Council, Berkshire, England,[15] independently demonstrated that the number of chromosomes in man was 46, rather than the 48 previously believed. The methods developed by these scientists made possible the accurate study of human chromosomes. They also led to the recognition, in 1959, that chromosomal irregularities are associated with a number of syndromes.[16-18] Victor McKusick, Johns Hopkins University, explains that these events actually led to the birth of "clinical genetics" in that they "gave the clinical geneticist 'his organ' like the cardiologist has his heart, the ophthalmologist his eye and so on." He adds that various biochemical methods developed since the 1950s, and somatic cell hybridization, a technique in which the genetic information from two different types of cells is combined, have helped researchers further define genetically-based biochemical differences in humans.[19]

At present, physicians and scientists use tissue culturing and karyotyping to detect chromosomal abnormalities. In this type of chromosome analysis, cells are allowed to divide in tissue culture. They are then arrested in metaphase, the stage of cell division during which the chromosomes are separated into exactly similar halves. The cells are then stained and the chromosomes are either observed under a microscope, and abnormalities noted; or, a microphotograph of the chromosomes is taken and the chromosomes arranged according to a standard classification system. This arrangement of the chromosomes is called a karyotype. The karyotype is then studied for structural or numerical irregularities. A process called banding, in which the patterns of bands on the chromosomes are studied, enables scientists to observe, with great precision, material that may be present, absent, or irregularly located on the chromosome. Incidentally, the word karyotype should not be confused with eukaryote or pro-

karyote, although these words are all derived from the Greek "karyo," which refers to the nucleus of the cell.[20] A prokaryote is an organism—bacteria, for example—that does not have a true nucleus, so that nuclear material is scattered in the cytoplasm of the cell. A eukaryote has a true nucleus, bounded by a nuclear membrane.

More recently, with the development of diagnostic methods such as amniocentesis, ultrasound, and radiologic examination, it became possible to diagnose chromosomal aberrations, certain inborn errors of metabolism, and other congenital abnormalities in the fetus.

Amniocentesis,[21-23] the most widely used method of prenatal diagnosis, is a process in which amniotic fluid is drawn from the womb during the fourteenth to sixteenth week of gestation and analyzed for those diseases and chromosomal abnormalities suspected in the fetus. The fluid itself is analyzed for neural tube defects, and cells within the fluid are cultured and analyzed for many chromosomal abnormalities and more than 100 inborn errors of metabolism.

The predominant application of amniocentesis so far has been for detection of Down syndrome (mongolism) in the fetuses of women 35 and over. During this period the risk of giving birth to a child with a chromosomal disorder appreciably escalates. About 40 other disorders have been diagnosed through amniocentesis, including Tay-Sachs disease, a deficiency of brain lipid metabolism; galactosemia, a biochemical deficiency of carbohydrate metabolism; and thalassemia, a hemolytic anemia caused by abnormal synthesis of hemoglobin.[24] Amniocentesis is a fairly painless and safe procedure. Its main risk, if any, is a less than one half of one percent chance of inducing abortion.[25]

Ultrasound, another method of prenatal diagnosis, involves the passage of high frequency sound through the womb. This enables physicians to locate the fetus and placenta,[26] and is usually used in conjunction with amniocentesis. Ultrasound makes it possible to detect multiple fetuses. By accurately locating the fetus and placenta, the physician can avoid fetal injury when drawing amniotic fluid through a needle. Examination of the fetal head through ultrasound also can help in the diagnosis of anencephaly, the absence of a cranium, and other structural defects.

The most direct way of examining the fetus is through a fetoscope, a tube which can enter the womb and be used to remove a sample of fetal blood or tissue.[27,28] Disorders such as sickle cell anemia and thalassemia can be diagnosed this way. Unfortunately, the fetoscope, which is still in the research stage of development, has an appreciable risk of fetal loss.[24] As a result, this method is infrequently used.

Another method, amniography, or X-ray examination of the fetus,[29] is useful for finding disorders that are characterized by the absence, or gross structural abnormality, of specific bones.[30] One such example is achondroplasia, a type of dwarfism, which can be recognized radiologically at between 20 and 24 weeks of pregnancy.[19]

Finally, a relatively new method of diagnosing neural tube defects, a class of malformations of the brain and spinal cord including anencephaly and spina bifida, is the alpha-fetoprotein (AFP) test.[31] Neural tube defects, which can lead to death, paralysis, and mental retardation and occur somewhat randomly, can be prenatally detected by analyzing the mother's blood serum for levels of alpha-fetoprotein. This protein normally rises in concentration in the mother's serum during pregnancy. Higher than normal quantities may indicate the presence of a neural tube defect, multiple pregnancy, fetal death, or other defects. When found, this indicates a need for additional tests. Kits for this test, which could be used for widespread screening, are currently being evaluated by the US Food and Drug

Administration.[32] Incidentally, the primordial publication on the AFP test[31] was recently a *Citation Classic*.[33]

Of course, most diagnostic tests reveal that the fetus is normal, which can relieve parents of the anxiety they may have from suspecting it is defective. When a defective fetus is detected, this knowledge—besides giving parents the choice of abortion—enables the physician to begin treatment at birth and, in some cases, treat the fetus in the womb.

