The Epidemiology and Genetic Basis of Common Diseases

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The fact that susceptibility to many of the common chronic diseases, including diabetes, heart disease, and various cancers, is inherited is not a new concept for most people. The statement that a given disease "runs in the family" is one clinicians commonly hear when collecting family history information from patients. However, despite this generally held appreciation of inherited susceptibility, the exact mechanisms by which such susceptibility develops has until recently remained frustratingly elusive.

In part, one reason that it has been so difficult to determine the role of genetic susceptibility in the development of these disorders is that they are indeed so common. Breast cancer and prostate cancer, for example, occur in women and men with lifetime frequencies of 1/10 or more, respectively, whereas diabetes will affect roughly 1/15 to 1/20 adults at some time in their lives. Close to one third of the population will develop arteriosclerotic coronary artery disease. As a result, it would not be unexpected to find a few cases of one of these conditions within a family purely by chance alone. Therefore, deciding when a clustering of diseases within a family represents more than random aggregation can be very difficult. Additionally, because of how common these conditions are, it is likely that there are multiple etiologies for them. As a result, the genetic defect or defects in one family may be completely different from those in another family that appears clinically to have the same condition.

In order to make any progress in understanding the genetic basis for the common diseases, the first objective is to appreciate the importance of genetic risk factors in the development of the common chronic diseases.

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2. To understand the methods that can be used to evaluate the importance of genetics in disease predisposition.

3. To learn the role pediatricians can play in prevention of adult-onset diseases.
that must be addressed is conclusively demonstrating that the diseases do indeed have a genetic basis. Several lines of evidence can be used in this process, but often the first approach is to assess the familiality of a given disease. By examining the proportion of affected individuals who report a positive family history for a disorder such as diabetes and comparing it to the proportion of unaffected individuals who report a positive family history, it is possible to demonstrate that indeed more diabetic individuals will have a family history of the disease than do control subjects. Even more precisely, detailed family histories can be obtained and empiric risk figures generated and compared with the general population’s risk for the disease.

There are difficulties with studies of this type, however; individuals who have a disorder may be more knowledgeable about the presence of the same condition in other family members than are unaffected individuals. Thus, there may be an apparent excess of disease in the family histories of affected members when, in reality, there is simply underreporting by unaffected subjects. Efforts can be made to track down medical record documentation for other family members, but this becomes quite difficult. Even when such studies are performed carefully and the familiality of a disorder is documented, it does not immediately follow that the familial aggregation is a result of inheritance; in addition to sharing common genes, relatives also tend to share common environments. Thus familial aggregation could be seen due to common dietary habits, common occupational exposures, or the like.

To separate genetic from environmental factors, a commonly used approach has been the twin study, in which identical twins (who are also genetically identical) are compared with same-sex fraternal twins (who are genetically no more alike than any two siblings, sharing on average 50% of their genes). Because twin pairs are likely to have very similar environmental exposures, particularly during childhood, the rates of concordance (both twins affected with the disease of interest) within twin pairs can be compared between the identical and fraternal twins. Numerous studies of this type have been performed and demonstrate quite strikingly that there is greater concordance among identical twins than among fraternal twins. The fact that the concordance rate is not 100% in the identical twin pairs is an indication that the development of these disorders is not wholly genetic. What is inherited is susceptibility to disease, and an environmental trigger appears necessary to produce overt disease. Thus, an individual may have been genetically susceptible, yet not have any clinical abnormality simply by virtue of escaping exposure to the required environmental stimulus.

Most of the common diseases appear to have a complex, “multifactorial” etiology in which a variety of predisposing genes, not just one gene, interact with environmental factors to produce disease. In addition, because these diseases are so common in the general population, it is likely that different combinations of genes may be responsible for disease susceptibility in different individuals. This is referred to as genetic heterogeneity and confounds the search for susceptibility genes. To reduce heterogeneity, clinical features can be used to subdivide patients into more homogeneous groups. One example of where this has been done very effectively is in diabetes. Based on the appreciation that childhood-onset diabetes, with its propensity to ketoacidosis, was clinically different from adult-onset diabetes in which the patients are generally overweight and relatively ketoacidosis resistant, it was reasonable to hypothesize that there might be two separate forms of diabetes. This hypothesis was corroborated by the twin concordance studies in which childhood-onset identical twin pairs were shown to have a concordance rate of 30% to 50%, whereas adult-onset twin concordance rates were in the range of 90% to 100%. The difference in concordance rates not only suggested that adult-onset and childhood-onset diabetes might be separate disorders, but also that, although both have an appreciable genetic component, genetic factors appear to play a stronger role in adult-onset diabetes than in childhood diabetes. Further genetic dissection was possible with the appreciation that, although most young-onset diabetic patients are thin, ketoacidosis-prone, and insulin-requiring, occasionally adolescent patients are seen who clinically look like adult-onset patients and who can be successfully treated with oral hypoglycemic agents rather than insulin. When careful family histories were taken on these patients with “MODY” (maturity-onset diabetes of youth), it was found that many had family histories consistent with an autosomal-dominant, single gene form of diabetes. Because it is much simpler to locate and characterize the genes for straightforward Mendelian conditions, the identification of MODY as an autosomal-dominant form of diabetes has been very instrumental in finding diabetes genes, as will be discussed later in this article.

