During August 10–12, 1983, a workshop was held in St. Louis, Missouri, on the Genetic Epidemiology of Coronary Heart Disease: Past, Present, and Future. This was jointly sponsored by the National Heart, Lung, and Blood Institute, the Division of Biostatistics of the Washington University School of Medicine, St. Louis, and the Departments of Medicine and Psychiatry of the Jewish Hospital of St. Louis. The organizing committee consisted of the six authors of this report. Nearly 100 scientists attended the workshop, with 32 primary presentations and 11 major discussions. The proceedings, with the same title as this report, were published by Alan R. Liss in March 1984.

Considerable attention has been paid to the role of familial factors in the etiology of coronary heart disease (CHD) in humans. Several conferences held over the past decade have specifically highlighted research priorities and have characterized the relevant phenotypes known or suspected to be precursors of a variety of CHD endpoints. However, disciplinary isolation continues to be a limitation despite some collaborative efforts. So long as geneticists, epidemiologists, and clinicians continue with parallel approaches alone, no one is likely to resolve the etiologic basis of complex human diseases such as CHD. It would be a sound strategy to forge an interdisciplinary approach; this workshop, in which experts in various disciplines were invited to examine and constructively criticize the scientific value of each others' studies, was deliberately designed for this purpose. This report is organized into four sections that correspond to the organization of the proceedings: Past Studies, Methodology, Phenotypes, and Guidelines for Future Research.

The first session was preceded by a historical overview of the genetic epidemiology of CHD by Dr. Manning Feinleib. He reviewed four milestones in the history of cardiovascular genetics: The Symposium on Contributions of Genetics to Epidemiologic Studies of Chronic Diseases held at Ann Arbor, Michigan, in 1963; The Task Force on Genetic Factors in Atherosclerotic Diseases held under the auspices of the (then) National Heart and Lung Institute in 1974; the Conference on Genetic Epidemiology held at Honolulu, Hawaii, in 1977; and the Workshop on Genetic Analysis of Common Diseases: Applications to Predictive Factors in Coronary Disease held at Snowbird, Utah, in 1978. He emphasized that one common objective of these conferences, melding the methods of the geneticist to the interests and data bases of the epidemiologist, had not been fully achieved; thus, the present workshop will address these concerns.

Past Studies

On the first day of the conference, four major epidemiological studies, chosen as examples of representative, prospective cohort studies containing data on a variety of CHD risk factors, were discussed. Each was reviewed by two experts who had not participated in the study, first an epidemiologist and then a geneticist. This was followed by a formal discussion of these reviews conducted by one of the major contributors to the study, which generated additional discussion of similar studies. This format was designed to identify the extent to which earlier contributions have been received by the scientific community and to explore the potential opportunities that still exist. Only by recognizing the limitations and strengths of past studies can we hope to design future investigations more efficiently.

Tecumseh Community Health Study

The Tecumseh Community Health Study was first reviewed by Dr. George G. Rhoads from an epidemiological point of view. He pointed out that since this was a total community project for studying a number of diseases, the study's resources could not be fo-
cussed on CHD. As a result, substantial productivity was noted in areas other than coronary diseases.

Dr. Matthew K. McGue followed with a review from the genetic point of view. The large family data base and the information on 12 genetic markers were mentioned as strengths of the study. He emphasized that the data on polymorphic markers enabled scrutiny of the reported relationships among individuals: ABO, haptoglobin, Gm, and secretor were found to be significant predictors of cholesterol variation. The study also provided an opportunity to compare different analytic strategies used in genetic epidemiology. Dr. Moll discussed a number of ongoing and future investigations using this data base.

In an additional discussion, Drs. Millicent W. Higgins and Ira M. Longini emphasized that the Tecumseh Study should not be narrowly viewed as a study of the etiology of CHD, for it also included studies of hypertension, chronic obstructive lung disease, diabetes mellitus, arthritis, and obesity. They cautioned that adoptees and their adoptive parents could be biologically related. They also discussed a recent investigation confirming that genes, familial environment, and assortative mating (whereby spouses preferentially choose one another) are all significant factors in the familial aggregation of body mass. In an adjoining discussion, Dr. James J. Nora briefly reviewed the Denver Heart Study consisting of three components: Genetic Risk Factors in CHD, the Whole Heart Program, and the School Health Program.

