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Symposium on Coronary Heart Disease

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Edited by
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Foreword

The insistence with which coronary heart disease in all its varied manifestations confronts the physician and the rapid advances in our understanding of widely different aspects of the problem suggested the desirability of the following symposium at this time. Except in the brain and kidney, changes in the arteries nowhere else impose such profound effects on the organ involved and on the body as a whole.

The problem of disease poses different problems in different epochs. At the turn of the century, William Osler remarked that syphilis was "The only disease necessary to know. One then becomes an expert dermatologist, an expert laryngologist, an expert alienist, an expert oculist, an expert internist, and expert diagnostician." As this symposium demonstrates seven decades later, we may paraphrase Osler's pronouncement more properly in terms of atherosclerosis as the only disease it is necessary to know. One then becomes an expert geneticist, an expert anthropologist, an expert pathologist, an expert physiologist, an expert biochemist, an expert hematologist, an expert endocrinologist, an expert nutritionist, an expert internist and, hopefully, an expert judge of conflicting opinions.

I believe all of us have been impressed and perhaps even discouraged by this complexity of the many biological mechanisms involved in atherosclerosis. But this very complexity is not only a challenge; it is one of the most encouraging features of atherosclerosis. For the many elements that go to make up an atherosclerotic area also make the process more vulnerable. There are many mechanisms in the long chain of events, any one of which if interrupted may prevent or ameliorate the lesion and its consequences.

The authors of the various chapters represent a wide range of disciplines. The broad approach to atherosclerosis has yielded a rich harvest and new insights. It is surely the earnest wish of the contributors that their painstaking efforts in portraying the salient outlines of the diverse aspects of atherosclerosis will facilitate application of our present knowledge and identify more clearly the significant problems urgently awaiting solution.

Herrman L. Blumgart, M.D.

The Importance of Heredity in Coronary Heart Disease

By PAUL D. WHITE, M.D.

THE VITAL but neglected subject of the place of heredity in the background of coronary heart disease needs to be brought into the limelight to share at least on even terms in research with the sum of the possible environmental factors now being studied. Incidentally this is true of many other of the diseases of mankind in which the individual or host seems to have been lost in the preoccupation with the disease process. Practicing physicians not much given to intensive or extensive scientific research have had a long experience with so-called hereditary predisposition but either they must take up the subject more actively themselves or a new generation of human geneticists must be trained to help them; probably both these developments are needed.

One brief statement should be made in distinguishing between congenital and hereditary heart disease. The former may be hereditary or it may be the result of an acquired disease during fetal life.

There has recently been published a little book entitled *The Chemistry of Heredity* by Professor Stephen Zamenhof of Columbia University dedicated "to the enlightened programs of research grants in our country whose support made possible most of the recent discoveries in the field of the chemistry of heredity." Among the hereditary defects in man he cites alphabetically a list of 18 abnormalities beginning with albinism, which is due to failure to manufacture melanin, and ending with Wilson's disease, which is due to defective copper metabolism. In the middle of this alphabetical list is hypercholesteremia, simply stated as elevated blood cholesterol, still quite obscure as an inherited chemical defect but clinically well recognized as often related to coronary heart disease. He writes further as follows:

In all the above considerations we have referred to the "failure of the enzyme" or "lack of enzyme." However, the lack of enzyme does not necessarily mean that the molecule of the enzyme (or of the protein in general) is missing altogether; it may often mean that it is defective, i.e. changed so as to be partially or totally inactive. Just how much has to be changed to cause inactivation? What is the smallest change in the protein which the mutation has to produce to make itself drastically felt?

One example of the answer to these questions has been provided by a study of a hereditary disease called sickle cell anemia. This disease, caused by a single mutant gene, is characterized by the presence of defective erythrocytes which are in the form of sickles. The defect was traced to defective hemoglobin and the problem was to determine what is the chemical nature of the difference between this defective and the normal hemoglobin.

Pauling and his colleagues subjected the two kinds of hemoglobin to electrophoresis and found that the two have different electric charges. This behavior suggested some difference in the amino-acid composition. But how many were different? And which ones? A molecule of hemoglobin has some 600 amino acids of 190 different kinds, and the problem might have appeared hopeless. It was solved eight years later by Ingram who broke the molecule in half, and then into 29 smaller fragments (peptides). When such fragments from normal hemoglobin were compared with the corresponding fragments from the defective hemoglobin, all were identical, *except one*. And in this fragment, all amino acids were identical, *except one*. Thus, the disease was caused by a change of one amino acid in 300 (glutamic acid replaced by valine). This was all the mutation had to do to

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make itself seriously felt. One is tempted to speculate that the corresponding change in the hereditary determinant (DNA molecule) was just as small; perhaps it was a change in a single nucleotide.

