Review

Genetic Aspects of Arteriosclerosis

Uri Goldburt and Henry N. Neufeld

This review discusses the genetic factors in the development of arteriosclerosis and coronary heart disease (CHD). In several studies, multivariate analysis of prospective mortality/morbidity data and angiographic findings have indicated that a family history of CHD contributed to CHD risk independently of the established risk factors. In addition, ethnic groups that differ in the prevalence and incidence of CHD also markedly differ in blood groups and protein-enzymatic markers. These or other genetic differences may affect CHD rates. Data from fraternal and identical twins, the source of some early genetic CHD findings, are reviewed. Genetic disorders of lipoprotein metabolism and transport, such as familial hypercholesterolemia, as well as other monogenic disorders are discussed. The role of apoprotein E polymorphism in determining plasma LDL variability among individuals is considered. Recombinant DNA technology, molecular cloning, and the identification of restriction fragment length polymorphisms are new tools for investigators who assess DNA polymorphism. Recent advances in that domain include: DNA polymorphisms affecting blood levels of apo A-I and A-II, association of a DNA insertion on chromosome 19 with severe premature atherosclerosis, and information concerning linkage of the genes for various apolipoproteins. In addition, the evidence for a major genetic component in diabetes mellitus and research into the genetic aspects of hypertension are reviewed. The male/female ratio in pathologically and epidemiologically assessed atherosclerosis may provide clues to the role of genetics. Early structural changes in the coronary artery intima are compatible with the ethnic and gender predilection. A key question in understanding underlying mechanisms in atherosclerosis is why coronary arteries are occluded in individuals whose other arterial systems are largely unaffected. The review concludes with a discussion of the directions and implications of future genetic research in arteriosclerosis with an emphasis on uncovering genetically determined differences in arterial wall response to blood flow. Subpopulations with different genetic risks may be identified, in which case universal preventive strategies might be replaced with specific ones. (Arteriosclerosis 6:357–377, July/August 1986)

The genetics of arteriosclerosis and coronary heart disease (CHD) have been the topic of intensive research for several decades. A considerable portion of this effort, however, has been circumstantial. At the beginning of the post-World War II era, we had little understanding of the arteriosclerotic process, of the closely associated lipoprotein metabolism, and of factors that might determine individual variations in arteriosclerosis and the arterial wall response. Despite the recent impressive volume of information and advancement of theories on the causes of atherosclerosis, which is the main form of arteriosclerosis, speculations still exceed concrete knowledge. One major problem is that no current theory can account for the ability of some human blood vessels to carry blood for a lifetime with little or no evidence of arterial disease, while other blood vessels, notably the coronary system, develop considerable, sometimes early, and often life-threatening, lesions.

Better planning and execution of prospective epidemiological studies and the advent of newer computers have made possible quantitative assessments of the contribution of risk factors to the loosely defined entity of "coronary heart disease." At the same time, epidemiologists, geneticists, and clinicians have become acutely aware of the fact that risk factors cannot account entirely for the development of CHD in individuals. The recent advent of genetic-epidemiologic methods followed a sobering recognition: information about cholesterol levels, blood pressure, smoking habits, diabetes, age, and sex is of limited value in prescribing either changes in lifestyle or drug therapy for disease prevention.

In attempting to separate biological from culturally determined risk factors, whether we consider elucidation of the net contribution of family history in a multivariate analysis of CHD incidence, segregation analysis to detect single-gene effects, studies of monozygotic (MZ) and dizygotic (DZ) twins, or path analysis, the evidence is observational and often depends on far-reaching assumptions as well as on the methods and units of sampling. Genetic analysis in children is an important innovation, but is just as circumstantial, and phenotypes that clearly predispose individ-

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Familial Aggregation of Coronary Heart Disease

The initial suggestion of genetic factors in the etiology of CHD came from findings of familial aggregation of the disease in a number of studies over the past 35 years. Recent methods fall short of an ideal, but unfeasible, experimental set-up in which the results of genetic manipulation could be observed. Still, recent developments have augmented our knowledge to an important degree. During the past decade the discovery of restriction endonucleases and molecular cloning are revolutionizing gene mapping and the understanding of human anatomy and pathology at the DNA level. A recent interdisciplinary approach involving geneticists, epidemiologists, and clinicians has been instrumental in advancing our knowledge. In this review, we will assess the different types of evidence for the genetic determination of indicators of atherosclerosis. We shall also discuss avenues of investigation that might lead us closer to the formidable, and so far elusive, task of disentangling the contributions of genetic and environmental causes of atherosclerosis, its precursors, and its sequelae.

Familial Aggregation of Coronary Heart Disease

The first-degree relatives of persons afflicted with CHD in an effort to segregate the risk factors from the familial effect. An important study of familial aggregation was conducted by Rissanen in North Karelia, Finland, and in a southern Finnish population. In North Karelia the CHD risk ratio was 3.5 for brothers of CHD index patients. The form of CHD in the proband brothers resembled that in the patients themselves, in both severity and in fatality. Among 1387 first-degree relatives of 203 male probands with confirmed myocardial infarction (MI) and 692 relatives of 106 age-matched healthy controls, Rissanen also showed that, for brothers of probands with early diagnosed MI, a greater risk of CHD by age 55 years (elevenfold if MI in the proband was established at or earlier than age 45) was found in subjects from North Karelia than in those from the south (which was sevenfold). This was an important point in light of the notorious regional differences in CHD in Finland. The risk of the probands' brothers increased sharply with decreasing age at onset of disease in the probands. In addition to this most impressive familial aggregation of the disease, Rissanen also showed that hypertension and hyperlipidemia were most common among the relatives of the younger patients, although the contribution of these risk factors diminished with the advancing age of the patients.

In a study of 98 healthy school children from Rochester, Minnesota, selected from 3666 participants and of 850 first- and second-degree relatives, Moll and co-workers showed that the adjusted grandfather CHD mortality risk increased among the children with increasing total chole-
terol levels and particularly with decreasing percentages of HDL/total cholesterol. Figure 1 describes these findings.

Another study in which the progeny (≥ 24 years old) of MI patients were examined is the biracial Princeton School Study. In that study, neither paternal nor maternal history of MI played a significant role relative to the established risk factors in their progeny, although maternal hypertension and stroke history did. The differing results may be due to the relatively older age of these latter progeny.

Recently, the associations of paternal MI and lipoprotein cholesterol levels and apolipoproteins were examined in the Bogalusa Heart Study. Lower mean levels of apolipoprotein (apo) A-I, the major HDL protein, and higher values of the atherogenic ratio of apo B to apo A-I were associated with paternal MI independent of race, sex, obesity, smoking, alcohol intake, and oral contraceptive use in 2146 youngsters aged 5 to 17 years. No associations of serum lipoprotein cholesterol to paternal MI were recorded in that study.

Hamby reported the results of a family study in 411 men from Long Island, New York, who had arteriographically ascertained coronary artery disease (CAD). CAD in at least one parent was ascertained in 56% of these subjects as compared to only 40% of 184 controls (men who had been catheterized because of atypical pains, mitral valve prolapse, or mild valvular disease) (p < 0.005). In 1105 siblings of the probands, the prevalence of CHD was 16%. Prevalence rose from 12% for those whose parents had no CHD, to 19% when only the mother was afflicted, 31% when only the father had CHD, and 55% when both parents had CHD. Despite methodological problems such as the selection from 5000 persons for most of whom the family history could not be ascertained and the nature of “the non-CHD controls” who nevertheless required catheterization, this study constitutes a rare example of an arteriographically documented familial aggregation of CAD.

In a careful angiographic-familial study of 223 patients with CAD and 57 patients without CAD, Shea et al. calculated the odds ratios for the prevalence of several CHD manifestations in 1319 first-degree relatives. The relative odds ranged between 2.0 and 3.9 (p < 0.01) for angina, MI, cardiac death, and any other CHD. Matching was done by a risk score based on age, sex, and five risk factors. Comparisons of patients at the lowest risk with those at higher risk showed a greater cumulative frequency and an earlier age of onset of CHD in relatives of low-risk patients, suggesting (according to the authors) that the independent effects of family history may be most important in individuals otherwise at low risk (Figure 2).

Recently, the independence of a family history of heart attacks before age 60 as a risk factor for CHD was examined in a random sample of 1044 men aged 40 to 70 years from the Jerusalem Lipid Research Clinics (LRC). The covariate-adjusted odds ratio for CHD prevalence (odds in those with a family history of CAD divided by odds in those without) was 1.63 (1.06 to 2.52) if all CHD was considered and as high as 2.72 (1.48 to 4.99) if only 48 asymptomatic patients who had positive reactions to an exercise test was considered. (The values in parentheses represent the 95% interval of confidence for the odds ratio.) The asymptomatic group tends to be free from selection bias or the over-reporting of family history done by patients suffering from symptomatic CHD.

Nora and co-workers studied 207 survivors of MI under age 55 who were matched with three controls each. These researchers assessed the CHD risk associated with 19 variables, including family history. Among those with first-degree CHD relatives, CHD risk was sevenfold if the disease occurred before age 65, and tenfold if it occurred before age 55, the largest of any of the adjusted risks estimated in the study (Table 1). The heritability for early

![Figure 2. Life-table comparison showing the increased frequency and earlier onset of coronary heart disease (CHD) in 240 case relatives and 128 control relatives, all of whom underwent coronary arteriography at the Presbyterian Hospital, New York. Group I signifies a group of 55 cases and 33 controls at the lowest quartile of the calculated American Heart Association CHD risk score among the study population. Reproduced with permission of the American College of Cardiology from S. Shea et al. Family history as an independent risk factor for coronary artery disease. JACC 1984;4:793-801.]