Framingham Heart Study

The Framingham Heart Study was reviewed by Dr. Millicent W. Higgins, an epidemiologist. She suggested that caution be exercised in generalizing the results to other populations and noted that the Framingham Study failed to identify all of the important factors that influence the development of cardiovascular disease; in particular, clotting factors and platelet aggregation were mentioned as unexplored areas. She emphasized that the excellent rates of follow-up and the vast amount of information collected over the last 35 years constitute a priceless resource that should be exploited in studies of stroke, senile dementia, aging, and longevity. She concluded by noting that this historic study has made enormous contributions to our knowledge of the epidemiology of cardiovascular disease.

In reviewing the genetic analyses based on this study, Dr. Kadambari K. Namboodiri noted some major limitations: problems of comparing environmental variables collected more than two decades apart; possible response bias; the availability of only two CHD risk factors (cholesterol and blood pressure) for intergenerational analyses; and the lack of blood marker data for potential linkage and association studies. She argued that a prudent application of genetic epidemiological methodology to this study could help improve the characterization of the disease, delineate homogeneous entities for biochemical investigations, and enhance the prediction of CHD risk in this population. Dr. Namboodiri thought that not much genetic analysis of this phenomenal data set had been done.

Dr. Christine Carter led the discussion and presented some preliminary results of analyses currently being undertaken. In particular, she confirmed the segregation of a dominant gene for LDL cholesterol in this population. She also reported that log-transformed systolic blood pressure failed to indicate a major gene. She concluded by remarking that other, possibly better, methods are now being used to more fully explore the nature of familial variation.

Dr. Kåre Berg, in the next discussion, presented a summary report on the genetic epidemiological approaches of the World Health Organization (WHO) to the prevention of CHD. A May 1983 meeting of WHO consultants resulted in the following recommendations: 1) genetic knowledge, expertise, methods, and research strategies should be incorporated into WHO efforts; WHO should initiate and coordinate a multicenter, prospective study of risk factors to evaluate their predictive values; 2) WHO should initiate and coordinate a multicenter, retrospective study of first-degree relatives of patients with premature CHD to describe the genetic risk factor distribution in these families as compared to that in control families; 3) WHO should stimulate studies of risk factors in existing, population-based panels of twins to resolve genetic, environmental, and maternal determinants, and include controlled intervention trials in disease-concordant twin pairs; 4) WHO should sponsor the development of protocols and organize a steering committee for the suggested studies.

Dr. Roger R. Williams then reported on an ongoing study of early coronary subjects and their relatives which seeks to characterize different syndromes of early familial coronary disease. A preliminary estimate shows that approximately 50% of early coronary disease is associated with a strong family tendency. Cigarette smoking appears to be a prominent precipitator of very early coronary disease.

Honolulu Heart Study

The third study discussed was the Honolulu Heart Study. An epidemiological review was presented by Dr. Michael P. Stern. It was pointed out that the probability of CHD, as estimated by fitting a multiple logistic function, is only one-half as great in this population as in the Framingham group; and this is not
adequately explained by differences in known risk factors. He raised the important question of whether the residual differences are due to genetic or environmental factors. He noted that despite a major effort to implicate the environment, in particular the sociocultural and psychosocial environment, it has not been firmly established that these factors account for the difference. He suggested a genetic basis for the observed difference. In conclusion, he noted that sociocultural and psychosocial factors may account for the observed differences in the symptomatic expression of underlying coronary atherosclerosis.