All this is a mere beginning. But the beginning has been made. And one is inclined to agree with Albert Einstein that the most incomprehensible thing about nature is that it is . . . comprehensible.

An apology to the reader. For the book being so long, yet failing to offer real answers to many formulated queries. The writer's excuse is that the subject is but an infant; if we have become able to ask nature embarrassing questions, it is already a crack in the wall. And an apology for the book being so short. The discussion of many hereditary diseases and of the cancer field has been omitted, partially because these subjects belong to special treatises, and partially because their connection with the chemistry of heredity is merely the object of future study.

A few months ago in Mexico City Dr. Irvine Page referred to this very point and suggested the eventual possibility of correcting the inherited defect and supplying the missing enzyme, which would mean a much more hopeful future for those who had not selected the most healthy ancestors. Just think what this may mean not only in our struggle against cardiovascular disease but in almost the entire range of the hazards to our health and to our very lives.

The practical aspects of heredity and coronary heart disease are, of course, a very different matter and they are beginning to be recognized. We practitioners know from experience the importance of heredity.

Thomas and Cohen found in their study that coronary heart disease was nearly four times more frequent among the siblings of individuals with coronary heart disease than among the siblings of persons not so affected. Thomas has studied in general the combined conditions of hypertension and coronary heart disease in a long-term follow-up of Johns Hopkins medical students with particular reference to the health of grandparents, parents, aunts, and uncles. She wrote,

In our analysis of the combined occurrence of hypertension and coronary heart disease in these two successive generations, the proportion of affected offspring was greatest where both parents suffered from some form of these disorders, and least where neither parent was affected. According to whether both, one, or neither of the parents was affected, the incidence in the offspring was 22%, 12%, and 8% respectively. Thus, 2.7 times as many offspring of two positive parents were affected by hypertension or coronary disease as were the offspring of two negative parents. The rate for those with one positive parent was intermediate (1.5:1).

Also coronary heart disease was much more common among the fathers of the students with, than among those without, hypercholesteremia by more than twice in the case of the students over 22 years of age.

Russek in a recent paper comparing 100 patients with coronary heart disease with a comparable 100 patients with other diseases found heredity as a possible factor in a ratio of 1.7 to 1. In his study he attributed greater influence to stress 4.6 to 1 and high-fat diet 2.7 to 1.

In a paper of my own entitled Genes, The Heart, and Destiny, published two years ago in the *New England Journal of Medicine*, I wrote as follows:

A few years ago in a study of our own of coronary heart disease among 100 young adults (under the age of forty years) compared with 146 controls, it was found that 37 per cent of the fathers in the coronary group died from coronary heart disease as compared with 18.5 per cent in the control group (of 62 dead fathers of the coronary group, 23 had succumbed to coronary heart disease in contrast to only 14 out of 76 among the controls). Five out of 58 dead siblings of the coronary group died of coronary heart disease (8.6 per cent) in contrast to but 1 (1.0 per cent) among 98 siblings in the control group. We included only 1 case of recognized familial xanthomatosis or hypercholesterolemia in this series. Eighteen of the patients with coronary heart disease had serum cholesterol levels of more than 330 mg. per 10 ml. (one was as high as 509 mg.) as compared with five of the matched controls. It is, of course, well known that in familial hypercholesterolemia and xanthomatosis coronary heart disease is common.

In every study of coronary heart disease in youth and middle age the male sex is represented in high preponderance—for example, in our series referred to above, in the ratio of 24 to 1 under the age of forty years, though with much lowered ratio in the next two or three decades. The sex factor is much more significant than he-

redity, however. Two other characteristics often noted, which are inherited, are a highly mesomorphic (broad muscular) build and a psychologic and physiologic drive; these are probably but manifestations of the candidate rather than causative factors as may well be a tendency, that seems to be commonly found, to excesses in many habits that may be aggravating rather than basic factors, such as excesses in eating, smoking, and the use of alcoholic liquor.

