Understanding Genetic and Environmental Risk Factors in Susceptible Persons

ROGER R. WILLIAMS, MD, *Salt Lake City*

Most major chronic diseases probably result from environmental factors accumulating over time in genetically susceptible persons. A detailed family history assessment can help identify the subset of the general population with a strong predisposition to certain major diseases. An understanding of the environmental factors promoting disease development will facilitate more effective prevention or delay disease in a targeted susceptible population. To effectively use this growing knowledge in genetics and epidemiology, health professionals need to motivate people to follow sound recommendations for preventing and delaying disease.

To increase the efficiency and effectiveness of strategies for health promotion and disease prevention, family history data can help determine those diseases for which persons have the greatest risk. They can then concentrate their primary efforts on those preventive measures that will most likely benefit them.

(Williams RR: Understanding genetic and environmental risk factors in susceptible persons, *In* Personal health maintenance [Special Issue]. West J Med 1984 Dec; 141:799-806)

What determines which diseases will most likely develop in a person? Is there a way to predict which few specific illnesses should be of greatest concern to a given healthy person? Realistically, will many persons effectively comply with all of the well-publicized recommendations for detecting early or preventing numerous common diseases? Can physicians help target a few screening and preventive measures of greatest value to specific persons? An understanding of the genetic and environmental determinants of disease can provide a solid rationale for more effective prevention, earlier detection and more specific and more effective treatment of disease. The following are the practical steps required to accomplish these goals.

Genes Plus Environment Equals Disease

Many common diseases seem to occur among genetically susceptible persons who have been exposed to the appropriate environmental factors. Age also plays an important role in the development of most diseases, but age probably represents the accumulated effects of both genetic and environmental factors over time. Many diseases also show different rates of occurrence according to sex. This probably represents either environmental or inherited differences between men and women. While some diseases appear to occur on a totally chance or unpredictable basis, the actual role of chance or random events seems to diminish considerably as more information is uncovered about the pathophysiologic mechanisms.

Several major types of environmental factors are listed in Table 1. Some of the first and most dramatic discoveries in preventive medicine came from infectious disease epidemiology. Application of that knowledge has led to the eradication or control of illnesses such as smallpox, polio, typhoid fever and tuberculosis, which were previously the most common causes of morbidity and mortality. Current epidemiologic studies focus on the causes of major chronic diseases. Early successes are already suggested by decreasing death rates for stroke and coronary diseases in the United States.[1] Studies of general populations and control subjects in clinical trials report improving profiles for major risk factors such as cigarette smoking,[2] hypertension[3] and hypercholesterolemia.[4] One would hope that continued application of expanding knowledge of environmental factors listed in Table 1 could lead to eradicating and controlling the chronic diseases that are currently the major health problems in well-developed countries of the world.

Some of the environmental factors listed in Table 1 aggregate strongly in families, accounting for some of the familial disease aggregation. Thus, the detection of smoking-related diseases within a family may help target a family with "a smoking tradition" that needs to be broken with a conscien-

From the Cardiology Division, Department of Internal Medicine, University of Utah School of Medicine, Salt Lake City.
Reprint requests to Roger R. Williams, MD, Cardiology Division, Dept of Internal Medicine, University of Utah School of Medicine, 50 N Medical Dr, Salt Lake City, UT 84132.

tious and cooperative effort of health professionals and family members.

Different types of genetic factors affecting disease occurrence are described in Table 2. Perhaps the genetic effects most easily understood are those following simple Mendelian inheritance. When biochemical or chromosomal markers have been discovered to trace the gene carriers, it can be shown that in some cases the genes are "highly penetrant," with a large percentage of persons who carry the gene also expressing the disease, such as men who have familial hypercholesterolemia. In other cases, genes have been found to have "low penetrance," with most of the gene carriers not expressing the disease, such as those who have insulin-dependent (type I) diabetes mellitus. One of the main goals of current research is to identify gene markers for specific inherited diseases and then identify the environmental and life-style differences between gene carriers who do and do not express the disease. Future prevention strategies will use this knowledge to prevent disease occurrence in known gene carriers detected soon enough to modify their environmental exposures.

Probably most physiologic traits and many diseases represent the blending of the effects of many different genes, so-called polygenic traits. There is often an additional blending of environmental factors leading to a truly multifactorial etiology. In addition, there is often a mixture of both major gene and polygenic effects in the population. As an example, serum cholesterol level is a polygenic trait in the general population, with a small but important percent of persons exhibiting major gene effects with very high serum cholesterol levels and a risk for early heart attack. In addition, there are environmental factors that can have substantial effects on a person's serum cholesterol level regardless of their major gene or polygenic determinants of serum cholesterol.