In reviewing the genetic analyses, Dr. Brian K. Suarez noted that the Honolulu Heart Study dramatically increased our understanding of the etiology of many CHD risk factors and was also responsible for the evolution of the methods needed to analyze it. In discussing the effects of outliers on the outcome of segregation analysis (an approach to detect single-gene effects), he cautioned that whenever the evidence for a major gene comes from just a few outlying families, the prudent course is not simply to trim those families and repeat the analysis, but rather to study the outlying families intensively. He noted that a failure to correct for the complex method of ascertainment was a major shortcoming of path analysis, a method used for an evaluation of the relative importance of genetic and environmental factors. He suggested that since fathers were pretested to ascertain an enriched sample, they should have been retested later when their spouses and children were tested.

In leading the discussion on this study, Dr. Newton E. Morton agreed with Dr. Suarez's suggestion that it would be ideal to test all family members together. He pointed out that the causes of a residual difference between the Americans of Japanese ancestry and the Caucasian Americans could be addressed in a hybrid population, but noted that in the foreseeable future genetic epidemiology will not advance to the point where racial differences pose readily answerable questions. He concluded that, despite such limitations, the Honolulu Heart Study marked a turning point in genetic epidemiology.

In an adjoining discussion, Dr. Wick R. Williams compared the outcome of segregation analysis of cholesterol in three studies differing in their racial and cultural make-up: the Seattle Study, the Honolulu Heart Study, and a Norwegian study. He noted a remarkable similarity across studies, suggesting a major locus for cholesterol. The Norwegian study did not have information on triglycerides, but he presented the results of a Cincinnati study together with those of the other two studies for this variable; he noted consistent evidence across these studies against a major locus, with the exception that inclusion of one pedigree in the Seattle Study provided significant evidence of a major gene for hypertriglyceridemia. He acknowledged the conservative nature of these results.

**Cincinnati Lipid Research Center Study**

The Cincinnati Lipid Research Center Study was the last of the four studies addressed. In presenting his epidemiological review, Dr. Robert B. Wallace complimented the investigators for their refreshing innovation in data-base exploitation. He recommended that certain characteristics of the nonparticipants might be contrasted with those of the participants to evaluate possible sources of bias. He noted some methodological limitations that apply to this, as well as to other Lipid Research Center studies. In particular, he raised the possibility that subjects defined as having a particular hyperlipidemia with top decile lipid values may possess a variety of biologically heterogeneous lipid disorders, thus raising doubts about the advisability of generalizing such findings to the entire population.

Dr. Chin Sik Chung reviewed the genetic analyses. In reviewing familial correlations based on random as well as enriched samples, he noted the heterogeneity among the correlations based on different sampling methods. The exact method of sampling should not be ignored in estimating correlations based on enriched samples. (This was also pointed out by Drs. Ranajit Chakraborty and Craig L. Hanis later in the workshop.) It was noted that the phenotypic association between HDL\(_c\) and VLDL\(_c\) involved both familial and nonfamilial environments. On the other hand, the phenotypic association between LDL\(_c\) and VLDL\(_c\) appeared to involve both genetic and familial environmental factors. In conclusion, he recommended that segregation analyses also be undertaken to investigate the role of major genes.

In the leading discussion, Dr. Charles J. Glueck and coworkers clarified that basically three different approaches were used on the data set: 1) preliminary analysis based on dyslipoproteinemic probes; 2) within-family correlations, and 3) path analysis. Using the first approach, they obtained empirical CHD risk estimates. Their investigation of familial correlations led them to conclude that the magnitude of such correlations (except for HDL\(_c\)) appeared to outlast the period of shared household environment. Path analysis indicated significant genetic and cultural inheritance for each lipid-lipoprotein variable except for triglyceride. In conclusion, they noted that all Lipid Research Centers gathered insufficient data on environmental experiences such as smoking and alcohol intake.

**Methodology**

As is clear from the preceding section, there are many interesting family data sets pertinent to CHD research that have not been fully explored. To provide some potential opportunities for ongoing and upcoming studies, a wide spectrum of methodological approaches were reviewed in this section.
Measurement of Genetic and Environmental Causes

At the outset Dr. Ching Chun Li examined the theoretical underpinnings for any attempt to measure the relative contributions of genetic and environmental causes to the population variability of a quantitative trait. The problem that he discussed concerns how to apportion that part of the variability that, given the data available, could be due to either cause. Dr. Li showed that path analysis and the method of commonality lead to different solutions because of the different framework each uses to interpret the data, but that whichever framework is used the ratio of the direct effects of the two causes leads to the same measure of the relative importance of heredity and environment.

