Atherosclerosis and Coronary Heart Disease

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Under the general editorship of
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ATHEROSCLEROSIS AND CORONARY HEART DISEASE

THE TWENTY-FOURTH HAHNEMANN SYMPOSIUM

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GRUNE & STRATTON, *New York and London*

Library of Congress Cataloging in Publication Data
Main entry under title:

Atherosclerosis and coronary heart disease.

Includes bibliographical references.
1. Arteriosclerosis—Congresses. 2. Coronary heart disease—Congresses. I. Likoff, William, ed.
II. Segal, Bernard L., ed. III. Insull, William, Jr., ed.
IV. Hahnemann Medical College and Hospital of Philadelphia.
RC692.A728 616.1'36 72-4226
ISBN 0-8089-0764-6

Grune & Stratton, Inc.
111 Fifth Avenue
New York, New York 10003

Library of Congress Catalog Card Number 72-4226
International Standard Book Number 0-8089-0764-6
Printed in the United States of America

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Preface

A full decade has passed since publication of the Seventh Hahnemann Symposium, which dealt with coronary heart disease. At that time this disease was recognized as the primary health problem of western civilization, with disability and death rates exceeding those of any other illness. Furthermore, there appeared to be no immediate likelihood of relief, because we lacked some knowledge concerning almost every facet of the problem, most particularly fundamentals such as pathogenesis of atherosclerosis, determinants of coronary blood flow and principles of myocardial metabolism.

The symposium did not offer a formal opportunity to explore future developments. Nevertheless, implicit in a number of presentations were predictions that the electron microscope would provide critical insight into the genesis of atherosclerosis and the mechanism of arterial lipid accumulation; coronary arteriography would be of inestimable aid in correlating pathology with functional disability, improving diagnostic acumen and clarifying the effectiveness of medical and surgical programs; new enzymes would be discovered, which would improve accuracy in diagnosing myocardial infarction; new drugs would improve coronary flow, increase myocardial oxygen uptake and control life-threatening arrhythmias; and more dependable, safer surgical techniques would be perfected to enrich the myocardium with new blood supply.

Over the years, so much less and so much more than was foreseen has been accomplished. To begin with, time has revealed little more about the genesis and nature of atherosclerosis. We continue to work with partial knowledge and to be provisionally content with probabilities. The lipid metabolic and platelet conglutination theories are locked in context, and there is scant reason to favor one above the other or to consider a different concept more favorably.

Elements of chance rather than precise law still appear to govern the correlation between arterial pathologic disease, the extent of myocardial damage, and clinical manifestations of coronary heart disease.

Basic mechanisms of myocardial metabolism remain obscure and leave a number of problems with differing prognostic and therapeutic implications unsolved.

Generations of drugs have appeared without providing prophylactic or therapeutic mastery over the frequency and intensity of angina pectoris. Amine oxidase inhibitors have quietly disappeared from the treatment shelf. The question of using anticoagulants remains moot after interminable trial and review.

Nonetheless, all deficiencies having been considered, there has been unmistakable progress. Much of it is recorded in this volume, the Twenty-Fourth Hahnemann Symposium.

Although our knowledge of certain basic issues such as the cause of atherosclerosis remains incomplete, probably imprecise, beclouded by equivocal evidence, it has become refreshingly meaningful in other fundamental areas. There are no better examples than in myocardial kinetics and the anatomy and pathology of the conduction system.

The past decade, however, has witnessed greater strides in more pragmatic matters. The multitude of doubts that assailed almost every investigator during

early clinical application of coronary arteriography has now vanished. It is clear that this technique is reasonably safe and accurate, and that it has upgraded the diagnosis of coronary artery disease immeasurably; coincidentally, it has offered evidence that myocardial ischemia and infarction may occur when coronary vessels appear normally patent. Arteriography has made surgery for obstructive coronary artery disease feasible, serving not only to guide the surgeon in his enterprise but, subsequently, to appraise what actually has been accomplished. How much the knowledge of coronary heart disease eventually will be broadened by coronary arteriography cannot be foretold, but judging from present contributions, the technique should exceed its predicted usefulness a thousandfold.

Patients with acute myocardial infarction almost universally are treated in coronary care units. The theory supporting this practical, effective system of care was hardly implemented in the early years of the past decade. Yet today, the physician/nurse team approach and constant surveillance with electronic monitoring have reduced the mortality rate from acute infarction by 50 per cent, mainly through prevention and early treatment of arrhythmias. This innovation, quite beyond prediction, grew out of its time, a product of past observations and knowledge, new ideas and technology.