A person's integrated risk of disease will represent the summation of genetic predisposition from major genes and polygenes, interacting with specific environmental factors whose strength and duration of exposure combine to produce a person's individual disease risk.

Some diseases may involve a large number of genetic and environmental factors.[5] While many of the details are still being identified by research studies, simple intuition can help us to see these principles in operation. In most heavy cigarette smokers, lung cancer does *not* develop. They must be persons who either lack genetic susceptibility or possibly even have genetically determined resistance to the well-documented carcinogenic effects of cigarette smoking. Figure 1 shows lung

TABLE 1.—*Environmental Factors Affecting Disease Occurrence*

Biologic and Immunologic
Bacteria
Viruses
Fungi
Protozoa
Insect and animal vectors
Allergens
Personal Habits and Life-style
Smoking
Physical exercise
Dietary intake
Chemical Exposures
Toxins
Pollutants
Medication
Solvents, fumes
Contaminants
Physical Environment
Climate
Radiation (ultraviolet, gamma and x-ray)
Physical trauma
Social/Psychological Milieu
Marital and family status
Occupational satisfaction and stress
Learned skills and coping capacity
Shared Environment in Groups
Families (spouse, siblings)
Geographic locations (sun exposure, altitude)
Ethnic and racial groups (diet customs)
Religious groups (health codes, sex taboos)
Individual communities (water supply)
Countries (food-processing systems)

TABLE 2.—*Types of Genetic Factors Affecting Disease Occurrence*

Major Genes (one or two loci, few alleles)
Dominant, recessive or additive?
Gene frequency high or low?
Autosomal or sex-linked?
Totally penetrant?
Partially penetrant?
Factors affecting penetrance (age, sex, environmental factors, other genes, chance)?
Polygenes (many loci and/or alleles)
Blending of effects, none predominate or stand out
Often blending with environmental factors (multifactorial)
Mixture of Major Genes and Polygenes
Noticeable effect of major gene (same characteristics as above)
Background variation around each major gene phenotype due to polygenes

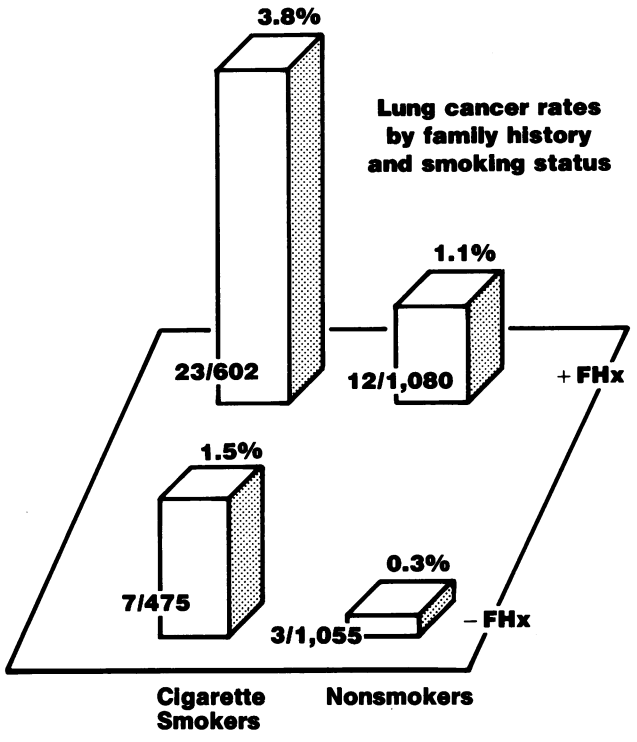

Figure 1.—Lung cancer rates by family history and smoking status (from Tokuhata[6]). + FHx = positive family history, – FHx = negative family history.

cancer rates reported for smokers and nonsmokers with and without first-degree relatives who have lung cancer. Whereas smoking and familial predisposition each seem important, their combined effects are most dramatic.

Past studies of Japanese men have shown rates of early coronary heart disease less than a fourth those observed in young men in the United States.[7] Initially one might have suspected that these differences were due to genetic factors. However, a study of Japanese men living in Japan, Hawaii and California showed parallel increases in serum cholesterol levels and early coronary heart disease rates.[8] Both were lowest in Japan, intermediate in Hawaii and highest among Japanese men living in California. This suggests that among genetically similar persons, significant changes in environmental exposures have dramatic effects on disease occurrence.