Maximum Likelihood Method

Drs. Michael Boehnke and Kenneth Lange then evaluated by means of simulation studies the maximum likelihood method of estimating the components of variance due to heredity and environment, paying special attention to the problem of how to correct for ascertainment and how to test the overall appropriateness of a proposed model. They found that the variance components were accurately estimated when pedigrees were randomly sampled, but were less accurate when sampled through probands and analyzed by their methods. Perhaps the most useful application of the goodness-of-fit tests they described is for spotting outlier pedigrees that may be segregating for rare dominant traits, and hence for choosing pedigrees to be included in a linkage study.

Path Model

In the next paper a path model for evaluating the relative importance of genetic and environmental factors in the etiology of coronary risk factors was described by Dr. D. C. Rao and his colleagues. The model was applied to HDL cholesterol data on nuclear families, and it assumes that for each member, an index of the relevant environmental variables affecting it is measured in addition to the trait of interest. They showed that the model is very robust against deviations from multivariate normality, and that it can be extended to describe temporal (i.e., developmental) changes in familial correlations. In an adjoining discussion, Drs. Ranajit Chakraborty and Craig L. Hanis cautioned that failure to correct for the ascertainment of nonrandom samples can lead to gross biases in the inference using any method of analysis. In particular, they discussed how estimates of familial correlations can be adjusted for the effects of nonrandom sampling.

Complex Models

If a risk factor has a large genetic component, it is of interest to determine if this can be largely due to the segregation of a single gene. This was the subject of a paper by Dr. Jean-Marc Lalouel, who described the principles and pitfalls of detecting major genes using complex models. Geneticists should carefully choose which phenotypes to study, should be ever aware of etiological heterogeneity, and should "recognize that, in attempting to provide simple answers to complex questions, we are only slowly inching toward a partial understanding of a mystery that will always elude us."

Segregation and Linkage Analysis Model

Dr. Newton E. Morton then described a model that can be used to investigate simultaneously in the presence of an additive, but independently acting modifier locus, the segregation of a major locus and its linkage and association relationships to a marker locus. This model is thus a synthesis of segregation and linkage analysis models, and should provide more reliable risk prediction. Currently linkage and association are seldom used to determine genetic risks for individual members of a family, but this will undoubtedly change in the future. In an adjoining discussion, Drs. G. Marc Lathrop and Jean-Marc Lalouel discussed multilocus problems in estimation of recombination, gene mapping, and calculation of recurrence risks. They briefly discussed their new computer program called LINKAGE to deal with multilocus systems.

Restriction Fragment Length Polymorphisms

Dr. Mark H. Skolnick and coworkers then discussed the impact of restriction fragment length polymorphisms (polymorphisms detected at the DNA level) on human gene mapping. After a detailed examination of the linkage information available in various pedigree structures, they concluded that it is realistic to assume that almost every reasonable linkage study will be successful in the future. Furthermore, we should have linked markers flanking both sides of the loci determining many important diseases. They also described the possibilities of multilocus methods of analysis, and pointed out that we must now develop efficiencies that were not required in the past in our approach to analytical problems.

Dr. Aravinda Chakravarti added a final touch to this topic by discussing some other practical issues: the extent of DNA variability, the use of multiple restriction fragment length polymorphisms in linkage analysis, and testing for heterogeneity in linkage.

Structured Exploratory Data Analysis

The next paper examined structured exploratory data analysis (SEDA), which has been proposed as a method for clarifying mechanisms of familial aggregation without making the restrictive assumptions usually made by other methods of analysis. Drs. Jean W. MacCluer and Candace M. Kammerer performed simulation studies to evaluate three SEDA...
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such as partitioned twin analyses and the twin family
design (twins, their spouses and children), promise
to resolve the relevant sources of genetic and en-
vironmental variation, and to determine whether cer-
tain disease associations are causal or just manifes-
tations of the disease-prone genotype.

