MEDICAL GENETICS: IMPACT AND STRATEGY

(genetic disease, birth defects, prenatal diagnosis)

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SUMMARY

Genetic diseases and birth defects have a major impact on all levels of health care because of their enormous consequences for the individual and family and because of the high frequency of occurrence. That over 3000 described disorders due to either chromosome aberrations, to single-gene mutations or to many genes acting together and with the environment have been described illustrates the diversity in these diseases. The concern of the medical geneticist is to establish an accurate etiologic diagnosis, to counsel patients and families concerning their risks of occurrence or recurrence and to devise and provide methods of preventing both the effects and ultimately the occurrence of genetic diseases.

INTRODUCTION

At the turn of the century, the rediscovery of Mendel's work heralded the beginnings of the science of genetics. But only in the last 10 years has the genetic approach to disease begun to make a significant impact on the practice of modern medicine. In the United States at the turn of the century, approximately 150 out of every 1000 babies died during the newborn period. It is estimated that 5 of those 150 babies died from a genetic disease or a genetically related birth defect. Genetic disease constituted a small portion of infant mortality in the year 1900. Today, 80 years later, because of dramatic advances in nutrition, antisepsis, and the control of infectious disease, infant mortality has been reduced 90%; and only 15 out of every 1000 babies die. But now, almost 5 of those 15 babies, approximately one third, succumb to a genetic disease or genetically related birth defect. If we broaden our perspective to consider not only infant mortality statistics but also the genetic conditions which lead to significant physical and mental disability throughout a lifetime, it becomes obvious that hereditary diseases constitute a major and

increasingly important cause of human suffering and mortality.

An accurate figure for the overall incidence of genetic disease is difficult to derive since many disorders evident in the newborn period cause death before adulthood, while many other diseases such as diabetes mellitus and adult onset coronary artery disease, though clearly influenced by genetic determinants, do not become manifest until later in life. Thus, it is necessary to consider the causes of genetic disease in different age groups. Beginning in the newborn period, we find that 3-5% of babies have a major birth defect or genetic disease which will either significantly alter their lifestyle or at least require corrective surgery. If the same cohort of infants are re-examined at one year of age another 2-3% will be discovered to have some previously occult genetic disorder such as a hearing loss or kidney malformation. And each additional year, new genetic disorders will become manifest in more children so by adulthood 10-20% of our original cohort can be identified to have a genetic disease.

The impact of genetic disease on society is only just beginning to be appreciated. A review of admissions to one general pediatric hospital revealed that 26% of all children were admitted with clearly genetic disorders (HALL, POWERS, McILVAINE, EAN, 1978). Another 26% had developmental or less well-defined familial disorders; only 46% of the admissions were clearly for non-genetic indications. Moreover, the patients with genetic disorders had a history of more frequent, more expensive, and longer hospital stays. Looking at children less than 14 years of age, birth defects and genetic diseases are the third most common cause of death.

Genetic diseases can be classified broadly in three groups: chromosomal disorders, single-gene disorders, and multifactorial or polygenic traits. The chromosome disorders were first described in the late 1950's following the development of techniques for preparing human chromosomes for study; in the 1970's with the introduction of precise banding methods, additional subtle and complex rearrangements were discovered. To date, almost one hundred well-defined chromosomal disorders have been described and the list grows each year (DE GROUCHY & TURLEAU, 1977). Data from cytogenetic surveys of unselected liveborn infants provide our best estimates of the frequency of chromosome abnormalities at birth. Based on studies of 43,558 infants, the incidence of chromosome abnormalities is 5.6/1000 livebirths (LUBS, 1977). Of these, 2/1000 are sex-chromosome disorders, generally an additional or deleted X or Y chromosome, and 1.7/1000 are autosomal aneuploidies, most frequently involving an extra chromosome 21, 13, or 18. Complex chromosome rearrangements, primarily translocations, inversions, and various other duplications or deficiencies, are found in 1.9/1000 livebirths. Table I outlines the overall incidence of chromosomal syndromes including the number of cases expected to be born in the United States each year. Each of these infants and their families will require a substantial outlay of medical and social resources for genetic and other medical evaluations, for special education, for hospitalizations and

surgeries and in many cases for institutionalization. Down's Syndrome, caused by the extra chromosome 21, for example, is responsible for 25-30% of individuals with severe mental retardation in the United States and it is estimated that more than $400 million dollars is spent annually in the United States to care for patients with this one disorder (RIMOIN, 1975).