Many of these diagnostic tests are used in conjunction with genetic counseling. As defined by C.R. Scriver, McGill University, genetic counseling is "a communication process that attempts to help an individual or family to comprehend medical facts, to appreciate how heredity contributes to the disorder, to understand the options for dealing with recurrence risks, to act upon these options in a manner appropriate for the counselee, and to make the best possible adjustment to the presence or risk of the disorder in themselves, their offspring or other family members."[11]

The genetic counselor generally performs a complete medical review of the individual's pedigree, or family tree. If there's a possibility that the parents are carriers of a hereditary disease or deleterious genes, they are advised of all options, including predictive tests when possible. In many instances, genetic counseling involves more than the purely scientific prediction of recurrence of hereditary disease. It may include helping the parents examine their attitudes toward having a defective child. Genetic counselors may also provide information about the financial and emotional aspects of raising such a child, and help parents who already have a defective child cope with their situation.

Most of this counseling had been done in the past by doctoral level geneticists. More recently, internists, pediatricians, and obstetricians with special knowledge of medical genetics have offered genetic counseling. And at least eight universities now offer programs leading to either a master's degree in genetic counseling or a master's in social work, with a genetic counseling specialty.[3] These include Sarah Lawrence College; University of California at Berkeley, Los Angeles, and Irvine; Howard University; University of Michigan School of Medicine; University of Pittsburgh; and University of Wisconsin–Madison.[3]

No US certification has been offered in this area in the past, but in December, the recently established American Board of Medical Genetics will offer certification through a series of five examinations. These exams, which will be administered by the National Board of Medical Examiners, will include a core exam to be taken by all medical geneticists, a clinical geneticist exam to be taken by physicians and dentists, a medical geneticist exam for persons with doctorates, a clinical biochemical geneticist exam, a clinical cytogeneticist exam, and an exam for genetic counselors. Hope Punnett, a member of the American Board of Medical Genetics, said the board hopes to offer an exam in clinical immunogenetics in the future.[34] The Canadian College of Medical Geneticists, which was incorporated in 1975, has been certifying MD and PhD medical geneticists for several years.[11]

Most people who consult genetic counselors do so after already having had a child with a hereditary disease. Others are patients with a history of genetic disease they don't want to pass on.[35] But many physicians advocate the use of genetic counseling prior to marriage. Even simple knowledge about Rh factors needs to be explained. In emphasizing the preventive nature of medical genetics, A. Milunsky, Harvard University, lists such options as careful selection of a mate, determining if you are a carrier, prenatal testing, abortion of severely defective fetuses, artificial insemination, and adoption. He also

recommends that individuals who suspect they are carriers of a genetic disease be screened for the disease in question.[30]

Population screening for carriers of genetic diseases has been successfully applied to Tay-Sachs disease, an enzyme deficiency carried by one in 30 US Jews of Ashkenazic (East European) descent, and, to a lesser extent, to sickle cell anemia, a blood disease carried by one in ten Black Americans. Screening for thalassemia has been done in several Mediterranean countries and in parts of the US.[30] Since genes for these diseases occur more frequently in these subpopulations, and fairly accurate tests are available for their detection, a widespread screening program can be cost-effective. But most genetic diseases occur less frequently in larger populations, so the costs of routine population screening for those few diseases which can be detected are less cost-effective.

Hereditary diseases can be passed on to progeny in a variety of ways. Most diseases are recessive, which means that a person must inherit a defective gene from *both* parents in order to manifest the disease associated with that gene. If both parents are carriers of the same gene, each child will have a 50 percent chance of being a carrier (carries the gene but does not have the disease). For each child there is also a 25 percent chance of having the disease and a 25 percent chance of not being a carrier or having the disease. Most forms of albinism, which affects the pigmentation of the skin, hair, and/or eyes, are recessive.[30]

With dominantly inherited diseases, at least one parent has a gene that dominates the counterpart, or "allele," contributed by the other parent. In this case, each child of an affected individual has a 50 percent risk of inheriting the disease. Certain dominantly inherited diseases may be expressed more severely in one member of a family than in another. One such example is neurofibromatosis, a disorder of the brain and nervous system in which some children may have mild and others severe symptoms.