**Table 1. Risk of Early Onset IHD, Retrospective Cases vs Matched Controls**

<table>
<thead>
<tr>
<th>Factor</th>
<th>Percent among cases</th>
<th>Risk ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>IHD — 1 deg. relatives 55 yrs</td>
<td>48</td>
<td>10.4</td>
</tr>
<tr>
<td>IHD — 1 deg. relatives 65 yrs</td>
<td>61</td>
<td>7.1</td>
</tr>
<tr>
<td>Juvenile diabetes — 1 deg. relative</td>
<td>6</td>
<td>4.7*</td>
</tr>
<tr>
<td>Cholesterol ≥270 mg/dl</td>
<td>24</td>
<td>4.3</td>
</tr>
<tr>
<td>Smoking &gt;10 cig/day</td>
<td>68</td>
<td>4.0</td>
</tr>
<tr>
<td>Physical inactivity</td>
<td>96</td>
<td>3.4</td>
</tr>
<tr>
<td>SBP/DBP ≥160/100 mm</td>
<td>21</td>
<td>1.6†</td>
</tr>
</tbody>
</table>

SBP = systolic blood pressure; DBP = diastolic blood pressure; IHD = ischemic heart disease.

*p < 0.05, †p < 0.01. All others, p < 0.001.

onset CHD, calculated by Falconer's method, was estimated at 0.63, and even after 31 probands with monogenic hyperlipidemia and their families were excluded, the estimate remained high (0.56).

Family History of Coronary Heart Disease as an Independent Predictor In Offspring

A number of prospective studies have examined the predictive strength of a positive family history after adjusting for other CHD risk factors. Among the 1 million people studied for 5 to 6 years by Hannond et al., CHD deaths in men initially free of CHD increased progressively and significantly with the decreased longevity of their relatives. Parental history was included as one of the variables in the multivariate analysis of 8.5-year CHD incidence in the Western Collaborative Group Study in California. Adjusted rates of CHD in men with a parental CHD history exceeded the rates among their counterparts without such history by 60% in the 39 to 49 age group and by 40% in the 50- to 59-year-old group.

A recent study by ten Kate and co-workers incorporated risk factors such as diabetes, cigarette smoking, hyperlipidemia into adjusted estimates of "pooled relative risks" for MI and all CHD among the families of survivors of MI. The risks of MI and CHD among those with a positive history were estimated at 2.14 and 1.71, respectively. The clear-cut distinction between relatives of MI survivors and relatives of controls is depicted in Figure 3. In a 9-year follow-up of some 4000 men and women aged 40 to 79 who lived in Rancho Bernardo, California, Barrett-Connor and Khaw estimated the independent contribution of a positive family history of heart attack to subsequent CHD death, adjusting for age, systolic blood pressure (SBP), plasma cholesterol, obesity, cigarette smoking, diabetes, and estrogen use (in women). The estimated adjusted relative risk (RR) associated with a family history of heart attack in men was 1.56. No such predictive power was observed among women, a discrepancy that is not understood. A paternal (but not maternal) history that is independently predictive of CHD, was also found among 7484 men in the Paris Prospective Study. In contrast to the above studies, Salonen and Puska in Finland reported no association between premature CHD in the family and risk of MI.

The most recent large study examining the predictive power of parental MI history in women utilized the information available from the U.S. nurses' Health Study of some 120,000 married women, aged 30 to 55 years. In this study, the questionnaire-assessed parental history of MI at or before 60 years of age was strongly and independently predictive of MI (RR = 2.8), angina pectoris (AP) (RR = 3.4), and fatal CHD (RR = 5.0) after adjustment for established risk factors as well as for oral contraceptive use, menopause, and postmenopausal hormone use. This parental history was associated with an increase in AP and fatal CHD, although these risks appeared smaller than for those whose parents had MI at younger ages. The continuing follow-up of that cohort holds great promise for elucidating these associations.

The evidence from most pertinent studies of family history of CHD shows that family history is important as an independent predictor among men. The increased net risk appears to be about 1.5-fold to twofold. Although the available evidence is not conclusive, paternal history of CHD at an early age may also be a risk factor for women. Family history of CHD appears to be most strongly related to premature, clinically manifested events as well as to angiographically documented CAD.

Studies of Twins

A comparison of concordance rates between MZ and DZ twins has long been a source of quantitative estimation for the heritability of a trait or disorder. Concordance can be examined for morbidity, mortality, or other events with or without limitation on the age at which the event has occurred, according to the hypothesis of interest. Heritability is calculated as:

$$h = 2(r_{MZ} - r_{DZ})$$

Early estimates of concordance rates for MI calculated among Danish MZ and DZ pairs, were 0.39 and 0.26 ($p < 0.05$) respectively for men and 0.44 and 0.14 ($p < 0.01$) respectively for women (Harvald and Hauge). Liljefors' thesis on CHD in 91 male twin pairs indicated rates of 0.48 for MZ and 0.28 for DZ pairs. In a comprehensive work on CHD in decreased discordant twins, de Faire examined a subsample of the Swedish Twin Register. Concordance rates for CHD, based on 108 men and 97 women aged 46 to 70 years were as follows: 0.90 in MZ male twins, index twin dead from CHD, as compared to 0.36 for MZ pairs where the index twin died from other causes ($p < 0.01$). The respective rates among women were 1.00 and 0.70 (smaller numbers). In DZ twins, the respective CHD concordance rates were 0.68 and 0.55 in...
men and 0.89 and 0.67 in women. These figures indicate that CHD deaths were genetically more strongly predictable than other causes.

In a Norwegian study of about 2000 MZ and 3000 DZ same-sexed twin pairs, 56 MZ pairs and 114 DZ pairs had experienced the death of one sibling by the age 41 to 65 years. The resulting estimates of MZ and DZ concordance rates for CHD were 0.65 and 0.25, respectively. When only 21 pairs with CHD occurring before age 60 were considered, the concordance rates were estimated at 0.83 and 0.22, respectively. In comparing scores (0 to 5 per arterial region for 10 regions) of angiographically determined arterial obstruction (a high score representing increased obstruction), the mean total score decreased progressively in examinations of families with high, intermediate, or low familial clustering.

Twin studies also yield information on the heritability of diabetes and of continuous traits. The NHLBI twin study of cardiovascular disease risk factors among many others, contributed to an early appreciation of the role of genetics in the variability of major CHD risk factors. Using correlations within same-sexed Norwegian twins (158 pairs), Berg found notably higher correlations with MZ than with DZ twins; heritability estimates were 0.34 for total cholesterol and as high as 0.66 for apolipoprotein (apo) B, which resides in the atherogenic LDL. The corresponding results for the HDL- containing apoproteins were particularly impressive and are shown in Table 2. (There were 198 pairs.) The heritability estimates are 0.90 for both apo A-I and apo A-II. These figures rise to 0.94 and 1.00, respectively if only the 131 pairs in whom sera were collected from both brothers (or sisters) on the same day are included. A further analysis by the authors suggested the possibility of a major gene effect in apo A-I. Several estimates of heritability based on MZ and DZ twin correlations for serum cholesterol and blood pressure appear elsewhere in this review under these respective headings. Even in behavioral phenotypes, significant MZ correlations have been identified for components of the Thurstone Temperament Schedule and JAS, but not for Type A behavior. In a very large Finnish twin study of 5419 male pairs, interclass correlations of 0.25 for MZ and 0.05 for DZ twins were found (representing a heritability estimate of 0.40) when Type A behavior was examined by the Bortner Scale by means of a mail questionnaire.

Another application of twin studies for estimating genetic effects is the analysis of the intrapair difference in MZ twins grouped by genotype. When 97 MZ twin pairs were grouped by blood marker phenotypes, the mean intrapair cholesterol differences differed significantly between M positive and M negative pairs (relating to the MNS blood group). The same was found for the Kidd group (Jka + showed a within-pair variation of 0.86 standard deviations, as compared to the 0.46 standard deviations for Jka −, although mean cholesterol was the same in the Jka + and Jka − phenotypes).

Data for twins can be interpreted as having a purely genetic meaning only if no differences in environmental similarities exist between MZ and DZ twins. This is not necessarily true. It is difficult to find a sufficient number of twins raised apart to determine whether similarity between twins is a pure outcome of genetics. An alternative approach is to control for covariates.

Hrubec et al. studied the age-specific death risk in 21,890 Swedish twins born between 1886 and 1925 as a function of co-twin survival, and they adjusted for smoking, marital status, and police registration for alcoholic abuse. Co-twin survival persisted through this adjustment as an independent correlate for those born in 1905 or later. Although the analysis pertains to total (not only coronary) mortality, the adjusted relative risks, which were between 1.38 and 1.60 for a deceased co-twin as compared to a living co-twin, suggest that for CHD mortality an even greater association may be found. Clearly, additional variables such as hypertension and lipid data would have to be controlled for.

It may be difficult to evaluate whether, and to what degree, environmental similarities between MZ twins exceed those between DZ twins. The above study, however, highlights the potential value of data about twins collected through the continuously updated twin registries for providing information on the role of genetics in CHD. The present registries hold much promise for future research on familial traits.

### Genetic Markers and Coronary Heart Disease

Limited evidence links genetic polymorphisms directly to CHD prevalence and incidence, and the evidence available toward the end of the last decade has been reviewed by Berg. The emerging associations with apo E phenotypes provide the best known recent example. Examination of CHD rates by ABO blood groups has contributed some additional information. Almost invariably, an excess of either A or B blood groups, or both, and a deficit of O were found among subjects with MI, as compared to controls. Most of these findings have been summarized by Mourant et al. The mean pooled relative incidence of A compared with O was 1.30.