It seems very probable that in the present almost frantic search, which, I might add, is highly important and should go on, to establish a safe program of life for the protection of our citizens from the present devastating epidemic of coronary thrombosis, we should not expect to find one program equally suited to all. It is a very complicated business, for we are dealing with the intricacies of diet, of stress and strain, of physical and mental effects, of climate, of infections, and of personal habits in addition to all manner of humankind, but the main point I want to make is that we must recognize our duty in the study of the host as well as in that of the agent (or environment), just as we would do in an infectious epidemic. Doubtless, there are general measures of positive health that are good for everyone and certain dangers that are bad and should be avoided, and these are at least in part already evident but the details of both host and agent are still to be added. We can supply, much more than we are doing now, the important ancestral and immediate family history in every case; this is bound to be helpful at the very start.

Although this is a truism recognized by every practicing physician it is astonishing how little attention is paid to it when we obtain and record the history of the individual patient. Often, though by no means always, we are in the habit of noting the age at and the cause of death, or the current state of health of parents and siblings, but rarely is this information noted for the grandparents or other relatives, despite its importance. To be sure, such information is at times unobtainable, but even when it is obtainable it is not often recorded.

Here, I would enter a plea to the public at large. In the first place a family genealogic record or tree would be very helpful for the doctor; it has much more than sentimental value, for it helps to determine the health hazards for descendants for generations to come. We physicians should spread the importance of this far and wide. A second valuable aid concerning the future health of any family is the information to be derived from postmortem examinations; the natural emotional reaction of the family at the time of death should not obscure the importance of these examinations after death. Even as far back as 1706, over two hundred and fifty years ago, the Church, in the person of Pope Clement XI, urged the carrying out of autopsies to obtain invaluable information; this was done by his physician, Giovanni Maria Lancisi, and churchmen and scientists alike still strongly recommend to the public that such examinations be done.

For the sake of argument let us suppose that on the average, heredity and environment are equally responsible for both the maintenance of health, the induction of disease, and the length of life in mankind as a whole but with very variable influences in any given person.

However, this ratio of the relative importance of heredity and environment in the acquisition of coronary heart disease is a pure and simple guess. We should make every effort to determine the true ratio. Quite likely it varies very much in different individuals but in any case heredity is of great importance and its influence must not be neglected in the appraisal of any individual whether only a candidate or actually a patient.

Before concluding I would like to mention one other point or factor that may eventually prove to be of much greater significance than we may now realize and that has been almost not at all investigated. That is the actual anatomic configuration of the coronary arterial tree and network, which very probably is in part at least a familial inheritance. A study of this possibility is greatly needed. As an example of this let me cite the case of a patient of mine who died suddenly less than a fortnight ago during moderate physical exertion. He had suffered myocardial infarction of moderate degree a few years ago but had had a good recovery except for some residual cardiac hypertrophy and a slight limitation of myocardial reserve. Autopsy revealed acute pulmonary edema, no fresh coronary thrombosis, but a relatively small atheromatous left coronary artery tree and network; the right coronary artery was much larger than the left. May not this restricted left coronary arterial blood supply, congenital in origin, have played an important role? Let me quote in this connection from a recent publication of Professor Victor McKusick of Johns Hopkins University:

Genetically determined differences in the anat-

omy of the coronary arterial tree might account for its increased vulnerability to the effects of atherosclerosis. Direct evidence on familial similarities in coronary anatomy is not available and obviously is difficult to obtain. Demonstrations of the hereditary basis of other vascular patterns in man, such as that of the anterior chest wall, the antecubital fossa, the aortic arch, and the hand of the fetus, provide a precedent. In man, three patterns of major coronary branching have been identified: 1) right coronary artery predominant; 2) balanced coronary artery pattern; and 3) left coronary artery predominant. Hearts with the third type are most vulnerable to fatal coronary occlusion and those of the second type are least vulnerable. Furthermore, intercoronary anastomoses vary in animals. In man, the extent of intercoronary anastomoses is thought to be genetically determined.

Certain epidemiologic population studies now being planned or actually underway should bring us some useful information concerning the relative importance of heredity. Such a study is that of a comparison of the amount of serum cholesterol and the prevalence of important degrees of coronary atherosclerosis in Irishmen living in Greater Boston and in their brothers living in Ireland. The ideal study, even in only a few such couples, would be a similar comparison of identical twin males.

One should also refer to the infants who die of coronary heart disease due to left ventricular myocardial necrosis from the lack of oxygen in the blood supplied by the left coronary artery congenitally arising from the pulmonary artery; this is more likely, however, to be due to a fault in vascular development during fetal life than to an inherited defect.

As helpful illustrations of hundreds of my own patients who apparently inherited the liability to coronary heart disease I shall cite several cases.