Diseases With Genetic Predisposition

Hundreds of well-defined major gene syndromes leading to rare genetic diseases have been described.[9] Methods for screening and genetic counseling are well developed and often efficiently applied for some of these rare disorders. The main emphasis of this report is to concentrate on the possible benefit that can be gained from increased awareness of genetic predisposition to *common* chronic diseases encountered often by practicing physicians. Some of these common chronic diseases are summarized in Table 3. Perhaps the most striking example is early coronary heart disease. Several approaches indicate that a very strong family predisposition to early coronary heart disease occurs in about 5% of the families of the general population, and yet these coronary-prone families account for more than 50% of cases of coronary disease occurring before age 55.[10-12] In about a fourth of these families, a single serum cholesterol test may identify greatly elevated levels as the major inherited causal factor.[10] While coronary disease usually develops by age 45 in men who have familial hypercholesterolemia, there is evidence that men who carry this gene could be protected by healthy environmental factors. Pedigree analyses of great-grandfathers of current hypercholesterolemic coronary victims found definite gene carriers living in the 1800s who survived into their 60s, 70s and 80s (R. R. Williams, MD, and colleagues, unpublished data, December 1984). Developing data from clinical trials also support the feasibility of lowering coronary risk through the treatment of hypercholesterolemia.[13,14]

Preliminary data suggest that 34% of high-risk families have cigarette smoking as the only known concordant risk factor among brothers with coronary disease in their 30s and 40s.[10] Thus, in some persons, avoiding or stopping smoking may totally eliminate a very high risk for premature coronary disease. Results of this study of high-risk coronary families also suggested a magnified detrimental effect of cigarette smoking among coronary-prone men regardless of their underlying risk factor.[10] Multifactorial risk reduction may have its greatest practical benefit in high-risk families.

Hypertension also seems to play a significant role in about a fourth of coronary-prone families. Methods for early detection and treatment of hypertension are already well developed and practiced by many physicians. If these efforts are concentrated in high-risk families, the benefits could be substantial.

Opportunities for early detection and risk factor modification for the prevention of other strongly familial diseases are suggested by the list in Table 3. A detailed discussion of each of these disorders individually is beyond the scope of this review. Just to reinforce the potential for *current* practical application of intervention in high-risk families, a few other examples will be cited. Cancers of the breast, colon and lung are the most common and the most familial.[15]

In a study of 1,000 population-based breast cancer deaths in Utah a third of the patients had sisters with breast cancer, suggesting a strong familial tendency (Mark Skolnick, PhD, unpublished data, August 1980). Preliminary reports already suggest possible chromosomal markers to identify persons carrying this genetic predisposition.[16] Table 3 lists several reported environmental risk factors for breast cancer.[17-21] It is possible that genetically predisposed persons have a multiplicative risk from exposure to these variables and could benefit from their removal. Even if control of environmental risk factors does not completely eliminate the familial risk of breast cancer, applying effective screening procedures (breast self-examination, physician screening, mammography and the like) can lead to the early detection and surgical cure of breast cancer in many of these women.

Colon cancer is also strongly familial in certain persons. Some knowledgeable gastroenterologists working with high-risk families strongly feel that careful screening of high-risk persons can result in early detection of colonic polyps before cancer has developed or spread and effectively eliminate the risk of metastatic colon cancer in most persons with strong predispositions.[22]

The combined contributions of genes and environment to lung cancer are dramatically shown in Figure 1. From this illustration it is self-evident that avoiding cigarette smoking is an important preventive measure for persons who have relatives with lung cancer.

The application of this preventive strategy is not limited to common and prominent diseases such as cancer and coronary heart disease. While they are less common and perhaps less well appreciated, disorders such as hemochromatosis should also be targeted for preventive strategies. In the past, this disorder has often gone undiagnosed. Accumulating iron stores in heart tissue or pancreas have led to heart failure or diabetes mellitus. Unsuspecting physicians have provided only symptomatic treatment, with eventual early death of patients. Screening tests can now be used among close relatives of patients known to have hemochromatosis to identify those carrying the disorder.[23] Frequent phlebotomy is an effective treatment that should eventually produce a normal life span in persons carrying this disorder.