This symposium volume contains suggestions for the immediate care of individuals suspected of having acute infarctions. These guidelines parallel practical recommendations contained in the 1971 report of the Inter-Society Commission for Heart Disease Resources and in an editorial (Circulation 44:979, 1971) titled "A Stratified System of Coronary Care." If put into common practice, these recommendations will denote as crucial a departure from the customary treatment of prehospital patients as coronary care units denote in the treatment of hospitalized patients.

There are even more comforting reflections. The capacity for controlling arrhythmias and conduction defects is encouraging. Beta-adrenergic blocking agents have awakened the promise of controlling angina pectoris. Direct surgical techniques are available to bypass coronary arterial obstructions and to correct important structural defects after infarction.

Nevertheless, no matter how many difficulties are surmounted, how many goals are realized, what progress has been made, we are still appalled by the rising incidence of coronary heart disease, its inexorable progression in those afflicted, and the shocking morbidity-mortality rates. It is these problems that dictate the nature of future pursuits.

The faculty of this symposium has outlined the boundaries of our understanding with candor. In the decade since the preceding publication, a great deal has been accomplished, but it is minuscule compared to what remains to be achieved.

We are deeply grateful to the contributors and the faculty; to Frederick K. Heath, M.D., Executive Director and Associate Dean, School of Continuing Education; to Mrs. Sage Cordell, Assistant Director of Administration, School of Continuing Education; and to Mrs. Edith Schwager, Editor, School of Continuing Education, without whom this text would not have been possible.

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Hereditary Aspects of Coronary Atherosclerosis

By COLIN M. BLOOR, M.D.

IT IS GENERALLY ACCEPTED that coronary atherosclerosis is a multifaceted disease in which heredity plays an important role. Supporting evidence for this view comprises the demonstrations of familial aggregation for coronary artery disease.[1-5] In these family studies, the usual approach is to compare the frequency of the disorder in the family of probands with that in the family of control subjects similar with respect to age, sex, race and socioeconomic status. Thus, in the studies of Gertler and White,[1] coronary artery disease is twice as frequent a cause of death in the fathers of patients as in the fathers of control subjects. The percentage of patients' sibs dying of coronary disease was nine-fold that observed in sibs of controls. When Russek and Zohman[2] surveyed for a history of cardiovascular disease, the frequency of a positive history was 67 per cent in one or both parents of patients as compared with 40 per cent among the control subjects.

In Thomas and Cohen's study,[3] it was shown that when both grandparents had coronary artery disease, 21 per cent of their sons were similarly affected, whereas, when neither grandparent had the disease, only 4 per cent of the sons were reported to have the same condition. In matings between one affected and one unaffected grandparent, the frequency of coronary heart disease among their sons was 8.2 per cent. The daughters of grandparents showed a similar but less steep trend. When the subjects' fathers were affected, the brothers of the subjects showed a frequency of coronary disease (15.8 per cent) four times greater than was the case when the fathers were free from coronary disease. Coronary disease is also more frequent among the sisters of affected fathers. Deutscher and coworkers[5] reported that fatal coronary heart disease was commonest when parental death from coronary heart disease occurred before 65 years of age. Nonfatal coronary heart disease was more common when parental death from coronary heart disease occurred after 65 years of age than when it occurred prior to this age. Thus, they concluded that familial factors play an important role in the development of premature coronary heart disease.

The aforementioned family studies focusing on clinical coronary artery disease do indicate a familial aggregation of these cases. However, what is at issue is not whether aggregation occurs in families, but how it is to be interpreted. Familial aggregation may also be well explained by dietary, smoking or other habits common to members of the family, communicated rather than inherited. It is unlikely that this impasse will be resolved by the accumulation of further data unless they are accompanied by the development of means of extracting more pertinent information from them. A study by Deutscher and his colleagues[6] attempted this by comparing the degrees of familial aggregation by age. An appreciable degree of resemblance was found among siblings below the age of 16, who may be presumed to share the same environment to a great extent. Aggregation was less marked for siblings between the ages of 16 and 40, a time when less of the same environment is shared, but it rose again after age 40. It is postulated that the observed rise after age 40 is due to an

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increase in the penetrance of the gene or genes involved, at middle age and beyond. This fascinating postulate will be elaborated on later. In addition, this pattern of aggregation suggests that environmental factors, e.g. levels of serum cholesterol, blood glucose and blood pressure, may play a stronger role prior to middle age.