Over 100 hereditary diseases are known to be X-linked. These disorders result from a defective gene on one of the X chromosomes. In X-linked inheritance, each of a female carrier's sons will have a 50 percent chance of inheriting the X-linked disease, and each daughter, a 50 percent chance of being a carrier. If only the father has the disease, the daughters will all be carriers and the sons will not be affected. Finally, if the father has an X-linked disease and the mother is a carrier, there is a 50 percent chance a daughter will be affected and a 50 percent chance she will be a carrier. There is also a 50 percent chance a son will be affected. Many forms of mental retardation are believed to be X-linked.[36]

Most X-linked genetic defects cause overt disease only in sons. Daughters receive two X chromosomes, which may counteract each other, but sons receive only one X, and a Y which does not counteract the genetic disease carried by the X. So determining that a fetus is male is often the only way to find out if the mother is likely to have an affected child. For example, if the mother is a carrier of the hemophilia gene, which causes disease only in males, each of her male children will have a 50 percent chance of having the disease. Unfortunately, only six X-linked diseases—Hunter syndrome, Fabry's disease, Lesch-Nyhan syndrome, Menkes syndrome, several forms of hemophilia, and chronic granulomatous disease—can actually be detected in the fetus itself. So mothers who are carriers of other severely debilitating hereditary disease genes may choose to abort all male fetuses.[30] This was formerly done, on occasion, with hemophilia, but new methods of therapy are improving the prognosis in this disease and selective abortion of males is becoming questionable. Since there is no adequate ther-

apy, carriers of certain types of muscular dystrophy genes sometimes elect to abort all male fetuses.

While some carriers of X-linked diseases may have mild manifestations of the disease, there may be some advantage to being a carrier, particularly of a recessive disease. In some instances, carriers may have increased resistance to an unrelated disease. For example, carriers of the sickle cell anemia gene have greater resistance to malaria.[30] Similarly, individuals with Duffy negative blood group have greater resistance to a certain type of malaria.[37]

There are three basic types of genetic disease. In Mendelian inheritance, which I discussed above, single genes or gene mutations are inherited in recognizable patterns. This accounts for about 25 percent of genetic disease. Chromosomal aberrations, or an abnormal number of chromosomes caused by mutation or inheritance, account for about 13 percent, and multifactorial or polygenic inheritance, in which the interaction of genes and nongenetic (environmental) factors cause disease, accounts for about 44 percent.[38]

Despite the fact that about four percent of all liveborn children will have some hereditary disorder,[24] there are only about 231 genetic counseling and screening programs in the US[3] and 843 worldwide.[39] The lack of insurance payment for genetic counseling has probably been a factor in the paucity of programs. In fact, at least one study showed that the majority of patients who come for counseling are in the middle and upper income brackets.[35]

When you consider that it costs at least $250,000 for lifetime support of a person with Down syndrome,[30] the justification for insurance payment for these services becomes evident. Milunsky emphasizes the price paid by parents who have not availed themselves of genetic services. "The presence of a child with serious birth defects in the home becomes a chronic emotional and physical drain on the parents, leading often to a severe state of exhaustion affecting all avenues of their life. Economic hardship may follow and almost invariably increases marital conflict.... Separations and divorce are only too well known in families where such tragedies have occurred. The enormous drain on the energies of the parents frequently leads to a relative neglect of the unaffected children."[30] (p. 9)

Although the emphasis of medical genetics has been largely on birth defects and prenatal screening, this is by no means the only field in which an understanding of the genetic basis of disease has been applied. As I mentioned earlier, members of the biomedical community are investigating and, in some cases, applying their knowledge of genetics to hereditary diseases that manifest themselves later in life.

While research on the genetic basis for such diseases is still fairly new, investigators are beginning to emphasize the individuality of each person's genetic profile. Scriver and colleagues, in discussing the evolution of medical genetics, explain that the genetic paradigm for disease "recognizes the role of intrinsic (genetic) factors for individual homeostasis and susceptibility or resistance to disease.... Because individuals have their own genetic signature, it follows from the genetic paradigm that each person is at his or her own specific risk for a particular disease."[11]

Coronary heart disease, for example, is often associated with high blood levels of cholesterol or triglyceride—conditions which are partially determined by genetic factors. One such condition, familial hypercholesterolemia, is transmitted through a dominant form of inheritance. It can be treated through reductions in the intake of cholesterol and saturated fat. The gene for this disease is carried by about one in every 500 individuals in the US.[30]

Another disease, familial hypertriglyceridemia, affects about one in every 300 individuals in the US. In addition to coronary disease, individuals with familial hypertriglyceridemia have a higher frequency of diabetes and obesity, and may be resistant to insulin.[30]