Additional evidence that genes are important in common disease susceptibility comes from studies of various ethnic groups. Hypertension, for example, occurs with a higher prevalence in African Americans than in whites. Although dietary differences may contribute to the higher prevalence of hypertension in African Americans, and it has been suggested that more stressful living environments may play a role, there is also an indication that genetic differences are partly responsible. Studies performed in western Africa in those populations from which people were taken for the slave trade have not demonstrated a particularly high prevalence of hypertension. One hypothesis has been put forth suggesting that the extreme conditions on the slave ships, which caused many deaths during the Atlantic passage, acted to select individuals who were most able to retain vital body salt and water stores. Although this trait would have increased the
probability of surviving the trip to America, the same genetic trait in the descendants of that person increases the risk for hypertension in our modern environment, in which our diet commonly contains excess salt. A similar type of hypothesis has been used to explain the very high prevalence of obesity and non-insulin-dependent diabetes in certain ethnic groups, such as the Pima Indians in the Southwestern United States and the Nauruans of Micronesia. In these populations, there was virtually no obesity and no diabetes until about 100 years ago. In the past century, however, as these groups of individuals have abandoned their traditional (and subsistence-level) lifestyles for the high-calorie, sedentary "Western" lifestyle, the rates of obesity and diabetes have increased to the point that the Pima and the Nauruans have the highest diabetes prevalence rates in the world, exceeding 50% of their adult populations. The high prevalence rates cannot be explained purely on environmental grounds, because other populations that have adapted the same Western lifestyle have nowhere near the same rates of diabetes and obesity. Over 30 years ago, James Neel put forth the "Thrifty Gene Hypothesis," which speculated that there was a gene or genes that increased survival during times of famine (which were very common in pre-agricultural societies) by making the body more efficient in storing calories (as fat) when food was available.4 Although such genes would have increased genetic fitness at one time in human development, the same ability to efficiently store calories in modern times, when caloric excess is the norm, becomes detrimental by leading to obesity, insulin resistance, and diabetes. Presumably, many of the genes that today put us at risk for common diseases at one time were actually beneficial, explaining how they could have become so prevalent within the population.

Other evidence corroborating the role of genetic predisposition to disease has come from the observation that a number of rare genetic disorders feature one or more of these common conditions as part of their expression. Thus, for example, children with achondroplasia have an increased tendency toward obesity, as do children with Prader Willi syndrome and teenagers with Turner syndrome.5 Children with Bloom syndrome, neurofibromatosis, and the basal cell nevus syndrome are all at increased risk for cancer.6 Although these conditions are individually relatively uncommon, the fact that specific genetic disorders can be associated with various common diseases implies that genetic causes can explain these conditions, even in non-syndromic circumstances.

Animal studies have also been important in implicating genetic factors in the etiology of common disease. Not only are there specific gene defects that cause these disorders in certain animals, such as the autosomal-recessive ob/ob mouse model, which develops severe obesity and diabetes, but classic breeding experiments have shown that strains of animals with very divergent risks for a given disease can be developed by selective breeding. Baboons have been bred selectively for high- and low-cholesterol values, for example, and the NOD (nonobese diabetes) mouse strain has been developed from an original breeding stock that did not develop diabetes.7,8

Despite these types of studies, all convincingly demonstrating the importance of genetic susceptibility to common diseases, the actual identification of the specific genes and mutations accounting for this susceptibility has been very difficult. Clearly, the genetic heterogeneity present in the common diseases—with different genetic factors able to produce the same clinical condition and, in many cases, the requirement of alterations in several different diseases being necessary for susceptibility—has confounded the search for genetic mutations. Quite dramatic progress has been made in the past decade, however, due in large measure to technologic developments in two areas. First, the advent of rapid, automated molecular genetic methodology (described in the article in this issue by Gregg and Grody entitled "Diagnostic Molecular Genetics: Current Applications and Future Technologies" on pp. 553-561) has made it possible to perform many large genetic studies. Second, computerization of mathematical genetic analysis has provided the tools to analyze the results of the molecular studies.9