The incidence of CHD in ABO groups was reported from two large prospective studies. In the Israeli Ischemic Heart Disease (IHD) Study of 9556 men, Medalie et al. report...
vascular events and various blood groups merely reflects the chronic nature of angina pectoris in the O group. Notably, the Jewish immigrants from Yemen, the group with an outstandingly low CHD incidence, had an exceedingly high percentage of phenotype O (56%) coupled with a very low (9%) frequency of B, and an extremely low (2%) AB. They also differed markedly from the ethnic groups in the study, in Rh, Kell, and MNS distribution. No association was found between CHD and the Rh, MN, Kell, and Duffy blood groups, while the Kidd Jk\(^a\)-group experienced somewhat higher rates of both MI (50/1000) and AP (47/1000) as compared to the Jk\(^a\)-group (43/1000 and 36/1000, respectively). Extremely high rates of both CHD manifestations were observed in the 191 men with both A,B and Jk\(^a\)-; this requires further verification because no prior hypothesis had been made.

In an analysis of the Framingham Heart Study of 4125 persons, Garrison et al. found no association between ABO blood groups and CHD. However, a significantly lower rate in the O group was found for intermittent claudication. In 461 men with venous thromboembolism in West German towns, Dick et al. identified a B:O relative risk of 1.63. In the Israeli IHD study, A blood predisposed subjects to abrupt increases in blood pressure during the 5-year study. The relative risk of A:O, adjusted by ethnic origin and age, was 1.50 (p = 0.026).

A somewhat lower mean cholesterol level in patients with the O blood group was found in both the Israeli and the Framingham Study. Combined data from 10 different populations analyzed by Berg et al. indicated that serum cholesterol and triglyceride levels were higher in individuals with Ag(x-) as compared with Ag(x+). The cholesterol differences were usually about 5 to 18 mg/dl. These effects apparently became manifest late in life. Sing and Orr showed higher cholesterol for Gm(a) women and the Hp2 gene, and reasserted the slightly smaller means associated with the O phenotype.

One speculation of an etiologic link between the ABO blood group and cardiovascular disease implies the involvement of a clotting mechanism, but there has been too little research so far to shed sufficient light on the nature of these associations. In fact, a recent study from the Institute of Medical Genetics in Oslo did indicate evidence for a major effect of ABO phenotype on coagulation factor VIII level. The authors determined factor VIII and IX levels in 74 of 191 men with both A,B and Jk\(^a\)-; this requires further verification because no prior hypothesis had been made.

Blood group data, as a whole, offer limited evidence of genetic variability of lipid levels and of cardiovascular events. It would appear that blood group O is associated with a protective effect, but this might reflect other genetic properties of a possibly weak correlation with the ABO locus. A link may also be found between ABO blood groups, coagulation factors, and the probability of thrombosis.

### Genetic Disorders of Lipoprotein Metabolism and Transport

The case of the rare homozygous familial hypercholesterolemia (FH) with demonstrated xanthomatosis (observed as early as 1939) is well known, as is the tendency of heterozygotes for this disorder to exhibit elevated cholesterol levels. In a widely acclaimed series of investigations, Brown and Goldstein demonstrated the absolute lack or major deficiency of a specific cell membrane receptor in homozygotes, discussed the implication of this for pathogenesis and therapy, and discussed the antenatal diagnosis of homozygous FH.

Goldstein et al. selected 158 hyperlipidemic individuals from a sample of 500 survivors of MI and described a disorder in which two or three abnormal phenotypes coexisted within the same families. Goldstein et al. considered this to be a monogenic inherited disorder, which became known as familial combined hyperlipidemia (FCHL). Similar findings were reported by Nikkila and Aro. Kissebah et al. examined the mechanisms of the disorder and found increased LDL apo B synthesis in both Type II and IV subjects; they consider this increased synthesis to be a characteristic feature of FCHL, as it is for FH, noninsulin dependent diabetes, and obesity. They suggested an investigation of the molecular processes underlying the enhanced apo B synthesis.

Brunzell contended that abnormalities in body weight might be inherited as a part of FCHL (as with noninsulin dependent diabetes). He suggested that this may be a different form of obesity than that seen in the otherwise normal obese population and may provide a solution to the enigma of obesity failing to manifest itself as a coronary risk factor in most epidemiological studies.

In stark contrast to the importance that the above investigators attributed to FCHL, Williams and Lalouel suggested that the disorder might represent an artifact of multivariate two-stage selection. This was based on their complex segregation analysis of the very same Seattle sample that Goldstein et al. originally investigated. Williams and Lalouel claimed that a dominant allele could be supported only for hypercholesterolemia, but not for hypertriglyceridemia.

Segal et al. reviewed genetic factors in lipoprotein variation in great detail and listed the known disorders, their primary defects, their possible inheritance modes, and clinical manifestations. Those and several additional lipoprotein disorders are listed in Table 3. As knowledge progresses and molecular biology methods pave the way for new discoveries (discussed later in this article), these lists will require continuous updating and revision.

A recent thorough review by Schaefer has specifically outlined the current knowledge of the clinical, genetic, and...
Table 3. Inherited Lipoprotein Disorders

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Lipoprotein abnormality</th>
</tr>
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<tbody>
<tr>
<td>Familial hyperchylomicronemia</td>
<td>Increased chylomicrons</td>
</tr>
<tr>
<td>Familial lipoprotein lipase deficiency</td>
<td>Increased chylomicrons</td>
</tr>
<tr>
<td>Familial apo C-II deficiency</td>
<td>Increased chylomicrons</td>
</tr>
<tr>
<td>Familial hypercholesterolemia</td>
<td>Increased LDL</td>
</tr>
<tr>
<td>Familial dysbetalipoproteinemia</td>
<td>B-VLDL present</td>
</tr>
<tr>
<td>Familial hypertriglyceridemia</td>
<td>Increased VLDL, increased chylomicrons, reduced HDL</td>
</tr>
<tr>
<td>Familial combined hyperlipidemia</td>
<td>Increased VLDL and/or LDL in family</td>
</tr>
<tr>
<td>Familial B-lipoprotein deficiency</td>
<td>No LDL, no VLDL, no chylomicrons</td>
</tr>
<tr>
<td>Recessive abetalipoproteinemia</td>
<td>No LDL, no VLDL, no chylomicrons</td>
</tr>
<tr>
<td>Familial hypobetalipoproteinemia</td>
<td>Decreased LDL</td>
</tr>
<tr>
<td>Normotriglyceremic abetalipoproteinemia</td>
<td>No VLDL, no LDL, no chylomicrons</td>
</tr>
<tr>
<td>Familial HDL deficiency</td>
<td>Decreased HDL</td>
</tr>
<tr>
<td>Tangier disease</td>
<td>Decreased HDL</td>
</tr>
<tr>
<td>A-I Milano</td>
<td>Decreased HDL, increased VLDL</td>
</tr>
<tr>
<td>A-I absence</td>
<td>Decreased HDL</td>
</tr>
<tr>
<td>Familial LCAT deficiency</td>
<td>Decreased HDL, decreased cholesterol esters, increased VLDL and LDL</td>
</tr>
<tr>
<td>Cerebrotendinous xanthomatosis</td>
<td>Abnormal HDL</td>
</tr>
<tr>
<td>$\beta$-Sitosterolemia and xanthomatosis</td>
<td>Abnormal HDL</td>
</tr>
<tr>
<td>Fish-eye disease</td>
<td>Markedly reduced HDL (almost only HDL$_{3}$)</td>
</tr>
<tr>
<td>Presence of Lp(a + ) antigen</td>
<td>Increased Lp(a)</td>
</tr>
</tbody>
</table>

Abbreviations: apo = apolipoprotein; HDL = high density lipoprotein; LCAT = lecithin:cholesterol acyltransferase; LDL = low density lipoprotein; VLDL = very low density lipoprotein.


biochemical features of the familial HDL deficiency syndromes. In many of these disorders, the HDL deficiency has been associated with abnormalities or deficiencies of apo A-I, the major protein of HDL. The genetic pattern observed in the HDL deficiencies as reviewed by Schaefer appeared to be most consistent with an autosomal codominant mode of inheritance in which the biochemical abnormality observed in homozygotes is partially expressed in heterozygotes.

In an earlier editorial, Utermann highlighted the significance of discovering familial deficiencies in order to better understand normal lipoprotein metabolism in humans. Utermann et al. were also the first to report genetic polymorphism in apo E, a major apoprotein that mediates binding to receptors of chylomicron remnants and a subclass of HDL. Berg predicted that this polymorphism has a significant influence on lipoprotein variation. Indeed, Robertson and Cumming studied 337 middle-aged persons in Scotland and found that LDL was reduced by 20% in men and 12% in women with the apo E-3/2 phenotype as compared to the more common apo E-3/3. These workers consider that a significant proportion of the genetically determined variation of LDL cholesterol arises from segregation at the apo E locus.

Recent additional evidence appears to support these findings. In data from Nancy, France, the average effect of the E-2 allele was to reduce serum cholesterol by nearly 20 mg/dl. About 20% of the genetic variability in total cholesterol was attributed to the apo E polymorphism. This, as well as the cholesterol-elevating effect of E-4, are in accord with increased E-2 frequency and a decreased E-4 frequency in male octogenarians. Remarkably similar to the Scottish data is a 20 mg/dl decrease in age-adjusted LDL cholesterol levels among men, a parallel 10 mg/dl decrease among women, associated with the apo E2 allele, and a 12 mg/dl E-4-associated LDL cholesterol increase in women that was recently reported in a preliminary analysis of 1051 Framingham offspring study subjects. As these findings are being confirmed, the commonly accepted assumption that the overwhelming majority of genetic cholesterol variance is polygenic becomes doubtful.