What Can Be Learned From a Thorough Family History

A thorough family history can help answer questions like these: Did a genetic predisposition play an important role in this person's early heart attack? Do close relatives need screening or further follow-up? How strong is this family disease tendency? Does it affect men and women the same? What is the usual age among family members at onset of disease? Before what age should screening and preventive measures be instituted? Which risk factors have been present in affected family members? What is the pathophysiologic mechanism leading to the disease? What specific suggestions

TABLE 3.—*Chronic Diseases Thought to Have Genetic Predispositions*

Disease	*Pathophysiology (or Hypotheses)*	*Genetic Details*	*Environmental Factors*
Coronary heart disease (especially *early* disease)	Familial hypercholesterolemia		Dietary fat
	LDL receptor defects	Dominant	Saturated fat
	Other high cholesterol	?	Polyunsaturated Total fat intake
	Low HDL	?	Exercise, alcohol, diet
	Endothelial factors	?	
	Platelet factors	?	Smoking
	Apolipoproteins	?	?
	Diabetes I and II	See below	See below
	Hypertension (especially early onset)	See below	See below
	Multiplicative interactions of family history and risk factors		
Stroke	Hypertension and diabetes	See below	See below
Hypertension	Heterogeneous	Polygenic?	Salt, stress, obesity
	Age at onset	Major gene?	Polyunsaturated fat
	Severity? Cause?	Highly penetrant?	
Type I diabetes mellitus (insulin-dependent)	Islet cell destruction	Recessive?	Viral infection
	Immunologic cause	<50% penetrant	Seasonal variation
		HLA linkage and association on chromosome 6	Complications a function of blood sugar control for years
Type II diabetes mellitus (non-insulin-dependent)	Insulin resistance	80% to 100% penetrant	Obesity
	or	Dominant?	Dietary sugar and fiber
	Decreased production	RFLP association to insulin gene on chromosome 11	Exercise protective Complications a function of blood sugar control and function
Breast cancer	Estrogen-related	Some dominant	Age when first child born
	Certain benign tumor precursors	50% to 90% penetrant in some families	Obesity Dietary fat Alcohol use Female hormones
Colon cancer	Several different types of syndromes	Some dominant	Fiber intake
	Often benign polyps are precursors		Dietary fat (converted by bacteria to carcinogens)
Lung cancer	Chemical carcinogens from environment encounter enzymatically susceptible subjects	Known familial aggregation ± smoking	Cigarette smoke Environmental pollutants Radiation exposure
Rheumatic heart disease	Immunologic cross-reactivity to bacteria and heart valves	Familial aggregation	Group A β-streptococcal bacterial infection
Asthma and other allergies	Immunologically reactive	Familial aggregation	Many possible allergens—fur, dust, pollen, mold, etc. Avoidance to prevent
Autoimmune disorders	Autoantibodies to thyroid, adrenal, synovium, platelets	HLA-linked on chromosome 6	Viral infections trigger immune responses
Rheumatoid arthritis Hashimoto's thyroiditis and Graves' disease Addison's disease Idiopathic thrombocytopenic purpura Type I diabetes mellitus Systemic lupus erythematosus			
Psychiatric disorders			
Manic-depressive Depression Schizophrenia	Neurochemical disorders in brain tissue	Strongly familial and likely genetic in twin, adoption and family studies	Uncertain influence Several dramatic drug therapies for manic-depression and depression
Kidney stones	Mineral-acid-base imbalance	Very familial	Milk? Soda pop? Other fluids?
Gallstones	Fat, cholesterol, bilirubin balance	Quite familial	Dietary fat Obesity?

ATPase=adenosine triphosphatase, G6PD= glucose-6-phosphate dehydrogenase, HDL=high-density lipoprotein, HLA=human leukocyte antigen, LDL=low-density lipoprotein, RFLP=restriction fragment-length polymorphism