Two types of genetic approaches have been utilized in the common diseases. One, called association, uses a case-control study design and asks the question whether a specific allele (form of a gene) occurs with increased frequency in affected individuals as compared with controls.10 Thus, for example, association studies in insulin-dependent diabetes have shown that two HLA-DR alleles, DR3 and DR4, occur with increased frequency (about 60% to 70% each) in diabetic patients as compared with the general, nondiabetic population (in which DR3 and DR4 each have a frequency of 20% to 30%).11 Such studies suggest that the HLA-DR genetic locus may play a direct role in susceptibility to insulin-dependent diabetes. Because these genes also determine major histocompatible antigens, this is not surprising given the autoimmune nature of this form of diabetes. Association studies can be very useful for "candidate gene" studies in which there is a prior reason to hypothesize that a specific gene may be involved in disease susceptibility.

The other type of genetic analysis commonly used
is linkage analysis. Rather than hypothesizing that a specific allele is causing susceptibility, linkage examines whether, within families, any allele at a given genetic locus segregates with disease. Thus, as shown in the Figure, if a genetic region is important in disease susceptibility, most affected members within a given family will have inherited the same allele, but the specific allele may be different in different families. Observing linkage in such studies provides strong evidence that a gene involved in disease susceptibility is present in a particular genetic region, but does not necessarily mean that the particular candidate gene or random genetic polymorphism being evaluated is itself the causative gene (see also the article by Gregg and Grody on pp. 553-561). Linkage targets the chromosomal region to study in detail for the researcher; it does not necessarily find the specific gene for you, however. Although linkage analysis has been utilized in genetic studies for several decades, it has become particularly important with the development of efficient molecular methods. Today, it is possible to perform genome-wide scans (sometimes referred to as systematic mapping) using highly polymorphic "microsatellite" markers. These markers are short-sequence (2 to 4 basepairs), highly-repeated segments of DNA that are scattered widely throughout the genome. Although most of these microsatellites do not occur in coding regions of genes and do not themselves directly influence gene function, the fact that they are inherited sequences that are highly variable in the population make them ideal for linkage studies. Now, rather than being limited to candidate gene studies, in which a specific gene has been isolated that may logically appear to be involved in a specific pathophysiology pathway, geneticists can perform linkage studies to identify chromosomal regions that are likely to contain susceptibility genes, even when no candidate genes have yet been found in those regions. Although such approaches may initially sound as though they have a low probability of success, this approach is now being used in many disorders and has, in insulin-dependent diabetes for example, led to the identification of about a dozen chromosomal segments likely to contain diabetes-susceptibility genes.

As the genes that can place individuals at increased risk are identified, a medical and ethical issue that will arise is the consideration of screening for genetic risk assessment in infancy or early childhood. In general, the consensus about screening minors for later-onset disorders has been that this should be delayed until individuals are old enough to provide informed consent. Although many parents may feel that they should have the right to decide to have their children screened, current opinion within the medical ethics community is that, unless it can be demonstrated that immediate action would be taken based on the knowledge gained from screening, the risks of stigmatization and the loss of autonomy in decision making for the child outweigh the parental right to know. At present, with few exceptions, as will be discussed later in this article under the specific diseases, there is little data to show that specific interventions would result from childhood screening. In the future, however, this situation may well change. As susceptibility genes are identified, we will learn more about the underlying physiologic mechanisms that lead to various diseases, and it is likely that highly specific therapies, perhaps medications or avoidance of particular environmental risks, will be developed. If it is shown that such interventions need to be initiated early in life to be effective, the potential benefits to the child may warrant testing with parental consent alone. By the time the field develops to this point, hopefully our society will also have addressed the issues of insurance discrimination, educational discrimination, and occupational discrimination that now confront adults seeking presymptomatic testing for such diseases as the inherited forms of cancer.

THE GENETIC BASIS OF DIABETES

As discussed briefly previously, some of the most extensive studies of the genetic basis of susceptibility to one of the common diseases have occurred in the area of diabetes. Abnormal glucose regulation can result from two primary problems, inadequate production of insulin or cellular resistance to the action of insulin. For 20 years, it has been appreciated that there are at least two separate forms of diabetes—type 1, insulin-dependent diabetes mellitus (IDDM) results from an
inability to produce insulin, whereas type 2, non-insulin-dependent diabetes mellitus (NIDDM), is primarily a disorder of insulin resistance. As mentioned earlier, twin studies have demonstrated that both forms of diabetes have a significant genetic component. Additionally, family studies have shown that the risks for these diseases are independent; having a relative with IDDM places an individual at increased risk for IDDM but not NIDDM, and having a relative with NIDDM increases the risk to family members for NIDDM but not for IDDM. 