One lipoprotein phenotype that is definitely genetically determined and is directly related to CHD is the Lp(a), or sinking prebeta lipoprotein (density 1.050 to 1.080 g/ml), or pre-B-1 lipoprotein. This phenotype contains the protein apo B, but not others, and the locus determining its variation may be on chromosome 13. Complex segregation analysis in 229 nuclear families indicated a major gene with complete dominance for pre-B-1 gene frequency of q = 0.10 and penetrance = 0.92. In 18 male MZ and 13 DZ twins in Sweden, de Faire et al. estimated the heritability of the pre-B-1 lipoprotein as 0.94, indicating a delayed insulin response in subjects with this lipoprotein. This phenotype was estimated to be present in no less than 20% of the Swedish population. In a Norwegian twin series, not a single MZ pair (but 21% of DZ pairs) were discordant for Lp(a + ). The Lp system was discussed in detail by Berg. Guyton et al recently illuminated an interesting racial aspect of Lp(a), previously measured mostly in Scandinavian populations. It appears that this atherogenic lipoprotein subtraction has mean values in black men (31.3 ± 2.8) and women (33.7 ± 2.3, mean ± SEM) that are approximately double those in white men (17.0 ± 2.3) and women (15.5 ± 2.2), according to data derived from 239 healthy volunteers ages 18 to 58 who were recruited from a Houston, Texas, hospital and medical college.

The genetic lipoproteinemias and the rapidly evolving knowledge of apo E alleles and Lp(a) represent a field fraught with controversy and, at the same time, hold valuable clues for the future. We speculate that upcoming research related to apo E will expand our ability to recognize individuals susceptible to CHD at younger ages than we now do. Obviously, the potential for antenatal intervention will raise controversy as to whether FH should be considered as severe as, for example, beta-thalassemia, in making a decision about fetuses that carry the mutant gene.
Low Level of Low Density Lipoprotein Receptor Activity and Atherogenesis

On the cellular level, a significant contribution has been made by the Oslo group who studied the possible genetic control of LDL cell membrane receptor activity in healthy individuals. Magnus et al.\textsuperscript{77} studied cell strains from a number of same-sexed twin pairs. Intrapair fibroblast\textsuperscript{120-121} LDL association and degradations were significantly larger for 21 MZ pairs than for DZ twins. This suggests that even in individuals unafflicted by FH, LDL cell membrane receptor activity may be strongly influenced by genetic factors. In heterozygotes screened for hypercholesterolemia, a four-way clustering, which is compatible with receptor activities specified by four genes, was observed; Maartmann-Moe et al.\textsuperscript{78} identified clearly lower fibroblast\textsuperscript{120-121} LDL association and degradation and markedly higher serum cholesterol (difference of about 55 mg, $p < 0.001$) in six members of twin pairs with MI, as compared to 43 counterparts free of MI (all aged 58 to 61). This indicates that a low level of LDL receptor activity is a risk factor for MI and a strong correlate of high cholesterol. These interesting data, which require further corroboration, have been summarized in detail by Berg.\textsuperscript{33}

Restriction Fragment Length Polymorphisms

With the advent of DNA technology, the past few years have brought great progress in the gene mapping of single locus traits. Restriction fragment length polymorphisms (RFLP) are altered patterns of gene fragments, observed when genomic DNA from different individuals is digested with a restriction endonuclease. RFLP have profound implications for family studies and will make a significant impact on analytical methods.\textsuperscript{79} The restriction endonucleases are bacterially derived enzymes that cut the DNA at specific DNA configurations and allow the cutting of DNA into a number of reproducible fragments. Molecular cloning has made possible the replacement of bacterial DNA by restriction fragments generated from the human genome, replication of the foreign (human) DNA in plasmids and bacteriophages, and growth of the latter in quantities large enough for study. Consequently, libraries of genetic DNA and complementary DNA (cDNA) can be constructed and the clone with the DNA sequence of interest can be selected from the library for study.

By isolating and characterizing DNA and genomic clones, investigators at Rockefeller University, New York\textsuperscript{80} placed the apo A-I and apo C-III genes on chromosome 11.\textsuperscript{81} The Ann Arbor, Michigan, geneticists, using radioimmunoassay-measured apo A-I levels in 27 pedigrees at high CHD risk, have suggested a model with a single locus of a major effect and many polygenes. They have identified a genetic etiology for quantitative levels of plasma apo A-I,\textsuperscript{82} a cofactor for lecithin cholesterol acyltransferase, which was previously shown to be a better marker than HDL cholesterol for identifying patients with angiographically assessed CAD.\textsuperscript{83} The Rockefeller group\textsuperscript{84} has also shown that the genes for apo E and apo C-II reside on chromosome 19 and have indicated\textsuperscript{85} that a DNA insertion in the region that codes for apo A-I is associated with severe premature atherosclerosis, providing perhaps the first demonstration of DNA insertion causing disease in humans.

Evidence for yet other genetic markers for atherosclerosis may come from an earlier Danish study\textsuperscript{86} of subjects homozygous for DNA restriction fragments of a large size class (U alleles) in a polymorphic region flanking the 5' end of the human insulin gene (on chromosome 11). The U alleles were associated with macroangiopathy in diabetic and nondiabetic subjects, in addition to being associated with noninsulin-dependent diabetes mellitus. The authors suggested that DNA sequences in the U alleles may dictate the development of atherosclerosis.

More recently, a common DNA polymorphism (Msp I restriction site polymorphism) adjacent to the human apo A-II has been shown to be strongly related to serum apo A-II levels.\textsuperscript{87} Levels were $35.4 \pm 1.7 (x \pm se)$ for eight homozygotes for the mutant allele, $31.7 \pm 1.3$ for 17 heterozygotes, and $25.4 \pm 0.6$ for 62 normal subjects. No noticeable differences in HDL cholesterol or factors affecting HDL were found. This report agrees with the Ann Arbor study and is a pioneering account of a common variant of an HDL protein gene that affects HDL composition. Such findings offer support for the optimism expressed earlier by Skolnick et al.\textsuperscript{79} that markers flanking both sides of the loci may determine many important diseases. As our understanding of how lesions in apoprotein genes dictate genetic susceptibility to atherosclerosis progresses from infancy to maturity, many of the secrets of the disease may unfold.\textsuperscript{89}

Genetically Determined Variability of Risk Factors

The presumably established 50% of CHD risk prognostication (more accurately, our ability to calculate theoretical probabilities placing at the top 20% about one-half of eventual cases\textsuperscript{90}) relies on variables that are themselves partly genetically determined, such as total cholesterol, HDL cholesterol, blood pressure, and glucose intolerance. Thus, the risk profile based on these variables and on cigarette smoking is clearly far from being a purely environmental index.

There is increasing evidence of the major genetic determination of lipid variation via combined major gene effects and polygenes. The variability of blood pressure also partly depends on a complex mode of inheritance that has caused much controversy,\textsuperscript{90} clearly augmented by the effect of lifestyle and environment. A detailed gene mapping is a formidable task for the future, with some encouragement provided by recent research. But long before this was even considered feasible, our inability to account for risk factor variability suggested that the important link of missing information is genetic. Population genetics methods have been increasingly used to estimate the portions of risk factor variability that are related to heredity, cultural inheritance, and environment.

Data presently available for estimation of the genetic component in risk factor variability has come from two main sources. One source is the analyses done on families whose members were evaluated at the same time. The other one relies on the analysis of prospective, epidemiological studies.
It has been recognized for some time that the failure to explain the individual variability of total serum cholesterol by relative weight, dietary intake, and environmental factors stems largely from the contribution of genes. In their review Sing et al. estimated the fraction of sib-sib correlation to be close to 0.80. Shortly after interest in low HDL cholesterol had been definitely revived by Miller and Miller, it became clear that both HDL cholesterol and the main apoprotein, apo A-I were considerably influenced by genes.

Over the last few years, significant new data have added to our knowledge in an important manner. Segal et al., whose review included a paragraph on quantitatively inherited lipid and lipoprotein variability, summarized the findings of population-based studies and studies of large kindred. Midparent-child correlations in most of these studies were slightly under 0.50. The authors considered the data reviewed (mostly published before 1982) too scarce to warrant substantial conclusions on the relative roles of shared genes versus shared household. Rao et al. in 1982 compared estimates of genetic and cultural heritability obtained from the Honolulu Heart Study and the Cincinnati LRC Family Study (Table 4). The estimates for the contributions of both shared and shared households (but particularly the former) were larger in the Cincinnati Study where all family members were evaluated at the same time, than in the Honolulu Study where the family members of participants were evaluated at a later date and where probands were those with CHD or hypercholesterolemia. This highlights the need for remeasurement of study participants' levels if and when the study framework is used in proceeding to family studies. It also emphasizes the substantial downward bias in correlations for the variable on which families are selected, which occurs even when probands are eliminated from analysis.

In the Bogalusa Pediatric Heart Study, Weinberg et al., investigated school-age children and arrived at similar conclusions. They stated: "The rather large estimates of heritability coupled with the small estimate of variability due to common environment suggest the existence of a long-term genetic component." Recently in the Jerusalem clinic of the LRC Study, 3118 17- to 18-year-old offspring and their parents were examined. In addition, 233 other siblings ages 17 to 18 were examined. The spouse-pair correlations for total and HDL cholesterol were smaller than the parent-offspring ones. Mother-child correlations were somewhat, albeit not significantly, higher than father-child correlations. Heritability in the Israeli LRC data was estimated at 0.46 for total cholesterol regardless of whether it was determined by parent-offspring regression or full-sibling correlations. The estimates for HDL cholesterol were the same order of magnitude when using both methods.

In 3496 white participants of the Collaborative Lipid Research Clinics Family Study, the pooled estimates from seven United States clinics and one Canadian LRC clinic for genetic heritability were 0.56 ± 0.03 for total cholesterol, 0.54 ± 0.03 for LDL cholesterol, 0.48 ± 0.03 for HDL cholesterol, and 0.36 ± 0.03 for triglycerides. The estimated cultural heritabilities were very small in comparison. Based on which lipid variable was assessed, between 40% and 55% of the phenotypic variance was attributed to random unidentified factors. The assumptions underlying the calculation of the above estimates are violated if a mutant gene with the megaphenic effects of an appreciable population frequency were present and also if gene-environment interaction were not negligible.