Case 1

Mrs. L.D., aged 52, a successful, driving business woman, still overweight despite a recent loss of 17 pounds, with a serum cholesterol of 360 mg. per cent. Diagnosis: Coronary heart disease, angina pectoris 3 months previously, and coronary thrombosis 6 weeks previously. In her family her brother had had coronary heart disease and died at 63 of a bleeding peptic ulcer; her mother is living and well at 83, but 3 paternal aunts all died at about 60 of coronary heart trouble.

Thus, this middle-aged woman had undoubtedly inherited from her father's side of the family a "tendency" to coronary heart disease.

Case 2

Mr. W.S., aged 40, married, educator. Present weight 178 with a height of 69 inches—a drop of 25 pounds in 4 years by diet. Serum cholesterol 325 mg. per cent. Diagnosis: Hypertension for 8 years, coronary heart disease, neurocirculatory asthenia, angina pectoris on effort for 6 years since the age of 34, and coronary thrombosis twice, on present occasion and 4 years earlier at 36. Family history showed that his father had coronary thrombosis first in his 40's and died of a second attack at 56; a grandfather died of coronary heart trouble in his 60's.

Case 3

Mr. O.B., aged 42, newspaper publisher. Weight 175 pounds, which is 20 pounds heavier than in his younger days, at a height of 69 inches. Serum cholesterol 280 mg. per cent. Diagnosis: Coronary heart disease with recent coronary thrombosis and questionable coronary thrombosis 3 years earlier. In the family history, the father died at 57 of coronary heart disease, as did also one uncle at 46, and 2 other uncles (twins) at 63.

He was obviously a candidate from the standpoint of family history alone.

Case 4

S.G., aged 38, executive. Weight 180 pounds 3 years previously, now 160 after dieting. Diagnosis: Coronary heart disease, myocardial infarction twice, 3 years and 1 year previously, and mild diabetes. Family history revealed that his father had died at 49 of coronary thrombosis, that his mother was living and well, and that a grandfather had been diabetic.

Case 5

J.F., aged 42, congressman. Diagnosis: Acute myocardial infarction with pericarditis. Family history showed that his father died at 66 of "heart trouble" and his mother at 48 of coronary heart disease.

Case 6

C.F., aged 40, executive. Diagnosis: Acute myocardial infarction, posterior in position, 1 month previously. Family history revealed that his father died at 57 of angina pectoris, his mother at 65 of cancer, and a grandfather of heart disease at an age unspecified.

Case 7

J.C.H., aged 41, cotton broker. Diagnosis: Acute coronary thrombosis. Family history revealed that his father died a cardiac death at 54, and his mother of a "stroke."

In conclusion, it has been clinically evident that heart disease due to serious coronary atherosclerosis does "run in families" and that there are other inherited characteristics such as a high serum cholesterol, mesomorphic body build, diabetes, and atherosclerosis in other arterial systems. The mechanism by which this inheritance occurs is still a mystery. It is very important that the practicing physician as well as the investigator pay more attention to the family histories of his coronary patients and, as a matter of fact, to the younger, especially male, still healthy members, of the families already affected at older ages. But as Dr. Page has also pointed out and as I would reiterate now, there is definitely hope for the future not only for those who are candidates for coronary heart disease but for many others, if we can initiate and maintain an adequate measure of both basic and applied research in the field of human genetics.

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Pathologic Physiology of Angina Pectoris and Acute Myocardial Infarction

By HERRMAN L. BLUMGART, M.D., AND PAUL M. ZOLL, M. D.

THE DISTRESS or pain of angina pectoris and of acute myocardial infarction is consequent to ischemia. In angina pectoris the ischemia is transitory because of temporary disproportion between the blood supply and the myocardial requirements; in acute myocardial infarction the ischemia is prolonged and leads to the irreversible changes of necrosis. The actual stimulus at the nerve end-organs that give rise to the pain has not been identified with certainty. Sir Thomas Lewis termed it the "P factor." It has certain characteristics in common with lactic acid: it is acid, is destroyed by alkali and by oxidation, and develops most rapidly under oxygen deprivation and carbon dioxide accumulation.

The predisposing cause of these two conditions is coronary obstruction. Atherosclerosis is the most prevalent lesion. Syphilitic aortitis distorting the coronary ostia and rheumatic arteritis are next in frequency. Rarely, periarteritis nodosa, scleroderma, amyloid, hemorrhagic diseases, vegetations of bacterial endocarditis or tumors impinging on the ostia, emboli, and the arteritis associated with systemic infections may be responsible. Congenital malformations and trauma are sometimes encountered. The chief effect of these lesions is to interfere with coronary blood flow and to prevent an adequate blood supply to the myocardium.