The only technique available for determining to what extent familial aggregation is genetic is comparison of the concordance rate of monozygotic twins with that of like-sex dizygotic twins. The results of several studies of twins are consistent with the hypothesis of a significant genetic factor. Verschuer[7] found a concordance rate of 19 per cent for "coronary sclerosis" among 21 pairs of monozygotic twins, whereas in 47 pairs of dizygotic twins the rate was 8.5 per cent. Benedict[8] reported a pair of identical twin females in whom coronary insufficiency developed at about the same age although their blood pressures, serum lipids, and cholesterols were well within normal limits. Harvald and Hauge,[9] in contrast, showed the concordance rate for deaths from coronary occlusion among 82 pairs over 60 years of age to be the same for monozygotic twins and dizygotic twins, whether of the same or opposite sex. Although Harvald and Hauge suggest that genetic factors play only a minor role in the genesis of coronary arteriosclerosis, the remainder of these studies support the view that coronary artery disease tends to aggregate among blood relatives. In another study of coronary heart disease in twins, Liljefors and Rahe[10] used a novel approach. Thirty-two pairs of Swedish monozygotic male twins (42 to 67 years old), who were discordant for coronary heart disease, were analyzed for variability in psychosocial patterns of subjects. The life dissatisfaction category provided the highest (significant) correlation with severity of coronary heart disease. Since there is a tendency to fatalism where genetics is involved, this study[10] should serve as a reminder that heredity is not the sole factor contributing to coronary atherosclerosis.

Assuming that there is a significant genetic contribution to this familial aggregation for coronary atherosclerosis, the question arises as to what the mechanisms are by which the genetically determined susceptibility to coronary artery disease operates. Of the many mechanisms incriminated in the pathogenesis of coronary artery disease, hypercholesterolemia and hypertension have been studied most extensively as to genetic control. Other factors that seem to be related to coronary artery disease, i.e. diabetes mellitus, coronary artery anatomy, obesity and hyperuricemia, may also be possible mechanisms, since they have a partly genetic background.

Although several investigators[11-13] have suggested that idiopathic hypercholesterolemia is subject to unifactorial inheritance of the autosomal dominant type, the findings of others[14-16] support the view that serum cholesterol levels are determined over the whole range of distribution by multiple genetic and environmental factors. Analysis of the evidence concerning blood pressure supports the view that it is subject to multifactorial genetic determination.[15,17-20] Thus, since two factors known to aggravate coronary atherosclerosis are in part genetically determined, the role of heredity in coronary artery disease is accentuated.

The initial studies of Schlesinger[21] suggested that differences in the anatomical pattern of the coronary arterial tree may be genetically determined and that in turn, such differences may account for an increased vulnerability to the effects of atherosclerosis. Indirect evidence for the genetic determination of coronary artery patterns included the variation of intercoronary anastomoses in animals[22] and man[23,24] and their differing extent in different races of man.[19,25] Pepler and Myer's demonstration[26] of coronary anatomical differences between the hearts of Bantu and Euro-

peans, and the report by Sidd and coworkers[27] of similar coronary angiograms in monozygotic twins are highly suggestive of a genetic basis for structural differences in coronary anatomy.

Bloor et al.[28] explored this thesis further by demonstrating four basic coronary artery patterns in unrelated, isolated populations of rats. A significant difference in the frequency distribution of the four coronary artery patterns was present among the three unrelated strains. The inheritance was not sex-linked since the frequencies of these coronary patterns within each strain were similar for both sexes. Two of the unrelated strains were cross-mated to produce F_1 and F_2 generations. The observed frequencies of the coronary patterns in these breeding experiments differed from those expected if classic Mendelian segregation involving single pairs of genes exhibiting dominance and recessiveness had been involved. All these findings indicated that polygenetic determination was the most likely mode of inheritance.

Quantitative genetic analysis was undertaken to define further the relative importance of genetic and environmental factors in coronary artery inheritance.[29] These studies confirmed the polygenic determinism of coronary artery inheritance. Estimates of the influence of genetic components indicated that 17 to 25 per cent of the phenotypic variance is attributable to genetic factors. The relative importance of environmental factors in determining coronary artery patterns was derived from a partitioning of variance based on the product/moment correlation among relatives (Table 1). It was concluded that special (transient) maternal environmental factors are the most important in determining coronary pattern variability.