The data relating to genetic heritability of total cholesterol and LDL cholesterol suggest that from 50% to 65% of individual lipid variation can be explained by genetic factors. For HDL cholesterol, the percentage is only slightly lower, with genetic variability accounting for as much as all unidentified factors; for triglycerides, however, the latter factors appear to be responsible for most of individual variability.

A point of major interest in CHD epidemiology and of possible genetic significance is the large variation in HDL cholesterol levels across diverse ethnic and sex groups. The levels are higher in women than in men and higher in American blacks than in whites. Known environmental agents, such as smoking, education, alcohol, and the use of sex hormones, have failed to explain these findings satisfactorily; the results remain consistent with a strong genetic influence. Glaueck et al. have investigated black-white differences in HDL cholesterol and related risk factors in great detail. They suggested that the higher HDL cholesterol levels in blacks are due to a genetic factor and even speculated about a mechanism linking selective survival of African blacks via protection against sleeping sickness, a selection postulated to be apparent after generations of American life.

Laskarzewski et al. studied the family resemblance for lipids in the Princeton School District's Family Study cohort of 160 white and 59 black nuclear families, and found higher genetic heritability estimates in whites, except for HDL cholesterol where the estimate was larger in blacks (0.80 ± 0.16) than in whites (0.59 ± 0.08). They suggested that a greater genetic effect accounted for higher HDL cholesterol levels in blacks.

In the above-mentioned Collaborative LRC Program Family Study, spouse correlations were close to zero and higher parent-child correlation was found with the mothers than with the fathers. Because in several studies, the mother-adult child correlations exceeded those calculated between the father and the same adult children, these data

<table>
<thead>
<tr>
<th>Lipid</th>
<th>Genetic heritability (h²)</th>
<th>Cultural heritability (c²)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LRC</td>
<td>HHS</td>
</tr>
<tr>
<td>Total</td>
<td>0.62 ± 0.09</td>
<td>0.49 ± 0.04</td>
</tr>
<tr>
<td>LDL</td>
<td>0.62 ± 0.09</td>
<td>0.39 ± 0.04</td>
</tr>
<tr>
<td>HDL</td>
<td>0.47 ± 0.10</td>
<td>0.28 ± 0.04</td>
</tr>
<tr>
<td>VLDL</td>
<td>0.34 ± 0.10</td>
<td>0.17 ± 0.04</td>
</tr>
</tbody>
</table>

Estimates ± SE are under "the most parsimonious hypothesis." Data are adapted from D.C. Rao et al. The Cincinnati Lipid Research Clinic Family Study: cultural and biological determinants of lipids and lipoprotein concentrations. Am J Hum Genet 1982;34:888-903.
could be suggestive of an X-linked inheritance of serum cholesterol levels or of factors controlling its levels. However, since we cannot assess the possible differences in the cultural transmission of factors controlling lipid levels associated with the parent's sex, and since the differences are small, this hypothesis might be premature.

Howard et al.\textsuperscript{107} has reported on the lipid levels of the Pima Indians, a genetically homogeneous group with a high prevalence for obesity and diabetes and a low frequency of CHD. Figure 4 compares HDL cholesterol levels in the Pima Indians and the LRC findings derived from Caucasian population samples. The increased HDL cholesterol levels among women, which are a prominent feature in Caucasians, are not found in the Pima Indians. The lack of difference between the sexes could not be explained by obesity. This finding is reminiscent of previous findings in Tarahumara Indians\textsuperscript{106} and in Polynesians.\textsuperscript{109}

The above multitude of studies, despite a variety of model assumptions, sampling units, sampling methods, and interpretation, highlight the obvious race-sex-genetic interactions in accounting for variations among groups and individuals, which go far beyond satisfactory environmental explanation. A highly significant source of variation appears to be the rapid decline of HDL cholesterol levels among boys in puberty, unparalleled among girls.

Tamir et al.,\textsuperscript{110} who examined lipid and lipoprotein distributions in white children ages 6 to 19 years, revealed a marked and continuous decline of about 25% in HDL cholesterol among boys in the 10- to 19-year-old age group, while the levels among girls remained constant. After accounting for risk factor changes, most of the HDL change during puberty in the LRC data remained unexplained.\textsuperscript{111} Recent investigations suggest that decreasing HDL cholesterol levels in adolescent boys accompany the production of testosterone.\textsuperscript{112} Our own data on children aged 10 to 18 years indicate a similar tendency of decreasing levels in boys during puberty. These have been confirmed in Israeli Jews of diverse ethnic origin.

**Hypertension and Blood Pressure Variability**

We have elsewhere\textsuperscript{113} reviewed some of the evidence for a genetic component in determining individual variability of blood pressure and have cited Platt's classical examples in MZ twins.\textsuperscript{90} Recently, Moll et al.\textsuperscript{114} reanalyzed the data of the Detroit Blood Pressure Study. Additive polygenes were associated with systolic blood pressure (SBP) variability in whites and with diastolic blood pressure (DBP) in blacks. The estimated house environment variance component was 0 in blacks for both SBP and DBP. In partial contrast, heritability estimates based on MZ and DZ correlations in the Collaborative Perinatal Project\textsuperscript{115} were high for DBP in both races (notably in blacks) and low for SBP in whites. Except for the early report by Feinleib et al.,\textsuperscript{116} which suggested a very high heritability for SBP (0.82), the other dozen or so studies using different methods suggested heritability estimates for SBP and DBP that are somewhat lower than those quoted above for total and HDL cholesterol.

Conceptually, the genetics of hypertension per se as a disease entity (a la Platt) could also be investigated. A recent extensive review by Williams et al.\textsuperscript{106} discusses the inheritance of blood pressure (BP) levels as well as of hypertension as an entity. A relationship of a genetic marker (blood group 0) to the incidence of hypertension has been indicated in the Israeli IHD Study (see paragraph on
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gene markers and CHD). The highly inbred Hamulas (extended families) of the Abu Gosh village in Israel show a high prevalence of hypertension with a possible interfamily variation.117

In our previous review,113 we stressed knowledge gained from the important model of spontaneously hypertensive rats (SHR), which indicates that gene-environment interaction is a major factor in the pathogenesis of hypertension.118 Emerging models in hypertension provide new insights into the involvement of genetics in hypertension, as reviewed below.

An exciting topic that has emerged in the last decade and that may eventually illuminate additional genetic aspects of hypertension is the abnormal response of both renal blood flow and adrenal secretion to sodium restriction coupled with diuretic-induced volume depletion119 or angiotensin II administration.120 A distinct group of “nonmodulators” (i.e., individuals with essential hypertension in whom dietary sodium intake does not modulate renovascular, adrenal, and pressor responses to angiotensin II) has been shown to account for close to 50% of hypertension cases. The failure of these individuals to increase the renal blood flow or to secrete aldosterone in larger quantities, in response to exogenous angiotensin II, may stem from either increased local production of angiotensin II or a defect of receptors for angiotensin II in target tissues of the latter.120 Both defects could be genetically influenced.

It has recently been ascertained that the abnormal renal blood flow response to angiotensin II can be corrected by converting enzyme inhibition.121 On the basis of the integrated data, the Brigham and Women’s Hospital Investigators, who are currently involved in a large-scale research project into nonmodulation, have suggested that the data are most consistent with an abnormal regulation of intrarenal angiotensin II concentration in nonmodulators. They have also concluded that age, degree of renal damage, or other clinical and electrocardiographic differences, as well as the duration of hypertension, are all unlikely explanations for nonmodulation. Among other things, nonmodulation may illuminate an association between a possible genetic disorder and the choice of treatment in hypertension.

Another relatively new and rapidly developing field of investigation relating to the genetics of hypertension is the research into sodium balance, erythrocyte cation cotransport, and countertransport. Some exciting recent results122, 123 appear to hold promise for further insights. The University of Utah’s cardiovascular genetics research projects124 produced significant information revealing that high sodium-lithium countertransport fell in increasing percentages from normotensives with no family history of CHD (4.8%), to those with such a family history (18.8%), to hypertensives (26.5%). This was closely, but inversely, mimicked by the decreasing percentages of low sodium-potassium cotransport. The same group125 examined 439 persons from 10 kindred and indicated that the data favored polygenic inheritance of sodium-lithium countertransport over major gene inheritance. They estimated the total phenotypic variance attributable to polygenic differences to be as high as 71%.

In a subsequent study based on 1400 Utah subjects aged 18 to 83 years, Hunt et al.126 estimated the correla-

tions of sodium-lithium countertransport, lithium-potassium cotransport, and furosemide-insensitive lithium efflux into magnesium chloride with plasma lipids. All three transport systems showed correlations of around 0.3 with tri-glyceride, −0.2 with HDL cholesterol, and 0.2 to 0.3 with weight. This suggested a relationship between blood lipids and membrane cation transport relevant to the pathophysiology of essential hypertension. The nature of the relationship (for example, whether lipids affect the erythrocyte membrane) remains to be elucidated.

In Japanese families127 a familial aggregation of the lithium-sodium and sodium-potassium transport systems has been also demonstrated with parent-offspring correlations in the order of 0.5. Similar to the Utah findings,125 no spouse correlations were found, eliminating shared household as a significant factor in determining cation transport rates. Williams et al.128 suggested that cation flux tests are potentially useful tools in sorting out the genetic heterogeneity of hypertension and could help us understand the underlying pathophysiology. Research into the role of genetics in determining the probability of developing clinical CHD in those who are already hypertensive is still lacking, but the recent development of research into the genetic aspects of the disease appears highly promising.