In familial combined hyperlipidemia, which affects nearly one in 200 in the US, there is a high blood fat level that can cause hereditary disease. Finally, in polygenic hypercholesterolemia, high blood cholesterol is caused by the interaction of genes and environmental factors. Other genetically related causes of heart disease include hereditary defects in the structure of the heart and hypertension.[30]

There is also evidence that cancer may have a hereditary component. For example, it has been found that women with breast cancer that occurs prior to menopause often have affected relatives, particularly when the cancer occurs in both breasts. It has been suggested that some susceptible women lack an enzyme (estradiol hydroxylase) that would normally process the estrogen made by their ovaries.[30] Specific cancers have also been associated with a number of chromosomal disorders, including Down syndrome and Klinefelter syndrome.[30] Additionally, it is currently believed that many malignant disorders occur in genetically disposed individuals exposed to environmental carcinogens. A review article by Purtilo and colleagues lists more than 240 tumors that may have a hereditary component.[40]

Studies to assess the genetic components of disease often involve comparing the behavior and disease patterns of identical and nonidentical twins.[41,42] Since identical, or monozygotic, twins have identical genetic profiles, a high concordance rate between them, as compared to dizygotic twins or siblings, suggests a genetic basis for the condition being considered. Researchers also conduct studies on adopted children in an effort to isolate the environmental factors that might contribute to disease. If a relationship can be made between the illness of biological parents and the child they've given up for adoption, genetic factors may be implicated.

In his review of genetic counseling for psychiatric patients, M.T. Tsuang, University of Iowa, reports that in severe alcohol abuse a concordance rate of 84.5 percent was found between identical twins, while the rate was 66.7 percent for fraternal twins.[43] He also notes that a Danish study of alcoholism among adoptees and their parents found a much higher rate of alcoholism in the sons who had been adopted from alcoholic biological fathers than among control adoptees. The rate was no higher for daughters who had been adopted from alcoholic fathers.

A number of other psychiatric disorders, including manic-depression,[44] schizophrenia, and presenile dementia,[45] also are believed to have a genetic component. George Winokur, University of Iowa, is among many scientists who believe that bipolar, or manic-depressive, illness can be genetically transmitted. He also suggests there is a genetic component in unipolar, or depressive, illness. Winokur estimates that the sibling of a manic-depressive individual has a 26 percent risk of being affected if one parent is affected, and a 43 percent risk if both parents are affected.[46]

Not surprisingly, "ecogenetic" studies—studies of genetic variation in susceptibility to physical, chemical, and biological environmental agents—are increasing as new knowledge of genetics becomes available.[47] These studies are concerned with many of the genetic diseases I've already discussed, particularly those that can be considered multifactorial.

Many types of cancer are suspected of being ecogenetic, since specific cancers occur more frequently in certain geographic areas. Researchers are exploring the possibility that "genetically determined differences in carcinogenic-

metabolizing enzymes affects susceptibility to various cancers."[40] Lactose intolerance[48] is thought to be a recessive ecogenetic disease, while the factors that determine whether or not caffeine will keep you awake at night may be genetically determined.[30]

A subfield of ecogenetics, pharmacogenetics, is concerned with hereditary factors that affect individual reactions to drugs and chemicals. Pharmacogeneticists emphasize the need to investigate each patient's genetic susceptibility to various drugs before they are administered and to tailor drug regimens to individual needs. Many hereditary conditions, which by themselves cause few problems, are activated when the affected individual is exposed to various drugs. A classic example is glucose-6-phosphate dehydrogenase deficiency, an inherited deficiency of an enzyme within the red blood cell. This disorder occurs most often among Orientals and Blacks. If a person with this deficiency takes any of a number of drugs, including aspirin, he or she may develop a hemolytic anemia, a condition in which red blood cells are destroyed.[30]

Alcoholism is also the subject of pharmacogenetic investigation. For example, Peter Propping, University of Heidelberg, suggests that genetic factors may influence an individual's ability to metabolize alcohol, as well as his or her tolerance of, and dependence on, this substance. A number of observations support a genetic basis for susceptibility to alcoholism. They include varying EEG patterns following alcohol consumption and differing enzymatic reactions to alcohol among various populations. Mongolian people, for example, respond to alcohol with rapid, intense flushing of the face and symptoms of intoxication much faster than do most Caucasians.[49]

Exposure of genetically disposed individuals to various chemicals is believed to cause cancer and other diseases. A number of chemicals, and ionizing radiation,[50] are known to cause genetic mutations leading to disease, reduced fertility, and the birth of defective children. Researchers at several institutions, including the University of British Columbia, the Chalk River Nuclear Laboratories, Ontario,[51] and the University of Oslo,[52] are looking at how these mutated genes are carried by future generations, and at the repair mechanisms of these genes.