**Insulin-Dependent Diabetes Mellitus**

The first genetic region to be implicated in the development of IDDM was the HLA region on the short arm of chromosome 6. Population association studies have shown that the class II HLA-DR gene is implicated in IDDM susceptibility, with the alleles DR3 and DR4 being more prevalent in patients with IDDM than in control subjects. In addition, the relative risk for IDDM in individuals who have inherited both DR3 and DR4 (compound heterozygotes) is greater than those homozygous for (having two copies of) either DR3 or DR4. This raises the possibility that there may actually be two different forms of genetic susceptibility, one associated with DR3 and one associated with DR4, that may act synergistically in increasing the risk for IDDM. In addition to the association studies, linkage studies in the HLA region have also been performed and show that, when there are two or more siblings with IDDM in the same family, they share entire HLA haplotypes (the sequence of HLA A, B, C, and DR alleles inherited on the same chromosome 6) more frequently than would be expected by chance alone. If there were no linkage, affected pairs of siblings would be expected to share two, one, or zero haplotypes in a ratio of 25% to 50% to 25%. Instead, the observation is that diabetic siblings share two haplotypes approximately 55% to 60% of the time, share one haplotype in approximately 40% of cases, and in only a few cases share zero haplotypes.

There is still some disagreement in the diabetes research community about which gene or genes in the HLA region account for IDDM susceptibility. The HLA region is complex, with many similar genes that all function in the body's immune system. In addition to the DR gene, the HLA class II region also contains DQ and DP genes, and there is some evidence to suggest that all three genes may be involved in IDDM. Studies over the next several years should better clarify their respective roles.

Although the HLA region contributes significantly, accounting for between 30% to 60% of genetic susceptibility to IDDM, it is clearly not the only genetic region involved. The second region to be identified was the insulin gene on chromosome 11. Although the insulin gene itself is structurally normal, there is a variable length DNA segment in the 5' regulatory region of the gene, which has been demonstrated in both association and linkage studies to account for some IDDM susceptibility, presumably by influencing the regulation of insulin production. This region is thought to provide, at most, 5% to 10% of total susceptibility. A variety of other genetic loci also appear to participate in the development of IDDM. Most of the other regions have been identified from genome scans using microsatellite markers. Based on these studies, it appears that there are IDDM susceptibility genes located on chromosomes 2, 6, 11, 14, and 15. Studies of these regions are underway, but for most of these chromosomal locations, the exact genes involved remain unknown.

Despite this increasing knowledge about the genes accounting for IDDM susceptibility, it is not yet possible to directly use this information for genetic counseling purposes. As a consequence, most genetic counseling for IDDM is based on empiric risk estimates that have been developed from both population-based and family-based epidemiologic studies. The empiric risk of recurrence for IDDM is dependent on the relationship of the individual in question to the affected family member. If the father is affected, the risk to his offspring is 4% to 6%, as compared with 2% to 3% if the mother is affected. For siblings, the empiric risk is approximately 5% to 10%. Sibling risks can be modified by determining HLA haplotypes (the sequence of HLA A, B, C, and DR alleles inherited on the same chromosome 6) within the family. If two haplotypes are shared, the risk increases to 16% to 17%, and is 20% to 25% if the haplotypes contain both DR3 and DR4. Siblings who share one haplotype have a risk in the range of 5% to 7%, whereas the risk is approximately 1% to 2% if no haplotypes are shared. It is important to realize that the sibling of an individual with IDDM still has a risk for IDDM that is increased above that of the general population, even when the sib shares no HLA haplotypes in common with the diabetic in the family. There is some concern regarding the benefit of performing HLA typing for the siblings of an individual with IDDM when there is no way to intervene and prevent IDDM from occurring. Research studies to test the possibility that immunosuppressive or thera-
As susceptibility genes are identified, we will learn more about the underlying physiologic mechanisms that lead to various diseases, and it is likely that highly specific therapies, perhaps medications or avoidance of particular environmental risks, will be developed.

To help the child's immune system be immunologically tolerant to insulin may help prevent or delay the onset of IDDM are currently in progress. If these studies prove intervention is feasible, identification of siblings at highest risk, based on HLA typing, may be important in selecting the most appropriate candidates for intervention. It must be kept in mind, however, that such therapies have not yet been clearly proven to prevent the development of IDDM and have the potential for serious complications.