Diabetes Mellitus

Coronary heart disease is the major macrovascular complication of diabetes mellitus, a notorious familial disorder and a relatively common chronic disease. Roughly, the risk of clinical CHD is doubled in diabetics.129 Insulin-dependent diabetes mellitus (IDDM) is a disease that has a clear genetic basis. Investigation of the genetics of IDDM129–131 has established beyond a doubt that the various disorders under the title of IDDM depend heavily on the HLA system (the latter determining as much as one-half to two-thirds of the overall genetic susceptibility to the disease).132 Many loci in the HLA complex have been implicated, new theories have been constructed and a number of modes of inheritance have been suggested. Although immunogenetics apparently largely dictates the susceptibility to IDDM, viral or environmental mechanisms or both may convert the latent susceptibility to clinically manifest disease.132

Noninsulin-dependent diabetes mellitus (NIDDM) also has strong genetic determinants. MZ twin studies demonstrate an almost complete concordance.34, 133 NIDDM is probably genetically heterogeneous, and its frequency tends to rise rapidly in immigrants who change abruptly from deprivation to affluence.134 One such example is the group of Israeli Jewish immigrants from North Africa and the Mideast.135 Two additional examples have been pointed out in populations which underwent quick modernization and urbanization, such as the Pacific Islanders136 and the Pima Indians.137 Among these the unusually high incidence of diabetes might also be related to frequent inbreeding. This genetically interesting phenomenon is surmised to occur on the basis of the genetic selection that reverses its role from one that is highly favorable for survival during starvation or severe deprivation to one that is diabetogenic during affluence.134

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HLA plays only a minor role, if any, in the etiology of NIDDM. Recently, a number of patients with discrete point mutations in the insulin gene and others at the cleavage site of the C peptide, resulting in hyperproinsulinemia, have been described. The associations of IDDM and NIDDM with a DNA restriction polymorphism of the insulin gene has also been reported. The relevant DNA insertions in the 5'-flanking region of the insulin gene, rather than in its coding portion, are more prevalent in NIDDM patients than in nondiabetics.

Rotter et al. thoroughly reviewed recent developments in the genetics of IDDM and NIDDM, with emphasis on a NIDDM subgroup, the maturity-onset diabetes of the young. These researchers also discussed the indications that the risk of vascular complication including CHD in diabetics has a genetic component. This was suggested by Nora et al. who found that juvenile diabetes in a first-degree relative ranked highly as an independent risk factor for CHD and by Owerbach et al. in their DNA polymorphism studies.

Genetics and Multiple Risk Factors

A recent study by Snowden et al. showed the concordance of CHD among the siblings of the Framingham Heart Study. The incidence of MI in the older brothers was significantly related to the MI experience of the younger brothers, even after the effects of total cholesterol, systolic blood pressure, and cigarette smoking were controlled in a multivariate analysis. The adjusted odds ratio associated with MI experience in older brothers was 1.51 for MI and 1.55 for CHD death, respectively, in younger brothers. The authors conclude that familial aggregation for CHD may result from a predisposition to disease that is not mediated through known risk factors. These findings support those by ten Kate et al. whose study of first degree relatives of survivors of MI showed that familial clustering of risk factors inadequately explained familial aggregation of CHD.

Sex Differences in Coronary Heart Disease

As early as 1936, Levy and Boas pointed out the lower incidence of CHD in women. Conversely, case fatality in men was at least as low as in women. Although both atherosclerosis of the coronary arteries and incidence of CHD are markedly higher in men, the sex difference for CHD is greatest among Western white persons, even after the effects of total cholesterol, systolic blood pressure, and cigarette smoking were controlled in a multivariate analysis. The adjusted odds ratio associated with MI experience in older brothers was 1.51 for MI and 1.55 for CHD death, respectively, in younger brothers. The authors conclude that familial aggregation for CHD may result from a predisposition to disease that is not mediated through known risk factors. These findings support those by ten Kate et al. whose study of first degree relatives of survivors of MI showed that familial clustering of risk factors inadequately explained familial aggregation of CHD.

The predisposition of white men to develop advanced coronary atherosclerosis and CHD without a similar excess of aortic atherosclerosis suggests that the coronary arteries of white men of European origin are peculiarly susceptible to atherogenesis. Even if the white man has high levels of established risk factors, this does not explain the selectivity of one arterial system. The severe coronary artery changes of marked intimal proliferation described in two congenital anomalies — coarctation of the aorta and supravalvular aortic stenosis — are also more frequent in men. Supravalvular aortic stenosis also occurs as a familial syndrome.

A great diversity of male/female (M/F) ratios is observed in CHD mortality rates in different countries as well as in different ethnic groups within one country. The M/F ratio is usually high, although not without exception, in countries with low mortality and high in countries with high mortality. In the International Atherosclerosis Project (IAP), the M/F ratio of severe atherosclerotic lesions was 1.14:1 in five black populations, as contrasted with 1.61:1 in 14 other groups. Strong et al. have shown that the M/F ratios of mean percentage intimal surface involved with raised coronary lesions was larger in New Orleans whites than in blacks aged 45 to 64. These ratios are compatible with the findings related to early thickening of coronary arteries, discussed below. McGill and Stern in an extensive review concluded that neither current risk factor differences, nor differences in the time of exposure of these factors, nor known sex differences in hormonal activity, are sufficient to explain the varying CHD mortality. A unique analysis by Wingard attempted to explain a 1.5 relative risk of 9-year mortality for men (aged 30 to 69) among 4700 adults studied in Alameda County, California, by the sex differences of 16 demographic and behavioral risk factors. The adjusted relative risk, in fact, was higher (1.7, p < 0.001) than the unadjusted one. Smoking, alcohol consumption, physical activity, weight, and life satisfaction were among the variables included in the analysis; although they contributed significantly to the risk of death, they did not serve to explain the sex difference in mortality.

In the United States, major changes in CHD mortality rates have taken place over the last 40 years. Despite the initial endemic rise and the subsequent fall, a profound excess of the M/F ratio in whites compared with blacks has persisted. Extreme differences between ethnic groups have also been identified in Israel. While the M/F mortality ratio dropped from 6.1 at age 35 to 44 to 1.1 at age 75, in each decade the M/F ratios were notably lower in Jews born in non-European countries than in those born in European countries. The ethnic variation was demonstrated by M/F CHD mortality ratios (at ages 25 to 74 years) of 2.15 for those born in Europe or America and 2.08 for those born in Israel (1966–1967 data), as opposed to ratios of 1.59 for North Africa-born Jews and 1.54 for those born in the Middle East. In an analysis of the national mortality data for Israel (1970–1974), M/F ratios from Jewish immigrants from Yemen and Morocco (ratios of mean annual rates, ages 25 to 74) were 1:1, while for the total Jewish population the ratio in mid-1972 was 1:84:1.5

World Health Organization data show that in Finland the 1975 ischemic heart disease mortality ratio at ages 40 to 70 years was high at 4.74; in Bulgaria it was 2.15; and in Israel it was low at 1.92. Table 5 shows this diversity of M/F ratios.
Table 5. Coronary Heart Disease Mortality Ratios In Selected Countries In 1977

<table>
<thead>
<tr>
<th>Country</th>
<th>Male/female ratios</th>
<th>Male</th>
<th>Female</th>
<th>Age 35–74</th>
<th>Age ≥25</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norway</td>
<td>537/156</td>
<td>3.44</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Finland</td>
<td>878/266</td>
<td>3.30</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>U.S.A.</td>
<td>670/252</td>
<td>2.56</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scotland</td>
<td>809/324</td>
<td>2.50</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Japan</td>
<td>103/50</td>
<td>2.06</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Israel (Jews)</td>
<td>527/290</td>
<td>1.82</td>
<td>1.58</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Born in:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Israel</td>
<td></td>
<td>1.89</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Europe/America</td>
<td></td>
<td>1.74</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Africa</td>
<td></td>
<td>1.41</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asia</td>
<td></td>
<td>1.18</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data are from death certificate diagnoses.

The widely varying sex ratios are difficult to interpret on environmental grounds because men and women share many common habits, including diet. Moreover, in the Moroccan-born and Yemenite-born Jews living in Israel, a considerably larger proportion of men smoke cigarettes in comparison to women. Therefore, the finding of equal CHD mortality rates in both sexes in these ethnic groups is puzzling if risk factor differences do account for the sex-specific disease rates. The outstanding dissimilarities between sex mortality ratios seem to enhance the role of heredity in determining who is at risk for CHD. The sex differences observed in morphologic studies (described later in this review) might indicate the age at which such dissimilarities originate.

Table 6. Risk Factors and Myocardial Infarction in First Degree Relatives by Sex and Ethnic Groups: Finnmark County Cardiovascular Study

<table>
<thead>
<tr>
<th>Ethnic group</th>
<th>Cholesterol (mg/dl)</th>
<th>SBP (mm Hg)</th>
<th>DBP (mm Hg)</th>
<th>W/H² (g/cm²)</th>
<th>No. cig. smoked/day</th>
<th>1st-degree relatives with registry-confirmed MI (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Finns (480)</td>
<td>272</td>
<td>138</td>
<td>82.7</td>
<td>2.45</td>
<td>9.4</td>
<td>19.8</td>
</tr>
<tr>
<td>Norsemen (1069)</td>
<td>258</td>
<td>138</td>
<td>80.3</td>
<td>2.40</td>
<td>8.1</td>
<td>13.9</td>
</tr>
<tr>
<td>Lapps (409)</td>
<td>273</td>
<td>132</td>
<td>80.8</td>
<td>2.52</td>
<td>8.0</td>
<td>4.6</td>
</tr>
<tr>
<td>Uncertain origin (382)</td>
<td>278</td>
<td>137</td>
<td>80.3</td>
<td>2.47</td>
<td>9.9</td>
<td>11.9</td>
</tr>
<tr>
<td>Females</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Finns (369)</td>
<td>272</td>
<td>126</td>
<td>76.8</td>
<td>2.37</td>
<td>5.4</td>
<td>18.9</td>
</tr>
<tr>
<td>Norsemen (977)</td>
<td>254</td>
<td>124</td>
<td>75.3</td>
<td>2.29</td>
<td>5.0</td>
<td>12.5</td>
</tr>
<tr>
<td>Lapps (398)</td>
<td>265</td>
<td>123</td>
<td>76.8</td>
<td>2.54</td>
<td>4.0</td>
<td>4.5</td>
</tr>
<tr>
<td>Uncertain origin (386)</td>
<td>265</td>
<td>126</td>
<td>76.6</td>
<td>2.40</td>
<td>5.2</td>
<td>14.1</td>
</tr>
</tbody>
</table>

Numbers in parentheses indicate number of individuals in study group. Values are age-adjusted mean values.