The diseases that may be environmentally induced as a result of genetic predisposition are too numerous to name here. However, a review of these diseases makes it eminently clear that many political and social problems will arise before a full understanding of genetically determined disease has been reached. Individuals susceptible to any of the diseases that can be provoked by exposure to chemical substances may be barred from jobs employing these chemicals. Food additives known to induce disease in predisposed individuals may have to be taken off the market.

Controversies and problems have already surfaced from what is known (or not known) about susceptibility to disease and about people who are carriers of harmful recessive genes. In the US, several Black people were barred from the armed forces and asked to pay higher insurance premiums because they carried the sickle cell anemia gene. And in Greece, young women discovered to be carriers of this trait found themselves ineligible for prearranged marriages.[30]

Even more volatile arguments are currently under way concerning prenatal diagnosis, abortion, and genetic research. Questions arise about the right to life of the defective fetus independent of the lifetime burden the handicapped child will be for its parents and society. Several authors have suggested that illnesses that are prenatally diagnosable but can't be treated at present may be ignored by medical researchers. These authors imply that, since fetuses

with these defects can be detected and aborted, researchers will feel there is no need to search for cures.

As Joshua Lederberg, president, Rockefeller University, points out, "Few subjects pose as many difficulties for rational discussion as does the bearing of genetic research on human welfare. It is monotonously coupled with such inflammatory themes as racism, the decline of the species, overpopulation, hidden genocide, religious debates on abortion and contraception, the plight of the individual in mass society, and 'how many generations of idiots is enough?' "[53]

Graham Chedd, in a recent issue of *Science 81*, examines many of the ethical implications of genetic screening. "There is also the fear that abortion for genetic disease could gradually evolve from being the 'responsible' to being the 'expected' thing to do," he writes. "Proponents of genetic abortion argue that knowing a fetus is defective increases the prospective parents' freedom of choice.... But seeing the benefits to society of mandatory abortion isn't difficult. Perhaps the deepest apprehensions about the use of genetic abortion stem from the ever-increasing range of prenatal diagnosis. If we see it as acceptable, even responsible, to abort now for Down's syndrome, what will be the attitude in the future when, say, muscular dystrophy can be diagnosed prenatally?"[54]

A number of legal questions have also been raised about the physician's obligation to provide genetic counseling and inform patients about prenatal diagnostic tests currently available. Several "wrongful life" lawsuits have been brought against physicians by parents and children because of the doctors' failure "to detect or disclose the possibility that a defective child will be born."[55]

Despite these questions, the value of genetic screening has been recognized by many governments, as well as researchers and physicians. In 1976, the US Congress passed the National Genetic Diseases Act which provides for a national program of information and education in connection with genetic diseases.[56] A National Clearinghouse for Human Genetic Disease has been established under this act, and funding has been provided to the states for genetic services.[3] In Canada, which has a universal health insurance program, the government also sponsors resources for the screening, diagnosis, counseling, and treatment of hereditary disease.[11] The Clinical Genetics Society in the UK recently prepared a report outlining the training requirements and functions of the medical geneticist.[57]

Although the preventive implications of this field are recognized, there is still some resistance to the incorporation of human genetics into medical practice. Barton Childs, Johns Hopkins University, reports that few physicians surveyed in 1975 considered genetic disease a serious practical problem.[58] As I mentioned in the preventive medicine essay, physicians are more concerned with "curing" patients of specific diseases than with preventing future illness. Childs also cites the physician's concern with individual patients, rather than families, and the episodic nature of medical treatment, as factors precluding the application of medical genetics to standard medical practice. In a later article, he points out that medical genetics is usually a minor part of the medical school curriculum, and is often not clinically-oriented.[59]

With more research on human genetics will come greater recognition of the preventive, or "predictive," value of medical genetics. Already, researchers are finding ways to track the inheritance of genetic disease through differences in the DNA at specific regions of the chromosome, called DNA polymorphisms. David Botstein, MIT, and Raymond White, University of Utah, are tracing the inheritance of these markers

through several generations, and investigating the relationships between these markers and specific genetic diseases.[60] Currently, other "markers," or traits carried by a gene on the same chromosome that carries the gene for a genetic disease, are used to trace inherited disease in families. These include blood group, color blindness, serum protein polymorphisms, the ability to taste phenylthiocarbamide, and HLA antigens.