Diabetes is not the only autoimmune disorder for which relatives of an individual with IDDM are at risk.11 Family members, as well as the patient, are at increased risk for autoimmune thyroid disease (Hashimoto thyroiditis, Graves' disease), pernicious anemia secondary to autoimmune gastritis, autoimmune adrenal disease (Addison's disease), myasthenia gravis, vitiligo, and celiac disease. A study looking at individuals with IDDM and their relatives found that 21% of the diabetics and 22% of their first-degree relatives had evidence of autoimmune disease. Seventy-five percent of the autoimmune disease in relatives occurred in families in which there was a proband with autoimmune disease, indicating that there may be increased genetic susceptibility to other autoimmune disorders in certain IDDM families. The most common form of autoimmune disease in families with IDDM is thyroid disease. It is estimated that approximately 15% to 20% of both IDDM patients and their first-degree relatives have thyroid disease. In contrast, the prevalence of autoimmune thyroid disease in non-diabetic white individuals is thought to be 4.5%. Although other autoimmune diseases are less common, autoimmune gastritis is seen in 5% to 12% of individuals with IDDM and 2.5% to 6% of their first-degree relatives. This gastritis may be clinically important because it can result in pernicious anemia.

Noninsulin-Dependent Diabetes Mellitus

The greatest success in determining the genetic basis of a form of NIDDM has been with maturity-onset diabetes of the young (MODY), an autosomal-dominant form of the disease.1 Although a fairly rare type of diabetes (MODY may account for 2% to 3% of all NIDDM), MODY is important for pediatricians because it may present in adolescence and must be distinguished from IDDM.

MODY has taken on great importance in the past decade because of the lessons it has taught about the loci involved in NIDDM and genetic heterogeneity. The first MODY (MODY 1) locus was identified by Bell and colleagues with the demonstration of linkage of MODY with the adenosine deaminase locus on the long arm of chromosome 20 in one large family.11 Not long after linkage to chromosome 20 was found, linkage in other MODY families was reported with the glucokinase gene (GCK) on chromosome 7p. Unlike the adenosine deaminase locus on chromosome 20, which was tested simply as a polymorphic marker in a systematic mapping approach, GCK was tested as a candidate gene because of its role in glucose homeostasis. Most MODY patients have a decreased insulin response to glucose, suggesting a primary pancreatic beta-cell defect. Thus, the glucokinase gene was an excellent candidate for genetic investigations. Following the demonstration of linkage, actual mutations within the coding region were identified. A significant number of MODY pedigrees were not linked to either chromosome 20 or to glucokinase, and in 1995 a third MODY locus (MODY 3) was mapped to chromosome 12q. In 1996, both the MODY 1 and MODY 3 genes were actually identified.15-16 MODY 1 encodes the hepatocyte nuclear factor-4a and is a member of the steroid/thyroid hormone receptor superfamily. It is an upstream regulator of hepatocyte nuclear factor-1a expression, a transcription factor affecting gene expression in the liver and in β-cells, which is the product of the MODY 3 gene.

The discovery that at least three different genes are responsible for causing MODY suggests that there is likely to be even greater genetic heterogeneity within "classical" NIDDM. Just as different MODY defects appear to cause varying degrees of diabetes severity and complications, the clinical and physiologic differences among NIDDM patients may well result from genetically separate forms of diabetes. Less progress has been made in finding the genes that produce susceptibility to the non-MODY forms of NIDDM. Some cases result from mutations in the insulin gene that cause defective insulin production, and mutations in mitochondrial DNA have been shown to cause diabetes in association with deafness, but these account for only a handful of NIDDM patients.11

Empiric recurrence risk data can still be used to advise individuals of their risk for developing NIDDM and to determine those who may warrant more frequent glucose monitoring. Empiric risks suggest that an individual who has a parent or sibling with NIDDM has a 10% to 15% risk of developing diabetes.11 In
some ethnic groups, this risk may be even higher, as, for example, in the Latino population, in which first-degree relatives may have a risk as high as 50%.

Although NIDDM is typically thought of as an adult-onset disorder, our own studies in Southern California have shown that NIDDM may account for as much as 50% of all childhood- and adolescent-onset diabetes in the Latino population. Thus, a Latino child who has a parent with NIDDM, particularly if the child is overweight, must be considered at high risk for early development of diabetes.