TABLE I

Estimated Annual Incidence of Chromosomal Abnormalities in the United States

Disorder	Frequency per 10,000 births*	Expected No. Born in U.S. Each Year (3.5 million)
Sex Chromosome Aneuploidy		
XXY karyotype (Klinefelter's Syndrome)	5	1750
XO karyotype (Turner's Syndrome)	0.5	175
XXX karyotype	5	1750
XYY karyotype	5	1750
Other	3	1050
Autosomal Aneuploidy		
Trisomy 21 (Down's Syndrome)	14	4900
Trisomy 18 (Edwards' Syndrome)	2	700
Trisomy 13 (Patau's Syndrome)	1	350
Other anomalies (balanced and unbalanced)	19	6650
Total	54.5	19075

*Lubs, H.A.
*Jacobs, P.A.

Single-gene disorders are caused by the presence of a mutant gene or allelic gene pair and the inheritance follows the patterns described by Mendel over 100 years ago. The McKusick catalogue (McKUSICK, 1978) of single-gene disorders records 2,800 specific Mendelian traits; the list has grown almost exponentially in the last few years as new disorders have been described, and older medical problems have been reinvestigated and their genetic bases clarified. Though most single-gene disorders are relatively rare, when considered individually, their combined incidence is high, affecting almost 2% of the population (TABLE II). Dominant disorders due to the presence of one abnormal gene generally cause structural abnormalities; examples of some of the more common dominant disorders include polycystic kidney disease, neurofibromatosis, achrondroplastic dwarfing syndrome, several types of hereditary deafness and blindness, and Huntington's Chorea. Each of these diseases occurs once in every 1000 to 10,000 livebirths. Other less

frequent dominant disorders include tuberous sclerosis, Marfan's Syndrome, porphyria, Alport's kidney disease, and myotonic dystrophy. Genetic counseling for heterozygotes with dominant disorders provides a prospective means of preventing genetic disability since each person with a dominant disease has a 50% risk for passing the disease on to each of his children. Parents carrying dominant disorders need to be aware of the risk. Recessive genetic disorders, each resulting from the presence of a mutant gene pair, occur with a combined frequency of 0.3%. Some of the more common recessive genetic diseases are sickle-cell anemia, cystic fibrosis, Tay-Sachs Disease, and phenylketonuria. Since the recessive diseases occur when an individual inherits the same abnormal allele from each parent, many of the diseases are found more frequently in specific ethnic groups or nationalities who are likely to share a common genetic heritage. Therefore, sickle-cell anemia is more common in the black population; cystic fibrosis in the European caucasians; Tay-Sachs Disease in Ashkenazi Jews, and beta thalassemia in Mediterraneans. Most recessive disorders however are wide-spread throughout the world regardless of ethnic heritage. Some of the more common examples are alpha-1-antitrypsin deficiency, Friedreich's ataxia, phenylketonuria, galactosemia, maple-syrup urine disease, albinism, Wilson's Disease, the amino acidopathies, glycogen storage diseases, and the mucopolysaccharidoses. For each recessive disease, once a child is born with the disorder or when both parents have been demonstrated to be carriers, the risk for each subsequent child is 25%.

TABLE II

Estimated Burden of Mendelian and Multifactorial Genetic Disease in the United States

Mode of Inheritance	Frequency per 10,000 births*	Expected No. Born Each Year In United States (3.5 millon births)
Autosomal dominant	60	21,000
Autosomal recessive	30	10,500
X-linked	10	3,500
Multifactorial	120	42,000
Total	220	77,000

*Lubs, H.A.