Disease	*Pathophysiology (or Hypotheses)*	*Genetic Details*	*Environmental Factors*
Obesity (probably very heterogeneous)	Less energy wasted? ↓ Thermogenesis in brown fat? Other basic energy differences like ATPase pumps? "Thrifty gene"?	Major genes in animals Clusters in families Assortative mating Monozygotic twin similarity > dizygotic Racial group (American Indians and Polynesians)	Dietary fat, sugar and total calories Stress, etc. affecting appetite Exercise level Cultural perceptions (attractive to be fat or thin?)
Gout	Several different enzyme defects found	Several autosomal major genes	Dietary intake of meat and the like
Multiple sclerosis	Autoimmune demyelination of nerve fibers	HLA association Poorly penetrant Monozygotic twins often discordant	Slow virus? Climate-dependent
Peptic ulcer disease	Excess acid production and/or decreased mucosal resistance	Biochemical markers of affected subjects Variable penetrance	Stress Diet Dramatic drug therapy
Hemolytic anemia	G6PD deficiency Red cell hemolysis precipitated by exposure to drugs or infections	X-linked recessive	Aspirin Antibiotics Infections
Lactose intolerance	Deficiency of lactase enzyme in intestinal mucosa	Very common in blacks	Milk products
Alcoholism	Associated with other psychiatric disorders Possible neurochemical origin?	Familial (due to genes and/or family environment?)	Ethyl alcohol intake Social factors
Hemochromatosis	Increased iron absorption	Linked to HLA on chromosome 6 Recessive Penetrant	Treat with phlebotomy and prevent organ damage from iron loading

ATPase=adenosine triphosphatase, G6PD= glucose-6-phosphate dehydrogenase, HDL=high-density lipoprotein, HLA=human leukocyte antigen, LDL=low-density lipoprotein, RFLP=restriction fragment-length polymorphism

could be given for disease prevention, screening and treatment?

Current research is concentrating on identifying specific syndromes and separating out the heterogeneity of many common chronic diseases such as diabetes mellitus, coronary disease, hypertension and cancer. Family history information will be increasingly useful in helping to identify these specific syndromes. This improved understanding of pathophysiology will lead to better prevention, screening and treatment.

How to Obtain a Good Medical Family History

The usual *brief screening family history* taken by a physician during a workup should include three questions. First, does the person know of any medical problems that tend to run in the family? Next, have any close relatives (parents, grandparents, siblings, aunts, uncles or offspring) had premature (before age 55) heart disease, cancer, diabetes mellitus, high blood pressure, stroke, bleeding disorders, emotional illness, serious problems with allergies or neuromuscular problems? Third, what was the age of onset and treatment for any relatives reported to have the disease? Even such a brief family history will often flag striking family problems that deserve further attention.

A *detailed family history* should be obtained when a brief family history suggests a possible disease tendency. It begins with enumerating all first- and second-degree relatives (see Figure 2). List at least first names to facilitate further questions and accurate communication. For each person, list vital status, age (now or at death) and cause of death. For specific targeted diseases that seem to occur in the family, the age of onset should be recorded for each family member with the disease. This is especially important for common diseases such as high blood pressure, diabetes mellitus and coronary heart disease in which an early age at onset would indicate a strong family history whereas a later age at onset may not be a flag of a positive family history at all. The number of spouses and children of each person and their current location or location at death can be useful as a springboard for further information gathering, screening and preventive measures.

To decrease the expense of family history screening, self-administered questionnaires have been developed and piloted among families of 12,000 high school students in Texas and Utah.[24] Self-administered questionnaires filled out by families in their own home have the advantage of allowing them to contact relatives to obtain information or to even review their own medical records or prescriptions while filling out the forms. Probably the best accuracy can be obtained from a combination of self-completed questionnaires subsequently reviewed by a physician or a nurse.

If a positive family history is indicated, further verification is often worthwhile before initiating extensive measures of screening and prevention in family members. For those relatives indicated to have specific diseases and risk factors, contacting these relatives to obtain the details of their medical problems and copies of the medical records can help distinguish about 10% to 30% of false-positives that may be reported in many family histories. Heart operations for rheumatic valvular heart disease will often be confused with coronary disease; benign growths may be confused with cancer and so forth. Only detailed medical records will help distinguish some of these confusing situations.