Abbreviations: SBP = systolic blood pressure; DBP = diastolic blood pressure; W/H² = weight/height² (Quetelet Index); MI = myocardial infarction.


Table 7 clearly illustrates that the risk for developing either MI or definite angina pectoris varies among the six groups beyond the degree to which a multiple adjustment

Differences between Risk Factor Levels and Coronary Heart Disease Prevalence and Incidence among Ethnic Groups

In Norway, Lapps, Norsemen, and Finns have been compared in terms of risk factors and the prevalence of CHD among first-degree relatives. A marked predominance was found in relatives of Finns compared with Lapps, despite great similarity in mean cholesterol and mean diastolic blood pressure and only slightly and non-significant lower levels for systolic blood pressure and cigarette smoking for the Lapps (Table 6). Although these were not incidence data, they strongly suggested that ethnicity plays a key role in determining susceptibility to CHD.

The authors concluded that "most of the risk determined by having one or more first-degree relatives with MI is independent of the common coronary risk factors."

The Israeli ischemic Heart Disease Study of 10,000 male civil servants and municipal employees, 8600 of whom were immigrants, provides information on risk factors, 5-year incidence of CHD and diabetes, and 15-year mortality. The sampling was stratified by using varying sampling ratios within six areas of birth: Eastern Europe, Central Europe, the Balkan countries, Israel, the Middle East, and North Africa. A detailed analysis of the genetic data on the Jewish population, including heterogeneity indices and distance measures, has been published. Logistic risk functions predicting the occurrence of MI over a 5-year period have been calculated from the pooled Israeli study data. We applied these "average" predictive functions to every individual, thus calculating the individual probabilities of developing a clinical manifestation of CHD. We subsequently summed up the probabilities in each of the specific sampling areas.

Table 7 clearly illustrates that the risk for developing either MI or definite angina pectoris varies among the six groups beyond the degree to which a multiple adjustment...
for risk factors can explain. Specifically, men born in the Middle East clearly have unaccountable attributes that protect them against the onset of clinical coronary disease, as the sum of their 5-year risks remains much lower than that of European-born men after risk factor adjustment.

Within the Middle Eastern groups, probably the genetically more heterogeneous Jews born in Yemen180 are of special interest. They lived in isolation for many years, and intermarriage with non-Jews was apparently very rare. Table 8 shows the adjusted relative risk for developing MI in the countries of birth in a manner similar to that of Table 7, by adding mean levels for several CHD risk factors. The estimated risk for Yemenite-born Jews is clearly below that of counterparts born in Europe, Africa, or Iraq. The incidence difference seems to go beyond risk profile dissimilarity. This finding is similar to the results of Gordon et al.181 from the tripartite analysis of the Honolulu, Puerto Rico, and Framingham Heart studies.161 The incidence of CHD in men from the earlier two studies was one-half that expected when calculated on the basis of the Framingham risk functions.

In viewing the low incidence of CHD in the Yemenite group, we should consider the length of stay in Israel as a potentially important factor that may be reflected in variables other than the ones adjusted for in the analysis. This group has, in fact, been in the country for an average of 30 years, 83% having emigrated from Yemen before the 1948 establishment of the State of Israel. Any protective environmental effect therefore would appear to be one active in childhood. If a Yemenite childhood outweighed genetically determined susceptibility, second generation Israeli Jews born to Yemenite parents of Yemenite descent should approximate the risk factor levels or disease rates of other Israeli Jews. The data collected in a group of 80 Israeli-born middle-aged civil servants and municipal employees whose parents were born in Yemen indicate that despite considerable excess of weight (9 kg) and skinfolds in comparison to Israeli IHD first-generation counterparts, the SBP, DBP, and cholesterol levels of the second generation Yemenites resembled those of the first generation Yemenites.162

Another finding on the Yemenite-born Israeli offers support for a major role of genetics. Within the first-generation subcohort, risk factor mean levels were progressively higher in subjects with a progressively longer stay in Israel,46 a finding confirming previous limited investigations.183 However, length of stay in the country was not correlated with 15-year CHD incidence in that group,46 nor was CHD mortality elevated in old-time Yemenite Jews living in Israel; in fact, it was lower.104 In the Jerusalem LRC clinic, 17-year-old, second generation Yemenites also had low cholesterol levels and a remarkably high percent of HDL cholesterol, which distinguishes them from Israeli youngsters born to parents from Iraq or Europe.185

This complex set of incompatibilities within one generation and across generations and between time trends of risk factors and CHD incidence and mortality further accentuates the possibility that the Yemenite community's partial genetic immunity against the impact of the Westernized Israeli society persists through the years and could be transmitted to the next generation. In opposition to this

![Table 7. Relative Risk of Developing a Myocardial Infarction or Angina Pectoris among Israeli Men by Area of Birth](http://atvb.ahajournals.org/)

<table>
<thead>
<tr>
<th>Area of birth</th>
<th>MI</th>
<th>AP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eastern Europe</td>
<td>1.18</td>
<td>1.09</td>
</tr>
<tr>
<td>Central Europe</td>
<td>1.22</td>
<td>0.81</td>
</tr>
<tr>
<td>Balkan countries</td>
<td>0.85</td>
<td>1.65</td>
</tr>
<tr>
<td>Israel</td>
<td>1.08</td>
<td>0.90</td>
</tr>
<tr>
<td>North Africa</td>
<td>1.04</td>
<td>1.00</td>
</tr>
<tr>
<td>Middle East</td>
<td>0.72</td>
<td>0.59</td>
</tr>
<tr>
<td>Total</td>
<td>1.00</td>
<td>1.00</td>
</tr>
</tbody>
</table>

1.00 = average risk for study sample.
Abbreviations: MI = myocardial infarction; AP = angina pectoris.

![Table 8. Relative Risk of Developing Myocardial Infarction and Angina Pectoris in Different Countries of Origin among Jews Living in Israel, 1963–1968](http://atvb.ahajournals.org/)

<table>
<thead>
<tr>
<th>Country of birth</th>
<th>Men at risk for MI (no.)</th>
<th>Diabetics (%)</th>
<th>Quetelet w2 index (g/cm2)</th>
<th>SBP (mm Hg)</th>
<th>DBP (mm Hg)</th>
<th>Total Cholesterol (mg/dl)</th>
<th>HDL (%)</th>
<th>Cigarettes (%)</th>
<th>O blood group (%)</th>
<th>MI or AP cases (no.)</th>
<th>Pooled adjusted relative risk of MI or AP in 5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yemen</td>
<td>383</td>
<td>7.1</td>
<td>2.34</td>
<td>133</td>
<td>81.7</td>
<td>193</td>
<td>21.4</td>
<td>45</td>
<td>56</td>
<td>3</td>
<td>0.20</td>
</tr>
<tr>
<td>Aden</td>
<td>132</td>
<td>4.9</td>
<td>2.41</td>
<td>133</td>
<td>82.1</td>
<td>187</td>
<td>19.5</td>
<td>51</td>
<td>39</td>
<td>1</td>
<td>(0.19)*</td>
</tr>
<tr>
<td>Morocco</td>
<td>430</td>
<td>3.6</td>
<td>2.53</td>
<td>133</td>
<td>83.2</td>
<td>199</td>
<td>20.7</td>
<td>57</td>
<td>37</td>
<td>13</td>
<td>0.90</td>
</tr>
<tr>
<td>Iraq</td>
<td>1149</td>
<td>5.1</td>
<td>2.53</td>
<td>136</td>
<td>84.1</td>
<td>207</td>
<td>17.5</td>
<td>60</td>
<td>22</td>
<td>39</td>
<td>0.72</td>
</tr>
<tr>
<td>Romania</td>
<td>1231</td>
<td>4.0</td>
<td>2.59</td>
<td>136</td>
<td>84.1</td>
<td>209</td>
<td>18.1</td>
<td>46</td>
<td>35</td>
<td>84</td>
<td>1.33</td>
</tr>
<tr>
<td>Poland</td>
<td>1267</td>
<td>4.1</td>
<td>2.57</td>
<td>135</td>
<td>84.0</td>
<td>217</td>
<td>18.2</td>
<td>44</td>
<td>34</td>
<td>82</td>
<td>1.21</td>
</tr>
<tr>
<td>Germany</td>
<td>496</td>
<td>4.0</td>
<td>2.52</td>
<td>136</td>
<td>84.5</td>
<td>226</td>
<td>17.9</td>
<td>43</td>
<td>36</td>
<td>26</td>
<td>1.00</td>
</tr>
</tbody>
</table>

*Number in parentheses denotes less than 10 expected incidence cases.
Abbreviations: MI = myocardial infarction; AP = angina pectoris.
The Jewish immigrants from Yemen are not the only group for whom the low level of risk factors is insufficient to explain differences in CHD mortality. Armstrong et al.\(^{167}\) have shown that the small differences in coronary risk factors between 177 Italian migrants to Australia and 176 age-matched native-born Australians of Australian, British, or New Zealand parentage were insufficient to explain the lower mortality among the Italian immigrants. In Johannesburg, South Africa, Indian CHD mortality levels (predominantly in young adults and middle-aged individuals) are markedly higher than the non-Jewish white levels, although Indian cholesterol levels are lower.\(^{168}\) For South African Indian CHD patients, MI occurs at extremely low cholesterol levels\(^{169}\) and this holds true, remarkably, in India proper. Similarly, CHD mortality rates are inexplicably high in South African Jews.\(^{169}\) In both cases, a genetic factor has been implicated. Findings from various ethnic groups, therefore, appear to parallel those from multivariate prospective analyses, and from studies of familial aggregation in suggesting that the disease-rate discrepancy exceeds the discrepancy between individuals or groups that could be expected on the basis of the known risk factors.