Genes mapped to the X chromosome are considered separately since the risk of occurrence differs for females with two X chromosomes and males with a single X and a Y chromosome. Hemophilia, Duchenne muscular dystrophy, glucose-6-phosphate dehydrogenase deficiency, and color blindness are well-known

examples of X-linked recessive disorders which affect males more than females. Another 200 clinically significant X-linked traits have been described including retinitis pigmentosa, agammaglobulinemia, ocular albinism, and Lesch-Nyhan Disease. Recently, there has been an increased interest in mental retardation caused by X-linked recessive genes. We know that in institutions there is a 50% excess in retarded males over females; many of these disorders may be due to either single or multiple X-linked genes. It is estimated that as many as 35% of all persons with IQ's of less than 70 have some form of X-linked mental retardation (LEHRKE,1974). The recent discovery of cytologically demonstrable fragile sites on the X chromosome of some men with X-linked mental retardation promises to be a valuable tool for the geneticist who is trying to coordinate clinical genetic and cytogenetic findings.

The largest number of medically significant genetic disorders are not due to single genes or gene pairs. Rather they are caused by multiple genes adversely acting together and with the environment. Cleft lip and palate, spina bifida (open spine), anencephaly (open brain), club feet, many congenital heart diseases, hydrocephalus, congenital hip dislocations, congenital scoliosis, many urinary tract anomalies, Hirschprungs Disease, and pyloric stenosis are all examples of birth defects or disorders which follow this inheritance pattern. These disorders each occur approximately once in every 1000 livebirths. Their combined incidence approaches 1% of the babies born in the United States. Many other common diseases which usually occur later in life including essential hypertension, athrosclerotic heart disease, atopic allergic conditions, schizophrenia, and some types of diabetes are also due to multifactorial causes. They occur in at least 10% of the population.

By tabulating incidence figures, we can only just begin to comprehend the real impact of genetic disease on society. Chilren born with serious birth defects usually face a shortened life span marred by frequent hospitalizations and surgeries. In addition, the financial burden of providing hospital, medical, and institutional care is enormous. For example, the average cost to provide care for one child with Down's Syndrome is $10,000 per year (RIMOIN, 1975). Since Down's Syndrome occurs in one of every 600 babies born in the United States, it is not difficult to recognize that the estimated annual expenditure of over $400 million for children with Down's Syndrome is conservative. Realistically, this figure must be multiplied many times to estimate the costs incurred for all children born with other birth defects or genetic diseases. And since individual families rarely have the financial resources to provide these services, the costs are assumed by society through numerous federal, state, and municipal governmental agencies.

But perhaps of even greater significance is the devastating impact of genetic disease on families. Following the birth of an affected child, parents suffer not only a profound sense

of sadness and loss but also experience undeserved and irrational feelings of guilt and shame. Couples feel a sense of failure and loss of self-esteem which leads to an inevitable breakdown in communications and mutual support. Family disruption and divorce rates more than double following the birth of a damaged child. Collapse of the family is catastrophic for both the affected child and for society. The child is more apt to be placed in a state school or foster home and society loses the commitment of the parents and family, who are our most powerful advocates in the crusade for continued progress in the fight to control and prevent genetic diseases and birth defects.

STRATEGY: PREVENTION

Genetic diseases cannot yet be cured. DNA cannot be manipulated to repair the deleterious genes which we all continue to pass from generation to generation. And so, without an available method to cure defects in the genome but faced with the increasing medical, financial and personal burdens of genetic disease, medical geneticists have focused their attention on the aspects of prevention. The key to our understanding of genetics has always been predictability. Utilizing our ability to accurately anticipate the occurrence of a disease, strategies of prevention have been and are continuing to be developed. Prevention can take many forms. Because most genetic disorders can not be recognized until after birth, geneticists emphasize the preventive potential of therapy, which is essential to prevent the deleterious consequences of many diseases. For example, surgical cleft lip and palate repair in the first few months of life can often completely circumvent the destructive effects that an unrepaired cleft would have on speech and personality development. Similarly, club feet and dislocated hips can be repaired before the time of walking so children won't be impeded in their acquisition of normal motor development. Drug therapy for seizures and insulin for diabetes prevent the complications of those disorders. In all these cases where the basic genetic defect is not yet understood, therapy to correct the existing problems remains a powerful though generally less than optimal method of prevention.