The fourth and final level of family history evaluation is the

MEDICAL FAMILY HISTORY QUESTIONNAIRE

Date: _____ I.D.# _____

Address: _____ Phone: _____

_____

	A FIRST NAME	B MIDDLE NAME	C MAIDEN NAME	D LAST NAME(S)	Number of MARRIAGES E	Number of CHILDREN F	Month & Year of BIRTH G	Month & Year of DEATH H	STATE (Now or at Death) I	BLOOD RELATIVE (+/−) J	LIVING OR DEAD (L/D) K	AGE (Now or at Death) L	SEX (M/F) M	RACE (W, B, H, I, A, X) N	SMOKES CIGARETTES (0, ½, 1, 2, (C or F)) O	DRINKS ALCOHOL (−, +, ++) P	WEIGHT (S, A, M, V, E) Q-1	WEIGHT OF SPOUSE (S, A, M, V, E) Q-2	NUMBER OF OVERWEIGHT OFFSPRING Q-3	LIST AGE AT ONSET: STROKE (Hospitalized or Died) R	HIGH BLOOD PRESSURE (On Treatment) S	DIABETES (On Treatment) T	HIGH BLOOD CHOLESTEROL U	HEART ATTACK (Hospitalized or Died) V	CORONARY BYPASS HEART OPERATION W	ANGINA CHEST PAINS (On Treatment) X	OTHER HEART DISEASE (On Treatment) (See Code) Y	LIST AGE: BREAST CANCER Z	LUNG CANCER (Started in Lung) AA	COLON CANCER BB	Write Down 3 Letter Code from attached list: OTHER CANCER CC	OTHER SERIOUS ILLNESS DD	CAUSE OF DEATH EE
1. YOU																																		
2. Father																																		
3. Mother																																		
4. Bro/Sis																																		
5. Bro/Sis																																		
6. Bro/Sis																																		
7. Bro/Sis																																		
30. Spouse																																		
31. Son/Dau																																		
32. Son/Dau																																		
33. Son/Dau																																		
34. Son/Dau																																		
50. Paternal Grandfather																																		
51. Paternal Grandmother																																		
52. Aunt/Uncle																																		
53. Aunt/Uncle																																		
54. Aunt/Uncle																																		
55. Aunt/Uncle																																		
56. Aunt/Uncle																																		
70. Maternal Grandfather																																		
71. Maternal Grandmother																																		
72. Aunt/Uncle																																		
73. Aunt/Uncle																																		
74. Aunt/Uncle																																		
75. Aunt/Uncle																																		
76. Aunt/Uncle																																		

Figure 2.—A sample of a Medical Family History Questionnaire for targeting first- and second-degree relatives.

TABLE 4.—*Medical Family History*

When	*Why*
1. *Patient with disease* that might be familial Check family history	1. If positive family history, help close relatives avoid the same problem
2. Patient *might* have disease Check family history	2. Positive family history increases suspicion Special tests or monitoring may be justified
3. General screening tool Broad family history overview	3. Be alert to family tendencies Plan future screening procedures

***How?* (What data should be collected)**

1. ***Sex, age, vital status* for *all* target relatives and spouse**
   1st-degree relatives: Parents, siblings, offspring
   2nd-degree relatives: Grandparents, [illegible]
2. ***Diseases and causes of death***
   Age at diagnosis? [illegible]
   Treatment given? [illegible]

What is learned from a detailed family history?

1. Is it familial?
2. How strong a tendency?
3. Affect men and women alike?
4. Usual age at onset?
5. Which risk factors involved?
6. Pathophysiology?
7. Which relatives need help?
8. Age to start screening?
9. Best way to prevent, screen or treat?

detailed investigation of a pedigree, including *screening* of *family members* when a particular disease is sought. Among families with hypercholesterolemia, blood specimens should be obtained from first-degree relatives of known affected persons. Sequential screening should in turn be focused on the next set of first-degree relatives of the persons found affected in the screening process. Members of a family at high risk for colon polyps and cancer should receive special screening for occult fecal blood, polyps and the like.

Of these four levels of family history evaluation (brief screening, detailed family history, verification and pedigree investigation), all except the first require special preparation, a substantial investment of time in training persons for collecting and processing family history information and conscientious follow-up in collecting material. A thorough family history will not be free. On the other hand, where family tendencies would appear to be present, an investment of several hundred dollars for personnel time and forms is probably more helpful than many laboratory tests of equal or greater expense generally applied in medical evaluations.

Need for Sensitivity to Patients' Privacy and Feelings Regarding Their Family History

Will highlighting a person's positive family history induce stress or relieve it? Should a strongly positive family history always be brought to the attention of a person? If measures are available for screening, prevention and more effective management of the disease for persons aware of their positive family history, then the net benefits of family history assessment outweigh the possible detrimental effects. In many cases, such as significant early coronary disease or breast cancer, the family members are usually aware of their family tendency but are often not aware of measures that can be used for better detection and prevention. Experience with members of coronary-prone pedigrees indicates that, whereas most of them are generally aware of their disease tendency, few of them are really receiving maximal medical support and help in screening and prevention.