TABLE 1.—*Partition of Variance Based on Correlation Among Relatives*

		Observed covariance				
Coronary artery	*Relationship*	*Maternal genotype*	*General maternal environment*	*Fetal genotype*	*Special maternal environment*	*Total*
Right	Full sibs	0.310	0.002	0.096	0	0.408
	Children of sisters	0.155	0	0.024	0	0.179
	Other first cousins	0	0	0.024	0	0.024
	Observed variance	0.310	0.002	0.192	0.496	1.000
Left	Full sibs	0.018	0.125	0.116	0	0.349
	Children of sisters	0.054	0	0.029	0	0.083
	Other first cousins	0	0	0.029	0	0.029
	Observed variance	0.108	0.125	0.232	0.535	1.000

From data of Leon and Bloor,[29] with permission.

In view of this precise delineation of the formal genetics involved in coronary anatomy heritability, further exploration of the precise mechanisms by which these different anatomical patterns predispose to atherogenesis seems promising. One such study by Vlodaver and coworkers[30] showed that Ashkenazic Jews in Israel, who have a higher prevalence of coronary artery disease than Yemenite Jews and Bedouins in Israel, have greater development of the intima and musculo-elastic layers of their coronary arteries than the other two ethnic groups. The rich concentration of collagen in the intima may enhance the rate of cholesterol synthesis and

thus contribute to the high incidence of coronary atherosclerosis in the adult population. In an experimental approach, selectively bred animals from two unrelated strains and their F_1 hybrid generation have been subjected to atherogenic diets.[31] When the severity of coronary artery disease was quantitated (coronary atherosclerosis index), definite differences appeared between the parental strains (Table 2). Even more striking were the findings in the F_1 hybrid generation. On a butter-fat diet, the severity of coronary artery disease was similar to that observed in one of the parental strains. In contrast, on the peanut-oil/butter-fat diet, the severity of coronary atherosclerosis was markedly elevated over both parental strains. Thus, further investigation should consider the possibilities that (1) the same sets of genes (polygenes) determining coronary artery anatomical patterns may be involved in susceptibility to myocardial infarction, hypertension or hypercholesterolemia; and (2) the polygenes involved in coronary artery inheritance may be unrelated to those involved in hypercholesterolemia and hypertension.

TABLE 2.—*Coronary Atherosclerosis Index in the Parental (WR and NNMC) and F_1 Hybrid Generations Subjected to Atherogenic Diets*

	Coronary atherosclerosis index (mean ± SEM)	
Generation	*Peanut oil + butter-fat diet*	*Butter-fat diet*
WR	1.87 ± 0.17	1.99 ± 0.12
F_1	2.82 ± 0.23	1.59 ± 0.22
NNMC	1.66 ± 0.15	1.52 ± 0.20

From Bloor,[31] by permission of the American Heart Association, Inc.

Since the various factors involved in the genesis of coronary atherosclerosis have been shown to be subject to polygenic determinism, it is unlikely that the occurrence of coronary artery disease in man will conform to some Mendelian pattern. Since the demonstration of such a pattern in the genetics of coronary artery disease is the ultimate goal, one should continue to strive for its attainment and be cognizant of the three major problems to be solved, as outlined by Murphy.[32] These, to be considered briefly, are: (1) age-dependence in the clinical manifestations of the disease and the interaction of ascertainment bias with it; (2) misclassification and the means by which it is to be minimized, especially where diagnosis depends on measurements of several different variables; and (3) testing of genetic hypotheses, with due allowance for the foregoing effects.

In some disorders, penetrance, i.e. manifestations of the abnormal gene, may not be accidental but may, like Huntington's chorea, be relentlessly age-dependent. It is conceivable that it is merely a matter of time before any person with the "right" genetic constitution would have manifest occlusive coronary artery disease, with myocardial infarction. The question at once arises as to why the onset of the disease should be delayed and why it should not occur at a uniform rate. Two mechanisms are apparent: (1) The speed of development of the disease varies, which might account for the importance of the risk factors. Alternatively, the crucial factors may be the configuration of the coronary vessels. The consequence of this mechanism, and one which could easily be tested, would be that not only should there be familial aggregation of coronary artery disease, but also the age at onset should show a correlation within families. It is interesting that Douglas[33] comments on the similarity