Diabetes and Pregnancy

Another reason why diabetes is of concern to the pediatrician is the increased risk for congenital malformations in the offspring of diabetic women. In the general population, the risk to have a child with a birth defect is 2% to 3%. For women with IDDM, the risk is increased threefold, to 6% to 10%, whereas for women with NIDDM, the risk is increased at least twofold. The malformations seen in infants born to diabetic women tend to be more severe than those seen in infants of nondiabetic women and include abnormalities of the skeletal, renal, cardiac, and central nervous systems. Virtually all anomalies occur with increased frequency in infants of diabetic mothers, but those that have the highest relative risk are caudal regression, renal agenesis, transposition of the great vessels, ventricular septal defects, atrial septal defects, situs inversus, and neural tube defects (anencephaly and meningomyelocele). Because of the increased risk for major structural malformations, prenatal diagnostic tests should be recommended for all pregnant women who have diabetes. Ultrasonography can be used to evaluate fetal growth and to rule out major fetal structural anomalies such as renal agenesis, neural tube defects, and caudal regression. Fetal echocardiography enables prenatal diagnosis of major structural cardiac malformations. Elevations of maternal serum alpha-fetoprotein (MSAFP) have been associated with open neural tube defects such as anencephaly and meningomyelocele; thus, MSAFP screening is recommended for all pregnant diabetics.

There is evidence that in the general population, folic acid supplementation, begun prior to conception, is helpful in decreasing the risk for neural tube defects. Although studies looking specifically at infants of diabetic mothers have not been reported, folic acid supplementation prior to conception should be strongly considered for all women because the potential benefits (i.e., possibly reducing the risk for neural tube defects) outweigh any known risks.

THE GENETIC BASIS OF CANCER

Numerous studies have demonstrated that a positive family history places an individual at increased risk for many forms of cancer (Table 1). Thus, for example, having a first-degree relative (parent, sibling, or offspring) with colon cancer places an individual at three times the general population risk for colon cancer. A family history of breast cancer increases a woman’s risk for breast cancer, particularly if the relative was diagnosed with premenopausal breast cancer. The risk is not necessarily only for the specific type of cancer that has occurred in a relative; thus, for example, a family history of breast cancer places a woman at increased risk for colon cancer, ovarian cancer, and breast cancer, and her brother will be at increased risk for colon cancer.
Even in those disorders where adult onset is the rule, the pediatrician can play a vital role.

In recent years, it has been possible to identify a number of genes which, when altered, are associated with autosomal-dominant inheritance of cancer risk (Table 2). Most of these genes appear to function normally as "tumor suppressors," inhibiting unregulated cell growth and division. When mutations occur, this regulatory activity is lost, and unregulated cell growth is more likely to occur.

It has also come to be appreciated that a single gene mutation is not sufficient to produce malignancy. In order for a specific cell to become cancerous, two or more mutations in one or more tumor suppressor gene need to have accumulated. In the case of an individual who is not genetically at high risk for cancer, environmental mutagenesis can over time produce such a result. In the individual who has inherited a mutation in one of these tumor suppressor genes, however, every cell in his or her body starts out with one of the necessary mutations already present. The probability that one or more cells will go on to acquire the additional mutations to produce cancer is therefore significantly increased. As a result, susceptible individuals not only have a higher overall risk of developing cancer, but commonly have a younger age of onset and a greater probability of second tumors.

COLON CANCER

The first inherited form of colon cancer with an identified genetic defect was familial adenomatous polyposis (FAP). This autosomal-dominant disorder is characterized by the occurrence of hundreds to thousands of benign adenomas in the colon and other portions of the intestinal tract. The risk of one or more of these adenomas becoming malignant is almost 100% and thus the treatment of choice is total colectomy once the presence of the adenomas has been detected. FAP can occur in two forms, one in which there are few other associated findings and one, called Gardner's Syndrome, in which other manifestations, including supernumerary teeth, osteomas of the jaw, and desmoid tumors, occur as well. The same gene is responsible for both forms of the disease and is located on chromosome 5. Called the APC gene, it has been found to be mutated in many sporadically occurring colon cancers and benign adenomas and it is presumed to be involved in one of the early, premalignant steps in the transformation of normal colonic epithelium to benign adenoma formation. The high risk of colon cancer in individuals who inherit mutations in the APC gene seems to be due to the very large numbers of adenomas they develop, because there is an increased risk of malignant degeneration occurring within adenomas.

Familial adenomatous polyposis is a disease of appreciable concern to pediatricians because colon cancer may occur in affected individuals as early as adolescence. Therefore, the recommendation is that children who have an affected parent (and thus are at a 50% risk to have inherited the disease) should undergo annual sigmoidoscopy looking for adenomas beginning at age 10 to 12 years. With the advent of DNA mutation analysis of the APC gene, DNA testing can now be performed to identify those individuals who have inherited a mutation and need colonoscopy as well as to identify those who have been fortunate enough to not inherit the mutation and are therefore at no increased risk for colon cancer.