Associations have been made between HLA antigens and such diseases as rheumatism, ankylosing spondylitis, arthritis, psoriasis, asthma, and Hodgkin's disease.[61,62] There may also be an association between these antigens and juvenile onset diabetes and myasthenia gravis.[61] Unfortunately, blood tests for these antigens are fairly expensive and difficult. Scientists are also mapping the locations of genes on chromosomes, and investigating transplantation and replacement of defective genes.[63,64] According to McKusick, "We now know the specific chromosome carrying each of over 450 human genes and the specific localization of that chromosome is known for many of these. For some segments of the DNA the anatomy is known now down to the individual nucleic acids."[19]

Medical genetics is a field that frequently interfaces with other areas of biomedical research. Several of the highly active specialties in *ISI/BIOMED*™ that deal directly with medical genetics touch upon many of the diseases and research areas I've mentioned here (see Table 1). For example, we have one research front that deals exclusively with genetic aspects of alcoholism, and several that deal with genetic aspects of cancer and other diseases.

Among the many co-citation clusters produced from our data base, there are several which focus on genetic diseases caused by enzymatic deficiencies. The work of McKusick and colleagues is particularly relevant to this essay and to these clusters.[65-67] McKusick, who will appear on our forthcoming list of 1,000 most-cited authors, is probably best known for his catalog of genetic diseases[68] and was one of the earliest clinicians to promote an understanding of the role of genetics in human disease. The entries for this catalog, which was first published in 1966, are kept in a computer file that is continuously updated. A recent count, in June, revealed that about 3,254 genetic loci have been identified, half of which "were quite clearly identified as real and distinct," and half of which were tentatively "identified and included for heuristic purposes and none other."[19]

The growth of this field is also evidenced by the presence of medical genetics papers in a wide range of journals, including *Lancet*, *Journal of the American Medical Association*, *American Journal of Psychiatry*, and *New England Journal of Medicine*. A number of the popular science magazines also publish articles on medical genetics.

The major sources of journal literature on the subject are the *American Journal of Human Genetics*, *American Journal of Medical Genetics*, *Annals of Human Genetics*, *Human Genetics*, *Journal of Medical Genetics*, and *Clinical Genetics*. All are covered by the *Science Citation Index®*, *ASCA®*, and *Current Contents®/Life Sciences*. The *American Journal of Medical Genetics*, *Clinical Genetics*, and *Journal of Medical Genetics* are also covered in *Current Contents/Clinical Practice*. These, and several other journals that publish papers related to medical genetics, are presented in Table 2 along with the number of articles published in 1980; the number of citations received in 1980 by articles published in these journals; their impact factor, a measure of the frequency with which the average 1978/1979 article has been cited in 1980; and their immediacy

Table 1: Some of the genetic disease research front specialties identified by co-citation analysis in *ISI/BIOMED*™.

GENETIC

GENETIC
The AH-LOCUS and GENETIC control of CARCINOGEN METABOLISM . . . 1980-0258
COLLAGEN synthesis and GENETIC POLYMORPHISM . . . 1980-0479
ENVIRONMENTAL CHEMICALS causing CANCER and GENETIC BIRTH DEFECTS . . . 1980-1204
EVOLUTION and GENETIC VARIABILITY . . . 1980-1833
GENETIC and ENVIRONMENTAL effects on DRUG METABOLISM . . . 1980-1868
GENETIC aspects of ALCOHOLISM . . . 1980-1506
GENETIC control of CELL-MEDIATED IMMUNE RESPONSIVENESS . . . 1980-2087
GENETIC control of COMPLEMENT PROTEIN structure by the HISTOCOMPATIBILITY complex . . . 1980-0100
GENETIC control of CYTOCHROME-P-450 . . . 1980-0258
GENETIC control of HYDROXYLASE activity . . . 1980-1453
GENETIC control of T-CELL SPECIFICITY . . . 1980-0342
GENETIC control of TUMORIGENICITY in HYBRID CELLS . . . 1980-1787
GENETIC effects of DYES on DNA . . . 1980-1936
GENETIC organization of NEMATODE CAENORHABDITIS-ELEGANS . . . 1980-0684
GENETIC studies of AGROBACTERIUM . . . 1980-0616
GENETIC variation . . . 1980-1033
GENETIC DETERMINANTS of resistance to ANTIBIOTICS by NEISSERIA-GONORRHOEAE and other BACTERIA . . . 1980-0240
GENETIC MAPPING of HEAT-SHOCK INDUCIBLE-GENES in DROSOPHILA-MELANOGASTER . . . 1980-1653
GENETIC POLYMORPHISM in FINITE POPULATIONS . . . 1980-1616
GENETIC POLYMORPHISM of ERYTHROCYTE ENZYMES . . . 1980-1317
GENETIC RECOGNITION and control SEQUENCES in the NUCLEIC-ACIDS . . . 1980-2273
GENETIC RECOMBINATION of ONCOGENIC VIRUSES . . . 1980-0325
GENETIC RESTRICTION of MACROPHAGE T-CELL interactions . . . 1980-1261
GENETIC, ENVIRONMENTAL, and DIETARY contributions to CHILDHOOD and ADOLESCENT GROWTH dynamics . . . 1980-2292
MODELS of GENETIC control of ENZYME activity . . . 1980-2130