Studies of Twins

Dr. Walter E. Nance reviewed the current state of
knowledge on the biology and epidemiology of twins
and the extent to which this unique relationship pro-
vides a powerful research paradigm for studies of
vascular disease. Their role in the presymptomatic
detection and management of the childhood
ancestors of heart disease is of paramount impor-
ance. Nonetheless, Dr. Nance cautioned that unless
it can be shown that the same genes that determine
risk-factor variation in adult life are also active in
childhood, a major rationale for presymptomatic risk
factor screening disappears. Newer approaches,
such as partitioned twin analyses and the twin family
design (twins, their spouses and children), promise
to resolve the relevant sources of genetic and envi-
ronmental variation, and to determine whether cer-
tain disease associations are causal or just manifes-
tations of the disease-prone genotype.

Sampling Considerations

Since the sampling unit can be as small as a pair of
relatives (e.g., twins) or as large as hundreds of peo-
ple in an extended pedigree, the issues surrounding
their ascertainment are crucial to scientific inference.
Drs. Robert C. Elston and George E. Bonney con-
cluded this session with an eloquent address of the
most fundamental sampling considerations: 1) the
unit of sampling; 2) how the units are sampled from
the population; and 3) the sample size. They pointed
out that certain biases arise when care is not taken to
match the appropriate study design with the specific
purpose of the study. This broad-based review cov-
ered sampling considerations when the investigator
intends to detect familial aggregation, to estimate
heritability, and to investigate linkage relationships.
Specific attention was paid to the problem of the
appropriate sample size required to attain adequate
power.

Phenotypes

Definitions of phenotypes and endpoints have
been evolving rapidly. Current and future studies can
and should take advantage of this progress, thus
coming closer to the gene product. This session was
devoted to a review of the state of the art. Any sum-
mary of the state-of-the-art papers on phenotypes
and their relation to coronary heart disease involves
focusing either on precursors or risk factors or on
specific diseases or endpoints. New methodological
issues emerge as our priorities change and meas-
urement devices improve. The first four presenta-
tions of the Phenotype Session dealt with estab-
lished or suspected precursors to end organ
damage, while the next two contributed a review of
two conditions that qualify as both risk factors and
endpoints: hypertension and diabetes mellitus.

Disorders of Lipid Transport

Dr. Gustav Schonfeld opened this session with an
interesting and highly informative description of the
disorders of lipid transport. He reviewed isolation
characteristics, chemical structures, and the molec-
ular defects that give rise to these disorders. He
pointed out that it is now possible to associate struc-
tural defects with specific loss of function for apoprote-
in, enzymes, and cellular receptors. In doing so, it
will be possible to categorize disorders of lipoprotein
metabolism by way of specific deletions or molecular
defects. A preliminary classification of this kind is
included in this review.

In an adjoining discussion, Drs. John D. Brunzell
and Arno G. Motulsky cited additional evidence sug-
gest that familial combined hyperlipidemia
(FCHL) may be a distinct entity. They distinguished
FCHL from pure familial hypertriglyceridemia, and
 speculated that the population prevalence of FCHL
is at least one percent.

Noninvasive Cardiology

The next presentation summarized the state of the
art in noninvasive cardiology. Dr. Daniel Savage and
coworkers described such procedures as M-mode
and two-dimensional echocardiography, phonocardio-
diography, and ambulatory ECG monitoring devices.
Together, these tools have revolutionized the field
of cardiology allowing the detection of many cardiac
irregularities. Mitral valve prolapse and hypertrophic
cardiomyopathy were specifically highlighted be-
because they tend to cluster in families. They reviewed
the application of echocardiography methods to data
on subjects participating in the Framingham Heart
Study.