Another autosomal-dominant form of colon cancer is known as hereditary nonpolyposis colon cancer (HNPCC). Whereas FAP is thought to account for no more than 1% of colon cancer, HNPCC accounts for 5% to 10% of all colon cancer. Unlike FAP, colon adenomas are relatively infrequent in HNPCC but still occur in the locations in which the colon cancers develop. As in FAP, annual colonoscopies are recommended beginning in adolescence, but primary colonoscopic removal of adenomas can be used for cancer prevention without total colectomy being necessary. In some HNPCC families, colon cancer appears to be the only form of cancer occurring with increased frequency, but in other families, there is also an increased frequency of a variety of other cancers, including ovarian cancer, endometrial cancer, and prostate cancer.

Over the past several years, four genes have been found that can produce HNPCC. These genes have been particularly interesting because they have brought to light a new category of cancer susceptibility genes, the DNA mismatch repair genes. These four genes, hMLH1, hMSH2, hPMS1, and hPMS2, are all normally involved in the pathway used for repairing DNA damage in the nucleus of the cell. When an individual inherits a mutation in one of these genes, this DNA repair process becomes less efficient and the cells are less able to correct acquired DNA changes. Thus, malignancy occurs in these individuals because they are more susceptible to the detrimental effects of environmentally induced mutations and sporadically occurring DNA replication errors.

The reason that dysfunction of the DNA mismatch repair process should lead to increased colon cancer risk alone in some families versus a wide but quite specific spectrum of other cancers in other families is not yet understood. Until it is understood, members of HNPCC families who have inherited a mutation in one of these four genes must be considered potentially at increased risk for all of the associated cancers. Thus, quite intensive surveillance, including endometrial biopsy, Doppler flow ultrasound examination of the ovaries, and CA125 measurement for women and prostate-specific antigen measurement for men, is recommended in addition to colonoscopy.
BREAST CANCER AND OVARIAN CANCER

Epidemiologic studies have long indicated that there is an interrelationship between the risk for breast cancer and ovarian cancer.22 Breast cancer survivors are at increased risk for ovarian cancer, ovarian cancer survivors are at increased risk for breast cancer, and their first-degree relatives are at increased risk for both. The genetic basis for this interrelationship has been clarified over the past 5 years, with the localization and eventual cloning of two genes, BRCA1 on chromosome 17 and BRCA2 on chromosome 13.23,24 Although these genes were named for their role in breast cancer (thus BRCA), they are both ovarian cancer susceptibility genes as well.

BRCA1 is responsible for approximately half of all inherited cases of premenopausal breast cancer and for 80% or more of families with hereditary breast and ovarian cancer (HBOC) in which women who inherit a mutation may develop breast cancer or ovarian cancer or both.23,24 Men who inherit BRCA1 mutations appear to be at an increased risk for prostate cancer, but are not at risk for breast cancer.23,24 Over 100 different mutations in the BRCA1 gene have been identified and, with the exception of a few populations, no particular mutations seem to occur with high frequency. This is not the case in some more inbred populations, in which specific mutations do account for most cases of BRCA1-associated cancer. Thus, in the Ashkenazi Jewish population, there are two specific mutations (del185AG and 5382insC) that are quite common. It is estimated that close to 1% of the Ashkenazi population carries the del185AG mutation.

In all probability, the overall risk for breast cancer and ovarian cancer will be different with different BRCA1 mutations. At present, it is not possible to quote mutation-specific risk figures, however, and the best that can be given are risk figures for all BRCA1 mutations combined. Based on these combined figures, the overall probability of a woman developing breast cancer is 85%, whereas the risk of ovarian cancer is in the range of 40%.23,24

BRCA2 mutations appear to place women at a similar risk for breast cancer as do BRCA1 mutations, but the ovarian cancer risk is less (in the range of 10%). Interestingly, men who carry BRCA2 mutations are at increased risk for breast cancer, but BRCA2 does not appear to be associated with prostate cancer risk in the same way as BRCA1.

The mechanisms by which BRCA1 and BRCA2 produce cancer risk are not yet understood. When these genes were cloned, they were found to be novel genes that bore little resemblance to previously identified genes, with the exception that they share some motifs that suggest that they are likely to interact with DNA. They are presumed to be tumor suppressor genes, but proof of this will need to await further elucidation of their normal cell function.24

Approximately 5% to 10% of breast cancer is thought to occur as the result of autosomal-dominant single gene disorders. Although BRCA1 and BRCA2 appear to account for many of these cases, there are likely to be other genes involved as well, particularly for those families in which there is inheritance of postmenopausal, rather than premenopausal, breast cancer. Because of the high prevalence of postmenopausal breast cancer in the general population, determining in which families a clustering of postmenopausal disease is truly due to inherited breast cancer susceptibility rather than to random chance can be very difficult, making the search for the susceptibility genes even more problematic.