While collecting and sharing family history data, health professionals should carefully protect the privacy of the patient. Information should not be shared even with a patient's relatives without express permission and notification. Illegitimate children, multiple marriages and sensitive illnesses are all details that may be embarrassing to persons if shared with others, including some close relatives. Probably the best approach is to have each family member interested in a family history evaluation complete detailed family history forms. Completing these forms will require communication among family members, in which case they will be mutually sharing information that they feel is appropriate.

Genetic counseling approaches one of the most sensitive areas of medicine. Health professionals should help patients operate within their own personal beliefs and not force beliefs upon them. If there is any need to discuss issues such as family planning, prenatal diagnosis and abortion, these topics should be dealt with carefully. Health professionals should educate patients regarding their options, but allow them to make their own decisions.

Expected Developments in the Near Future

Technologic advances are rapidly producing tools for characterizing specific syndromes. This will allow efficient dissection of the heterogeneity of many common syndromes such as early coronary disease, obesity and hypertension. A better understanding of the steps leading to the disorders in specific persons will pave the way for more specific management tailored to the mechanism of a disease's occurrence.

Dramatic advances in identifying major gene effects should follow the rapid application of *genetic markers*. In the past, geneticists have used a variety of cell and tissue antigens and protein polymorphisms in an attempt to identify chromosomal linkage with major gene traits. The success of these efforts in the past has been hampered by the high expense of obtaining these marker studies, the inconvenience of diverse biologic samples required to cover available markers and, perhaps most important, the lack of a high degree of polymorphism required to produce useful information from many mating situations studied. With only two or three different forms of a marker, spouses often have identical haplotypes, making it impossible to detect disease associations in offspring and siblings.

Restriction fragment-length polymorphisms (RFLP) represent a recent dramatic breakthrough in gene marker strategies.[25] Under this new system variations in biochemical patterns of the DNA molecules themselves are examined. One single biologic specimen (DNA material from the nuclei of leukocytes from about 50 ml of ordinary venous blood) has the potential of providing polymorphic gene markers that can map major genes on virtually any chromosome in the body. Most geneticists familiar with this new technology project that within several years they will have discovered RFLP markers equally spaced across each chromosome of the body that will make it possible to map approximately 95% of major genes. The leukocyte specimens can be frozen for future use, and the prepared DNA material can be analyzed multiple times for different markers, allowing much more efficient use of the specimens taken from patients.

TABLE 5.—*Why the Gap in Applying Pathophysiology for Prevention?*

Needs	*Sample Shortfalls*
Educating health professionals	Some still think "You can't change genes, so you can't help someone with a positive family history"
Finding and screening high-risk persons and families	Diseased probands are treated without offering screening and risk reduction to their offspring
Targeted "full dose" education for high-risk persons	Shotgun low-dose publicity does not get enough information to the small percentage who need it most
Better follow-up of screening results	"When they screened me, they said I was high, but I never have been treated"
Better follow-up for compliance with medication	"I stopped taking the medicine because I didn't feel any better"
Effective incentives for needed life-style modification	"I stopped smoking a dozen times"

If the entire effort in gene markers is concentrated on this single methodology, one would expect improving efficiency and increasing cost-effectiveness, enabling future screening efforts to identify gene carriers in families with known major gene disease predispositions.

Once markers are generally available, then known gene carriers can be studied for other factors to identify exactly which environmental factors affect a given gene's expression. The net result will be a detailed definition of the step-by-step processes in the pathogenesis of these major diseases. Examples are already available in illnesses such as type I diabetes mellitus and low-density-lipoprotein-receptor defects in familial hypercholesterolemia. This level of understanding for other major genetic syndromes will provide unprecedented opportunities for disease prevention, amelioration and targeted treatment.

Because these dramatic technologic advances are considered to be a near certainty by many experts, the real challenge of the future appears to be the behavioral and social issues highlighted in Table 5. Once disease prevention is understood, the question is, can we motivate patients to follow sound advice?

REFERENCES

1. Williams RR, Lyon JL, Brockert JE, et al: Decline in coronary mortality rates: Utah vs. U.S., *In* Havlick RJ, Feinleib M (Eds): Proceedings of Conference on the Decline in Coronary Heart Disease Mortality. US Dept of Health, Education and Welfare publication No. (NIH) 79-1610. Government Printing Office, 1979, pp 48-57

2. The Health Consequences of Smoking for Women: A Report of the Surgeon General. US Dept of Health and Human Services, Public Health Service, Office of the Asst Secretary for Health, Office on Smoking and Health, 1980, pp 17-42