GENETIC-LINKAGE
GENETIC-LINKAGE analysis for RECESSIVE diseases . . . 1980-1243

GENETICALLY
PHYSIOLOGY of GENETICALLY OBESE mice . . . 1980-0681

GENETICS
BACTERIOPHAGE-LAMBDA GENETICS . . . 1980-0040
GENETICS of mouse LEUKEMIA-VIRUS . . . 1980-0917
GENETICS of BACTERIAL RNA-POLYMERASES . . . 1980-1841
MOLECULAR GENETICS of human HEMOGLOBIN . . . 1980-0271
MOLECULAR GENETICS of FETAL HEMOGLOBIN . . . 1980-0271
MOLECULAR GENETICS of MITOCHONDRIAL DNA . . . 1980-0637
MOLECULAR GENETICS of THALASSEMIAS . . . 1980-0271
POPULATION GENETICS of NONHUMAN species . . . 1980-0280
TERATOCARCINOMA TRANSPLANTATION STEM-CELL GENETICS and IMMUNO-REJECTION LOCI . . . 1980-0232

HYPERCHOLESTEROLEMIA
NUTRITION and HYPERCHOLESTEROLEMIA . . . 1980-0859
RISK-ASSESSMENT of FAMILIAL HYPERCHOLESTEROLEMIA and HYPERLIPIDEMIA . . . 1980-2258

HYPERLIPIDEMIA
DIET and HYPERLIPIDEMIA . . . 1980-1640
RISK-ASSESSMENT of FAMILIAL HYPERCHOLESTEROLEMIA and HYPERLIPIDEMIA . . . 1980-2258

LESCH-NYHAN-SYNDROME
PURINE synthesis, HPRT deficiency, and LESCH-NYHAN-SYNDROME . . . 1980-1937

MUSCULAR-DYSTROPHY
CYTOPATHOLOGY and PATHOPHYSIOLOGY of MUSCULAR-DYSTROPHY . . . 1980-2030
ERYTHROCYTE PLASMA-MEMBRANE ABNORMALITIES in DUCHENNE MUSCULAR DYSTROPHY . . . 1980-1714

SICKLE-CELL
GELATION of SICKLE-CELL HEMOGLOBIN . . . 1980-1690

THALASSEMIA
IRON CHELATION THERAPY for THALASSEMIA and other clinical states producing IRON OVERLOAD . . . 1980-0369

THALASSEMIAS
MOLECULAR GENETICS of THALASSEMIAS . . . 1980-0271

ULTRASONOGRAPHIC
ULTRASONOGRAPHIC measurement of GESTATIONAL AGE . . . 1980-0823

index, a measure of how quickly the average article published in 1980 was cited.

Several computerized data bases are currently being developed, including two at Columbia University[64] and the University of California at San Francisco,[69] that are expected to serve research, service, and administrative needs in medical genetics. As I mentioned before, a National Clearinghouse for Human Genetic Disease has been established under the National Genetic Diseases Act. This clearinghouse, which can be contacted at P.O. Box 28612, Washington, DC 20005, provides information on genetic screening and treatment programs. An annual course in medical genetics and experimental mammalian genetics is offered jointly

Table 2: Selected list of medical genetics journals covered by *Current Contents®* and the *Science Citation Index®*, with the total number of articles they published in 1980, the total number of citations they received in 1980, their impact factor, and their immediacy index. Source: 1980 *SCI® Journal Citation Reports®*.

	1980 Articles Published	1980 Total Citations	Impact Factor	Immediacy Index
Advances in Human Genetics	5	122	.429	.800
American Journal of Human Genetics	89	2431	3.643	.382
American Journal of Medical Genetics	108	206	.944	.139
Annals of Human Genetics	33	1334	1.602	.697
Annales de Genetique	63	679	1.375	.095
Behavior Genetics	43	443	1.594	.256
Canadian Journal of Genetic Cytology	53	884	1.024	.208
Clinical Genetics	136	1340	1.566	.169
Clinical Pediatrics	131	802	.478	.031
Genetical Research	51	1133	1.070	.294
Genetika	229	955	.372	.240
Hereditas	85	1810	1.701	.329
Heredity	71	1573	1.309	.394
Human Genetics	223	2254	1.763	.318
Human Heredity	73	594	.894	.137
Japanese Journal of Genetics	48	452	.828	.292
Japanese Journal of Human Genetics	27	145	.774	.222
Journal de Genetique Humaine	44	156	.400	.091
Journal of Heredity	110	1438	.694	.127
Journal of Medical Genetics	109	1304	1.221	.183
Tissue Antigens	120	1453	1.657	.233

by Johns Hopkins University and Jackson Laboratory. For information on this course, which has been offered since 1960, contact Victor McKusick, Johns Hopkins Hospital, Baltimore, Maryland 21205, or Thomas H. Roderick, Jackson Laboratory, Bar Harbor, Maine 04609.