For a growing number of inborn errors of metabolism, our current understanding of the biochemical mechanisms allows elegant specific genetic therapy. For example, the infant with the autosomal recessive disorder galactosemia appears normal at birth. When milk feedings are introduced, however, vomiting and listlessness develop, the liver enlarges and jaundice develops. Approximately two thirds of the babies die before a correct diagnosis is made and if they survive and remain untreated their life is marred by severe mental retardation, cataracts and liver damage. However, when the diagnosis of galactosemia is recognized in the first days of life, the diet can be changed and a soy formula substituted for the milk formulas which contain galactose. This simple prescription will prevent all of the harmful consequences of galactosemia. The development of preventive therapy for galactosemia was

a major breakthrough in the treatment of genetic diseases and reflects our increasing understanding of the biochemical bases of the inborn errors of metabolism. Unfortunately, for many other genetic diseases, therapy will be too late and babies will be seriously damaged if we wait for a diagnosis to be made on the basis of classical medical presenting signs and symptoms. To circumvent this dilemma, medical geneticists have endeavored to find ways of screening for damaging conditions before they become clinically obvious. An increasing number of examples of the successful application of this approach occur in the newborn nursery (HOLTZMAN, 1978). Infants with these diseases are protected in utero by the mother's intact metabolic machinery. For example, the fetus unable to break down phenylalanine because of a deficiency of phenylalanine hydroxylase is not damaged as long as his nutritional and catabolic needs are being supplied by the mother. It is after birth that phenylalanine and its by-products begin to accumulate and cause insidious and irreversible damage to the nervous system. By testing all newborns in the first few days of life for increased levels of phenylalanine, but before the breakdown products build up, the few infants who are affected can be identified and appropriately treated before damage occurs. Screening for phenylketonuria (PKU) is now mandated by state law in all fifty of the United States; though the incidence is only 6-7 per hundred thousand infants screened, those who are identified are saved from mental retardation and its consequences. Similarly, maple-syrup urine disease caused by a branched-chain of ketoacid decarboxylase deficiency, galactosemia caused by a galactose-1-phosphate uridyl transferase deficiency, and congenital hypothyroidism can all be chemically detected in the newborn period before symptoms occur. Hypothyroid screening is now done in more than half the states and pilot projects designed to assess the efficiency of screening for numerous other disorders are underway. These studies are critical since the benefits of newborn screening must be precisely delineated for each specific disease before mass screening is initiated. Experience has taught us that the ability to test for genetic disease does not assure success of a screening program. Other considerations including the ability to reach the target population, methods of dealing with the false-negative and false-positive screening results, ways of assuring adequate followup and means of reducing the high cost of screening are problems which must be worked out before effective mass screening can be introduced for any of the genetic diseases.

For hundreds of other genetic diseases, damage is already present at birth and methods of treatment are not available even after the diagnosis is made. The availability of successful modes of treatment determines in large measure the burden of a disorder for the child and family; for most genetic diseases, no specific therapy is available. Children with Tay-Sachs Disease for example, always die in the first 3-5 years of life despite all the efforts of modern medicine. Their life is marked by a steady downhill course of neurological degeneration causing deafness, blindness, and seizures.Examples of other serious untreatable genetic diseases include Menke's

kinky-hair syndrome caused by an as yet poorly understood disorder in copper metabolism and Hurler's mucopolysaccharidosis which results in the inability to break down complex sugars. Children born with these disorders cannot be successfully treated. And the survival of babies born with severe malformations such as spina bifida and hydrocephalus generally depends on a series of major surgeries, complex medical care and frequent hospitalizations. Understandably, where morbidity and mortality is high, parents wish to prevent the birth of a second affected child. The query from parents, "Will it happen again?", generally initiates a genetic evaluation.