Hypertension

Although the field of genetic epidemiology is
young, a few diseases exemplify the complex nature
of the merger between the genetic, epidemiological, and clinical approaches. Hypertension and diabetes mellitus can be considered such models. Current strategies for disentangling the genetic and environmental contributions to the expression of hypertension were thoroughly reviewed by Dr. Roger Williams and coworkers. In addition to summarizing the evidence that increased weight, stress levels, and intake of saturated fats may contribute to this disease, they discussed the merits of new tests, such as membrane cation flux tests for evaluation of sodium, potassium and calcium levels. They described their family history score method and encouraged conference participants to consider adopting such quantitative methods for their own pedigree studies. Dr. Williams stressed that a combination of assessment methods, using biochemical as well as blood pressure techniques on accurately assembled family data, are requisites to sorting out genetic heterogeneity and identifying high risk individuals.

**Diabetes Mellitus**

Diabetes mellitus has for decades been considered an important risk factor for cardiovascular disease. An examination of the relation of genetics to the vascular complications of this disease was the purpose, in part, of the paper delivered by Dr. Jerome F. Rotter and coworkers. They began with an in-depth review of the specific HLA associations with insulin-dependent diabetes mellitus (IDDM) and a description of the complex etiological challenges posed by the heterogeneity found. They then explained the features of a heterogeneity model for IDDM. This model postulates a single locus linked to the HLA gene complex with two distinct susceptibility alleles for IDDM and a normal allele. This particular model better accounts for the heterogeneity of disease forms, the population prevalence data, and the HLA sib pair haplotype data. In addition, it reduces the need to invoke a variety of conditions, such as differential penetrance and complex modes of inheritance, to explain heterogeneous data. Other models, such as one involving up to three independent loci, were also introduced as potentially able to explain even more variation in the data.

Concerning the genetics of noninsulin-dependent diabetes mellitus (NIDDM), they summarized the exciting advances in molecular hybridization studies. Restriction fragment length polymorphisms of the 5' flanking region of the insulin gene are significantly more prevalent in patients with NIDDM than controls. These techniques contributed to localizing the insulin gene on the short arm of chromosome 11, and will further elucidate the characteristics of the neighboring regions, as well as serve as a marker for NIDDM.

In the discussion that followed, Dr. Ronald T. Acton and coworkers discussed a case-control study conducted in Georgia that was concerned with the association of genes at the major histocompatibility complex (MHC) with ischemic heart disease (IHD). The results indicate that loci within the MHC region of chromosome 6 may be involved in the natural history of early onset IHD.

**Role of Psychosocial Behavior**

The next paper discussed the interesting, yet at times controversial, role of psychosocial behavior on the subsequent development of CHD. Dr. Elaine D. Eaker argued that certain behavioral phenotypes, which have been associated with the risk of developing coronary heart disease, are essentially stable personality traits. These characteristics derive, to varying extents, from an individual's set of experiences as well as from genetic constitution. Such phenomena as Type A or B behavior, internal or external locus of control, and reactions of anger, describe psychometric tools currently in use to measure the behavioral risk factors for CHD. Dr. Eaker reviewed several major epidemiological studies that demonstrate the relation between these indicators and coronary disease. In addition, she highlighted several recent studies concerned with the extent and nature of the familial aggregation of these behavioral phenotypes in twins, sibs, and families. Dr. Eaker concluded that there is little evidence for a strong genetic component in the population variation of these traits.

**Chronic Obstructive Pulmonary Disease**

The session on Phenotypes ended with a stimulating report of a disease related to CHD through common risk factors. Dr. Harold A. Menkes and coworkers indicated advanced age, being male, smoking, increased coffee and diet soda intake, low socioeconomic class, and certain genetic markers as significant precursors to the development of chronic obstructive pulmonary disease (COPD). As in CHD, these factors in combination increase the risk of accelerated loss of vital organ function. Interactions between these variables cloud the issue somewhat. For instance, from analyses of cross-sectional data it appeared that some of the important risk factors, such as familial pulmonary disease and coffee intake, are statistically significant factors in smokers, but not in nonsmokers. Longitudinal studies indicate that despite significance, the entire group of COPD risk variables accounts for a relatively small amount in the decline in lung function (17% in females and 12% in males).