THE GENETIC BASIS FOR ARTERIOSCLEROSIS

Familial clustering of coronary artery disease (CAD) has long been appreciated, and a positive family history is the strongest risk factor for CAD.25 Among the best understood genetic factors in CAD are those related to lipid metabolism, but in recent years, there has been increasing suggestion that other factors, including the regulation of homocysteine metabolism and the regulation of the coagulation cascades, may also be involved in genetic susceptibility to CAD.

The best understood genetic form of arteriosclerosis is familial hypercholesterolemia (FH).25,26 This autosomal-dominant disorder is caused by mutations in the LDL receptor gene on chromosome 19, resulting in elevated plasma LDL concentrations.25 Mutations in this gene are quite common, with 1 in 500 individuals in the population having heterozygous FH. Homozygous FH, in which a child inherits LDL receptor gene mutation from both parents and produces no functional LDL receptors, is very rare (1 in 1,000,000), but results in severe arteriosclerosis and death in childhood.25 Heterozygous FH does not cause symptoms in childhood but, unlike most of the other disorders of lipid metabolism, does cause elevations in LDL cholesterol levels from infancy. Although drug therapy to reduce LDL levels is not recommended in childhood, it is prudent that children with FH be placed on low-fat diets once they are past the toddler period.

Less commonly, increased risk of arteriosclerosis can result from abnormalities in clotting function, including antithrombin III deficiency, protein C deficiency, protein S deficiency, abnormalities in plasminogen activator inhibitor-1 (PAI-1), abnormalities in tissue plasminogen activator (tPA), and factor V resistance to activated protein C cleavage. Many of these clotting disorders more typically present with venous rather than arterial thrombosis, but arterial disease has been reported.

Alterations in the metabolism of homocysteine have become of increasing interest in recent years. Several epidemiologic studies have demonstrated a relationship between plasma homocysteine levels and CAD.28 Homocysteine levels are, in part, regulated by
the presence or absence of a thermolabile genetic variant of the enzyme methylene tetrahydrofolate reductase. When individuals with this variant are folate deficient, they are at increased risk for CAD. One potential benefit of the plan under consideration to add folate supplements to grains (to reduce the incidence of neural tube defects) may be to reduce CAD risk in those individuals with this enzyme variant.

As with the other common diseases, even in the absence of a documented genetic alteration, a family history of coronary artery disease can be used to identify individuals who are at higher risk for CAD than the general population. Although much attention has been paid to dietary intervention to reduce cholesterol levels in the general population, many individuals who are at risk for coronary artery disease are not having their cholesterol levels adequately reduced, either because they have not been tested or because they are not compliant with medical recommendations. Studies have shown that patients will be more compliant with recommended screening and lifestyle modifications when they are told that they are genetically at increased risk for CAD. Thus, increased physician awareness of the importance of genetic factors in CAD may be effective both in leading to more aggressive medical management and greater patient compliance.

COMMON DISEASE GENETICS AND THE PEDIATRICIAN

Pediatricians may ask why, with all of the other medical issues confronting children, they should be concerned with disorders that primarily affect adult patients. There are a variety of reasons. First, not all of these conditions are exclusively adult in onset. IDDM and occasionally NIDDM are seen in children and adolescents, as is FAP. Even in those disorders where adult onset is the rule, the pediatrician can play a vital role. The processes that lead to these diseases begin in infancy—autopsies of children dying of unrelated causes already demonstrate the widespread development of fatty streaks in the aorta which will eventually become arteriosclerotic plaques. Lifestyle changes—smoking cessation, major changes in diet—are very difficult to make in adulthood, when habits have been established for many years and are less likely to be effective in preventing disease when years of damage have already occurred. If pediatricians, with their inherent preventive medicine perspective, pay attention to the clues that can be gleaned from taking a careful history, the process of education and lifestyle management so vital to the prevention of these disorders can be initiated early in life. A child who grows up eating a low-fat, high-fiber diet will be reducing his risks for CAD and colon cancer and will feel less deprived than if he or she attempts to initiate such a diet for the first time in his or her 30s or 40s. Finally, pediatricians know that when they impact one member of the family, they can actually benefit many others as well. By increasing a family's awareness of the genetic nature of predisposition to the common adult-onset diseases, it is possible that the at-risk parents will themselves adopt the same lifestyle changes that they are making for their children, and may also contact their own healthcare providers to discuss establishing a program of screening and intervention appropriate to their risks.

REFERENCES