The diversity of incidence rates between ethnic groups after risk factor adjustment poses a dilemma. What portion of the diversity is genetically determined? What portion might arise indirectly from a genetic basis (remembering that risk factor variability also has a pronounced genetic basis)? The following discussion of ethnic morphologic findings is relevant.

**Ethnic and Sex Differences In Early Structural Changes in Coronary Arteries**

Neufeld\(^{170}\) presented the hypothesis that ethnic differences in CHD mortality are related to differences in structural changes in coronary arteries. This hypothesis was prompted by the autopsy examination of 211 infants and children up to 10 years of age\(^{171}\) who belonged to three ethnic groups: Ashkenazi Jews (Jews of central and eastern European origin), Bedouins, and Yemenite Jews. Only specimens from children who died of noncardiac causes were used. Marked differences in the structure of the coronary arteries with advancing age were noted. The mean thickness of the intimal and internal muscular layers differed significantly in Ashkenazi boys and the two other ethnic groups.

These data complement a set of findings indicating that CHD incidence late in life may depend to a considerable extent on genetically determined ethnic and sex variations in structural changes in the coronary arteries. First, coronary artery intimal thickening was more marked in Ashkenazi boys than in Ashkenazi girls, Yemenite boys, or Yemenite girls. Second, the risk factor-adjusted CHD incidence remained very low in Yemenite-born immigrants who have lived in Israel for a long time. Third, the CHD mortality in the total Israeli Yemenite-born community was uncorrelated (or slightly negatively correlated) with the increased length of stay, although risk factors did tend to gradually Westernize. Fourth, in the Yemenite groups (characterized by the absence of sex differences in coronary arterial intimal thickening) the M/F CHD mortality ratio remained low into old age, while for the European-born Jews it was similar to values found in Europe and, like the latter, decreased progressively with age. A tentative explanation for these ethnic differences in the sex-specific mortality ratio is that the morphologic changes in their coronary arteries are genetically determined.

Similar changes in the musculoelastic layer and intimal thickening have been described by Dock,\(^{172}\) Schomage,\(^{173}\) and Pesonen et al.\(^{174}\) who also found more prominent changes in men than in women. The similarity of our findings to those of Pesonen et al. is of particular interest. They demonstrated that coronary artery thickening in Eastern Finnish children is markedly more pronounced than in Western Finns. The differences parallel the notorious East-West gap of CHD incidence and mortality.

A different genetic origin has been postulated for the people residing in East Finland. Rissanen\(^{12}\) has shown that the family history of early diagnosed MI implied a greater relative risk at an early age for relatives of young probands with CHD in North Karelia than in southern Finland, and Pesonen’s data provides an explanation that is compatible with Rissanen’s findings. In a reanalysis of Rissanen’s original data, Carmelli et al.\(^{175}\) applied a descriptive genetic analysis (offspring-between-parent plot) to serum cholesterol and triglyceride levels in relatives of probands with AP or nonfatal MI prior to age 55. Their plot contrasts suggest major gene effects for these lipids in North Karelia but not in southern Finland. The authors suggested that greater major gene effects for serum lipids in North Karelia corresponded with the considerably higher early CHD rates observed there.

The role of intimal thickening is further accentuated by Sims’ findings, in 352 autopsy examinations of the anterior descending branch of the left coronary artery (LAD) and the internal mammary artery. The coronary arteries showed severe intimal thickening that progressed in severity throughout life, whereas the internal mammary arteries showed slight changes with age (over 50% of necropsies of persons dying at ages 50 to 60 years revealed a coronary arterial intima less than 10% of the corresponding medial thickness). Cross sections of the anterior descending branch of the left coronary artery and the internal mammary artery from three patients who died suddenly are shown in Figure 5. In view of the fact that the LAD and mammary artery are similar in size, are subjected to similar chemical stimuli (pairs of arteries from the same individuals were used), and that internal mammary artery grafts clearly offer the best survival after bypass surgery for CAD,\(^{176}\) these observations provide evidence that intimal thickening is a response of the arterial wall to local, anatomic factors. Such factors are probably independent of environmental influence.

Although considerable space in this review has been dedicated to metabolic disorders and their interactions, we are reminded that CHD should not be considered merely a disease of the circulating blood and the possibly toxic ciga-
search into the genetic aspects of hypertension has as-

factors even in the absence of familial hypercholesterole-
effects which were previously unobserved or ignored. Re-

appear to be learning more about possible single gene

ing tool for a breakthrough in arteriosclerosis research. We

to CHD risk now appears to be well founded, and data

family history makes a prominent independent contribution

twins confirm the role of heredity in CHD. LDL mem-

brane receptor activity seems to be influenced by genetic

ponents of the MZ-DZ pair differences will need to be re-

sumed new directions; for instance, erythrocyte cation

transport rates have been shown to be largely inherited
and may provide clues to understanding the pathophysio-

ogy of essential hypertension. Whether nonmodulation in

hypertensives is a fully or partly inherited disorder is a

forthcoming significant study for investigation. The role of

HLA in IDDM is being recognized and evaluated. A further

evaluation of the role of genetic factors in dictating which

hypertensives and which diabetics will incur cardiovascu-

lar complications might assist in clarifying who will mani-

fest CHD as sequelae of other risk factors. The study of

twins will continue to furnish fascinating information; the

methodology to separate environmental from genetic com-

ponents of the MZ-DZ pair differences will need to be re-

It is not premature to forecast that some of the emphasis

in the genetic research of arteriosclerosis will be shifted

from the community and the family to the cell, that is, to the

domain of molecular biology. In the near future we may

slowly approach an intermediate goal: that of defining

— through DNA analysis of lipid disorders, for example —
genetic subgroups of individuals who differ in their suscept-

ibility to the environmental agents that putatively dispose
to disease and death. We should seek to identify sub-

groups with genetically controlled differences in the like-

lihood of response to antihyperlipemic or antihypertensive

intervention based on life-style, diet, or pharmacotherapy.

Then arteriosclerosis research may primarily involve in-

vestigation of arterial wall structure and metabolism. Until

recently, the major emphasis has been on research into

the composition of circulating blood, which tells only a part

of the story and may carry entirely different risks for differ-

t individuals and, within individuals, for different arterial

systems. Therefore, arterial wall response to circulatory

stimuli needs to be emphasized in future research.

The phase of direct intervention by genetic engineering

still appears remote, although we may assume that the use

of genetic engineering to cure, or of DNA variants to prena-
tally diagnose, simple monogenic diseases such as beta-
thalassemia will gain eventual success. Advanced tech-
nology, innovative methods, innovative thinking, priority

modification, and confrontation with seemingly insur-

mountable ethical problems will be required to pave the

way for the prevention of multifactorial disease in a sense

heretofore unfamiliar to arteriosclerosis research. This

need not come at the expense of current efforts to promote

a life-style conducive to a lower risk of clinical CHD or at

the expense of interventional cardiology which attempts to

provide the most immediate and efficient therapy to victims

of the clinical sequelae of coronary arteriosclerosis.

Conclusions

Considerable progress in genetic-epidemiologic meth-

ods and in the identification of significant apolipoprotein

polyorphisms, their location on chromosomes, and their

postulated indirect or direct effects on arteriosclerosis has

been achieved since our last review. The evidence that

family history makes a prominent independent contribution

to CHD risk now appears to be well founded. and data

on twins confirm the role of heredity in CHD. LDL mem-

brane receptor activity seems to be influenced by genetic

factors even in the absence of familial hypercholesterole-

mia. The description of RFLPs offers a particularly promis-

ing tool for a breakthrough in arteriosclerosis research. We

appear to be learning more about possible single gene

effects which were previously unobserved or ignored. Re-

search into the genetic aspects of hypertension has as-

Figure 5. Cross sections of the anterior descending branch of

the left coronary artery (top) and of the internal mammary artery

(bottom) from three patients who died suddenly. Coronary arte-

ries x 17.5; mammary arteries x 37.5. A. Indian man aged 55

years. B. Indian man aged 40 years. C. Indian man aged 60

years. Reproduced with permission from F.H. Sims et al. A com-

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1983;105:560-566.

Cigarette smoke. The presence of severe atherosclerosis in

some individuals and its absence in others is apparently

related to complex and variable arterial wall responses to

variable blood constituents in different individuals and

even to uniform blood composition in the different arterial

systems of a given individual. The coronary arterial system

reacts to stimulus, be it chemical or mechanical-turbulent, in

a poorly understood manner. The reaction probably de-

pends on anatomic patterns of the coronary arteries and on

individual differences in receptor cell activity.

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GENETIC ASPECTS OF ARTERIOSCLEROSIS

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Index Terms: apolipoproteins • atherosclerosis • coronary heart disease • erythrocyte cation transport • familial aggregation • genetic epidemiology • lipoprotein metabolism • twin studies

Workshop on Lipoprotein Heterogeneity

September 29–October 1, 1986
Rockville, Maryland

The National Heart, Lung, and Blood Institute is sponsoring a workshop on Lipoprotein Heterogeneity to be held September 29–October 1, 1986, in Rockville, Maryland. The objective of the workshop is to discuss the structural and functional heterogeneity of plasma lipoproteins as well as the implications of heterogeneity on interpretations of lipoprotein studies both in vitro and in vivo and on assessment of lipoprotein atherosclerosis risk factors. For more information, contact:

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Lipoprotein Metabolism — Atherogenesis Branch
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Genetic aspects of arteriosclerosis.
U Goldbourt and H N Neufeld

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