**Guidelines for Future Research**

The final session consisted of presentations by four scientists on possible guidelines for future research in coronary heart disease. The participants included Drs. Glueck, Kuller, Elston, and Motulsky.

Dr. Charles J. Glueck argued that the future research should emphasize apolipoproteins, dysapoproteinemia, and dyslipoproteinemia. He stressed
the need for family studies to assess the relative importance of genetic and environmental factors in the etiology of the major apolipoproteins, especially A-1, B, E, the E isoforms, C-II, and LDL apo B. He argued that heterogeneity of LDL and apo E are important areas deserving attention in future studies.

The next speaker, Dr. Lewis H. Kuller, outlined several major strategies for future studies. First, he emphasized that the identification of the biochemical abnormality is of utmost importance, whether it be a specific apoprotein or genetic marker and he called for strict standardization of laboratory methods for this purpose. Second, he noted that a better understanding of genetic and environmental interactions is required if risk is to be truly understood at the population level. Finally, Dr. Kuller stressed the importance of more adequately measuring the environment and cited some intriguing examples of how this could be done using a quasiclinical trial approach.

During the discussion, Dr. Kåre Berg mentioned that in addition to these new approaches it is now possible to test the 'nature' of the effect of certain genetic markers on variability induced by the environment. For instance, he cited the apparently restrictive effect of the M blood group on cholesterol levels artificially altered by diet. This new method is designed to detect marker gene effects on the variability of any quantitative trait.

Dr. Robert C. Elston addressed future trends in genetic analysis methodology and focused deliberately on the merits of linkage analysis as being "much more effective than segregation analysis for the detection of monogenic segregation." Since it is often necessary when performing segregation analysis to transform skewed data to better represent a normal distribution, and since this practice reduces the method's power to detect an existing gene, Dr. Elston recommended linkage analysis as a safer method. With the advent and growth of restriction fragment length polymorphisms as tools, it is conceivable, in his view, that markers will be available every 10 to 20 centimorgans on each chromosome, allowing progressive mapping of the human genome. He stressed that future studies concerned with the detection of major genes might benefit from linkage methods now that new molecular techniques are available.

In defense of newer segregation analysis methods, Dr. Jean-Marc Lalouel pointed out that further safeguards against false inference of a major gene have been incorporated in the mixed model analysis, (i.e., a test for no transmission of major effect). Both discussants agreed, nonetheless, that with the increased identification of DNA markers, linkage analysis by the family method will become much more useful.

The final presentation at the workshop provided a rousing testimony to the advances made in coronary heart disease research over the past decade. Dr. Arno G. Motulsky summarized the content and the spirit of the papers delivered at this conference. In doing so, he chronicled such major developments as the identification of receptor activity defects resulting from specific gene mutations and causing significant elevations of LDL-cholesterol, the use of bile sequestrants in the therapeutic reduction of cholesterol levels in familial hypercholesterolemics, and the potential elucidation of basic molecular defects associated with specific coronary risk factors through the use of DNA polymorphisms. Dr. Motulsky identified certain unanswered questions and warned that the known genetic risk factors only account for a portion of the variance. Undefined familial factors, assortative mating for lifestyle variables, and genetic-environmental interactions are but a few of the phenomena that seem to resist investigation. These areas and studies in molecular genetics of apolipoprotein and receptor variability were highlighted as being potentially most promising for the near future. Methodological issues will continue to be debated, but as Dr. Motulsky pointed out, "the methodology of genetic epidemiology will be most effective when combined with specific biologic approaches." Perhaps this advice best epitomizes the need for an interdisciplinary approach, combining the talents of the geneticist, the epidemiologist, and the clinician, towards a mutual goal: prevention of coronary heart disease.

Index Terms: epidemiology • coronary heart disease • genetics • familial disease • phenotypes • Tecumseh Community Health Study • Framingham Heart Study • Honolulu Heart Study • Cincinnati Lipid Research Center Study • twins • lipid transport • diabetes mellitus • psychosocial behavior • pulmonary disease
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