Genetic counseling is the popular synonym for the medical genetic evaluation. The process however is not limited to providing a risk of recurrence for the family. A specific diagnosis must be available before adequate risks can be estimated. Often the family and medical history provide the geneticist information on the etiology of the problems. For example, the family history may reveal other similarly or less affected relatives or could point to a specific mode of inheritance in that family. In some cases, an environmental factor such as maternal rubella, alcoholism or drugs taken in pregnancy is found to be the responsible agent. Frequently, the clinical evaluation requires the use of laboratory or radiographic tests to confirm the suspected diagnosis. The value of the diagnosis cannot be underestimated for it allows the geneticist to draw on the experience of other physicians and families in order to prognosticate both medically and genetically what the patient and family can expect in the future. Most patients affected with an unusual genetic syndrome or disease, whether due to a chromosome abnormality, a biochemical error of metabolism, or a physical malformation, will require the consultation of a medical geneticist to confirm the diagnosis and to establish the most likely mode of inheritance. If the risk of recurrence is high, and if the prognosis for the disorder is poor, couples must decide whether they wish to have other children. Contraception, sterilization, and adoption are possible options. When the father carries the detrimental gene or in autosomal recessive conditions, artifical insemination may be an option for some families.

In the last 10 years, prenatal diagnosis has provided many families with a new and positive alternative when the risks of recurrence were high and the prognosis was poor. Transabdominal amniocentesis at 16 weeks into the pregnancy has proved to be a safe and accurate procedure which allows the geneticist to sample fetal cells sloughed into the amniotic fluid and to utilize these cells and the fluid itself to diagnose specific genetic diseases (NICHD, 1976). In addition, ultrasonic techniques allow the fetus to be safely visualized and measured in utero providing both the geneticist and the obstetrician a means of detecting certain morphologic abnormalities early in pregnancy. Presently, all chromosome disorders, plus more than 70 biochemical disorders or structural birth defects can be diagnosed in utero. The list of defects which can be detected in the fetus continues to grow as new biochemical tests become available and as cytogenetic tests

are improved (MILES & KABACK, 1978).

Prenatal diagnosis adds a new dimension to genetic counseling by providing couples at risk for certain serious genetic disorders with an alternative and in many instances a positive course of action. Because the risk of an abnormality rarely exceeds 25%, as in autosomal recessive conditions, couples have an excellent chance through prenatal diagnosis of having unaffected offspring. This implies, of course, that such families would elect to monitor their pregnancies by amniocentesis and electively terminate those in which an affected fetus is identified.

Genetic counseling has been described as a process of communication during which the physician or other trained counselor helps the family to understand better the genetic and medical aspects of an inherited disease. The goals of genetic counseling are to provide families with complete and appropriate information, to aid them in making decisions that are in the best interestes of their family, and to help them make the best possible adjustment to those decisions.

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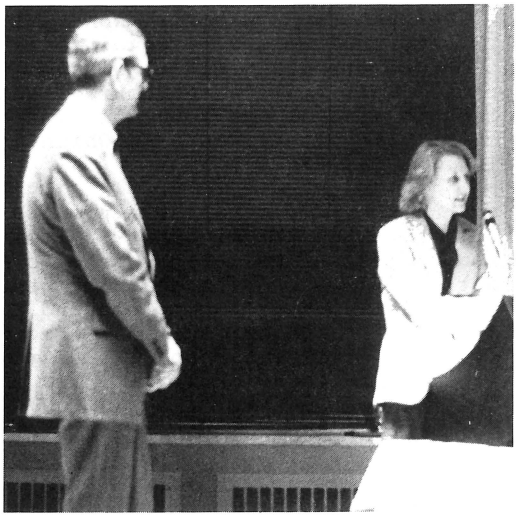

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