3. HDFP Cooperative Group: Five-year findings of the Hypertension Detection and Follow-up Program. JAMA 1979 Dec; 242:2562-2577

4. Beaglehole R, LaRosa JC, Heiss GE, et al: Secular changes in blood cholesterol and their contribution to the decline in coronary mortality, *In* Havlick RJ, Feinleib M (Eds): Proceedings of the Conference on the Decline in Coronary Heart Disease Mortality. US Dept of Health, Education and Welfare publication No. (NIH) 79-1610. Government Printing Office, 1979, pp 282-295

5. Hopkins PN, Williams RR: A survey of 246 suggested coronary risk factors. Atherosclerosis 1981 Aug-Sep; 40:1-52

6. Tokuhata GK: Familial factors in lung cancer and smoking, *In* Neal JV, Shaw MW, Schull WJ (Eds): Genetics and the Epidemiology of Chronic Diseases. DHEW Public Health Service publication No. 1163. Government Printing Office, 1965, pp 339-353

7. Goto Y: Hyperlipidemia and atherosclerosis in Japan. Atherosclerosis 1980; 36:341-349

8. Marmot MG, Syme SL, Kagan A, et al: Epidemiologic studies of coronary heart disease and stroke in Japanese men living in Japan, Hawaii and California. Am J Epidemiol 1975 Dec; 102:514-525

9. McKusick VA: Mendelian Inheritance in Man, 6th Ed. Baltimore, Johns Hopkins, 1983

10. Hopkins PN, Hunt SC, Williams RR: Magnified risks from cigarette smoking for coronary prone families in Utah. West J Med 1984 Aug; 141:196-202

11. Williams RR, Skolnick M, Carmelli D, et al: Utah pedigree studies: Design and preliminary data for premature male CHD deaths, *In* Sing CF, Skolnick M (Eds): The Genetic Analysis of Common Diseases. New York, Alan R. Liss, Inc, 1979, pp 711-721

12. Williams RR: A population perspective of early and familial coronary heart disease, *In* Proceedings of Conference on Human Health Data From Defined Populations—Banbury Report 4. Cold Spring Harbor, Cold Spring Harbor Laboratory, 1980, pp 333-350

13. Lipid Research Clinics Program: The LRC Coronary Primary Prevention Trial Results—II. The relationship of reduction in incidence of coronary heart disease to cholesterol lowering. JAMA 1984; 251:365-374

14. Miettinen M: Prevention of coronary heart disease by cholesterol lowering diet. Postgrad Med 1975; 51(Suppl):47-50

15. Skolnick M, Bishop DT, Carmelli D, et al: A population-based assessment of familial cancer risk in Utah Mormon genealogies, *In* Arrighi FE, Rao PN, Stubblefield E (Eds): Genes, Chromosomes, and Neoplasia. New York, Raven Press, 1981, pp 477-499

16. Skolnick M, Livingston GK, Fineman RM, et al: Genetics of breast cancer (Abstract). Am J Hum Genet 1980; 32:151A

17. MacMahon B, Cole P, Brown J: Etiology of human breast cancer—A review. JNCI 1973 Jan; 50:21-42

18. Williams RR, Horm JW: Association of cancer sites with tobacco and alcohol consumption and socioeconomic status of patients: Interview study from the Third National Cancer Study. JNCI 1977 Mar; 58:525-547

19. Williams RR, Feinleib MF, Connor RJ, et al: Case-control study of antihypertensive and diuretic use by women with malignant and benign breast lesions detected in a mammography screening program. JNCI 1978 Aug: 61:327-335

20. Brinton LA, Williams RR, Hoover RN, et al: Breast cancer risk factors among screening program participants. JNCI 1979 Jan; 62:37-44

21. Hunt SC, Williams RR, Skolnick MH, et al: Breast cancer and reproductive history from genealogical data. JNCI 1980 May; 64:1047-1053

22. Winawer SJ: Screening for colorectal cancer: An overview. Cancer 1980 Mar; 45:1093-1098

23. Edwards CQ, Carroll M, Bray PF, et al: Hereditary hemochromatosis: Diagnosis in siblings and children. N Engl J Med 1977 Jul; 297:7-13

24. Mason JO, Williams RR, Weber N: Family health trees: Targeting prevention strategies. Utah State Med Assoc Bull 1983; 31:14-16

25. Botstein D, White RL, Skolnick M, et al: Construction of a genetic linkage map in man using restriction fragment length polymorphisms. Am J Hum Genet 1980 May; 32:314-331