A number of organizations exist for professional geneticists and individuals interested in, or affected by, genetic disease. The American Society of Human Genetics, c/o Judith Brown, Secretary, Box 33 MCV Station, Richmond, Virginia 23298, is a professional society of physicians, researchers, teachers, genetic counselors, and others in the field. The American Genetic Association, 818 18th Street, NW, Room 250, Washington, DC 20006, includes biologists, zoologists, geneticists, botanists, and others in academic or government research. Individuals interested in any field of genetics can contact the Genetics Society of America, through its president, Burke Judd, NIEHS, P.O. Box 12233, Research Triangle Park, North Carolina 27709, or the Genetics Society of Canada, through its president, R.C. Von Borstel, University of Alberta, Department of Genetics, Edmonton, Alberta T6G 2E1, Canada. The International Genetics Federation, P.O. Box 1600, Canberra 2601, Australia, is comprised of societies concerned with both human genetics and plant breeding, and the Behavior Genetics Association, which can be contacted through the Institute for Behavioral Genetics, University of Colorado, Boulder, Colorado 80309, is a professional organization for individuals engaged in teaching or research in some area of behavior genetics. The National Genetics Foundation, 555 West 57th Street, New York, New York 10019, conducts educational programs for the public and physicians and operates a network of genetic counseling and treatment centers. The National Society of Genetic Counselors can be contacted through Beverly Rollnick, Center for Cranialfacial Abnormalities, University

of Illinois, Abraham Lincoln Center, 470-DMP, P.O. Box 6998, Chicago, Illinois 60680. The International Society for Twin Studies can be contacted at the Mendel Institute, Piazza Galeno 5, 00161 Rome, Italy, and the Association for Research into Restricted Growth can be contacted through Valerie Sims, Secretary, 5 Peak Walk, Witham, Essex, England.

There are also a number of voluntary organizations concerned with hereditary diseases. Included among these are the Hereditary Disease Foundation, 9701 Wilshire Boulevard, Beverly Hills, California 90212; the March of Dimes Birth Defects Foundation, 1275 Mamaroneck Avenue, White Plains, New York 10605; National Tay-Sachs and Allied Diseases Association, 122 East 42nd Street, New York, New York 10017; Cooley's Anemia Foundation, 420 Lexington Avenue, Suite 1644, New York, New York 10019; Cystic Fibrosis Foundation, 3379 Peachtree Road, NE, Atlanta, Georgia 30326; National Association for Down's Syndrome, Fullerton Avenue, Addison, Illinois 60101; National Foundation for Jewish Genetic Diseases, Inc., 609 Fifth Avenue, Suite 1200, New York, New York 10017; National Association for Sickle Cell Diseases, Inc., 3460 Wilshire Boulevard, Suite 302, Los Angeles, California 90010; National Hemophilia Foundation, 25 West 39th Street, New York, New York 10018; National Huntington's Disease Association, 128A East 74th Street, New York, New York 10020; Spina Bifida Association of America, 343 Dearborn Avenue, Room 319, Chicago, Illinois 60604; Parents Helping Parents, 47 Maro Drive, San Jose, California 95127; and Little People of America, P.O. Box 633, San Bruno, California 94066. Associations outside the US include Little People's Association of Australia, c/o Robert Wood, 10/16 Roslyn Gardens, Elizabeth Bay, NSW 2011, Australia; Les Petits Tailles, c/o Claude Stoll, Institut de Puericulture, Hospices Civils, 6730 Strasbourg, France; World Federation of Hemophilia, 1170 Peel Street, Suite 1126, Montreal, Quebec H3H 2J1, Canada; and Association for Research into Restricted Growth, c/o Mary Lindley, 2 Mount Court, 81 Central Hill, London SE19 1BS, England.

Medical genetics is making inroads into standard medical practice. Blood tests given adults are regularly screened for the presence of genetically influenced high cholesterol and triglyceride levels. Obstetricians are advising older pregnant women to take diagnostic tests. As McKusick pointed out in a recent letter, "...man is rapidly becoming the best studied of the mammals from the genetic point of view.... The big advantage that man has as an object of genetic study is, of course, the anthropocentric interest in our own species and the fact that we have such a large segment of the world's population working for us, in effect, collecting information on human variation from an anatomic, physiologic, pathologic and biochemical point of view."[19] However, before all this information can be used to fully benefit human health, a great deal of research must still be done on the detection, hereditary patterns, and treatment of genetic diseases, and easily administered, inexpensive tests must be developed to find them.

* * * * *

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