Various factors greatly influence the degree of ischemia. Among these are the anatomic distribution of the coronary arteries, the localization of the atheromatous lesions and the rates of development of the lesions, and the compensatory collateral channels.

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Anatomic Pattern of the Coronary Arteries: the Incidence and Localization of Arterial Occlusions

The 3 main coronary arterial branches, the left anterior descending, the left circumflex, and the right coronary vary from heart to heart in the relative size of the area they supply. Schlesinger classified hearts in 3 groups according to the anatomic distribution of these 3 arteries.[1] In group I, comprising half the hearts in his series, the right coronary artery predominated in the blood supply of the heart, nourishing the right ventricle and a large part of the posterior wall of the left ventricle. In group II, comprising approximately one third of human hearts, the coronary artery blood supply was balanced between the right and left coronary arteries. The right coronary artery supplied the right ventricle plus the posterior wall of the interventricular septum, and the left coronary artery supplied the left ventricle plus the anterior part of the interventricular septum. In group III, comprising one sixth of human hearts, the left coronary artery predominated and supplied more than the entire left ventricle and interventricular septum. In some instances the left coronary artery extended to the free surface of the right ventricle. There are various degrees of this preponderance of the left coronary artery. In the least marked form both the right coronary artery and the left circumflex coronary artery extend to the crux of the heart, and both terminate in parallel posterior descending branches. In other hearts the terminal branch of the left circumflex coronary artery constitutes the sole posterior descending coronary artery.

There is no great sex difference in the distribution of the groups although women evi-

dently have a somewhat disproportionately large number of the balanced group II hearts.

The degree to which these anatomic groups are hereditary and may be responsible for familial tendencies to myocardial infarction and angina pectoris is unknown.

Another variation in local anatomy of the coronary arteries that may significantly influence the effects of coronary occlusion is the presence or absence of a coronary artery to the area of the conus arteriosus (conus artery) [2] The coronary vessel supplying this area may arise as a branch of the right coronary artery or as a separate, third, supernumerary coronary artery with its own ostium from the aorta. Because of its separate origin the conus artery is independent of obstruction so often found at or near the mouth of the right coronary artery. The conus artery also appears particularly suited as a collateral source of blood supply to the heart. Its direct communication with the aorta and its location between the main left descending and right coronary arteries make it a ready source of anastomotic connection between the aorta and the coronary arterial system distal to the zones in which the incidence of occlusion is highest. Furthermore, the low incidence of occlusions in the conus artery, lower than in the other coronary arteries, enhances its value as an effective pathway of collateral blood supply.

The presence of a large, third division of the left coronary artery was described in the Bantu and suggested by Brink as an explanation for the low incidence of angina pectoris and myocardial infarction in that race.[3] Although the presence of this racial anatomic variation has been confirmed, it is not associated with significant anastomotic circulation between the left and right coronary arteries and does not appear to be of primary importance in the lowered incidence of clinical manifestations of coronary disease in this race.[4]

Pathologic Characteristics of Coronary Arteriosclerosis

Coronary artery occlusions are limited to the 3 main coronary arteries and their primary branches, and are almost entirely epicardial. The highest incidence of occlusions is not directly at the mouth of the vessel but a short distance distal to the mouth.[5] One half are within 3 cm. and 70 per cent are within 4 cm. of the coronary ostia. The lesions are mostly localized and segmental. In a study of almost 200 occlusions of the main coronary arteries and their branches in a series of 400 hearts, 64 per cent were less than 5 mm. in length and 40 per cent were less than 3 mm. in length. More than half of all the occlusions were in the main stems; the remainder were in the primary branches. Fibrosis and calcification may involve not only the intima but also the entire media. Occlusions in affected hearts tend to be multiple. In 100 consecutive hearts with occlusions, there were 248 occlusions or an average of 2.5 occlusions per heart. Only 33 of these hearts had but 1 occlusion.

Atherosclerotic narrowing or occlusion of a coronary artery may be caused by an atheroma with progressive fibrosis, by a superimposed thrombus, by intramural hemorrhage in an atheroma, or by rupture of an atheromatous abscess. Thus, in 6,800 consecutive autopsies, thrombosis on an arteriosclerotic basis (43 per cent), occlusions due to arteriosclerosis per se (41 per cent), and intramural hemorrhage (8 per cent) presumably on an arteriosclerotic basis made up 92 per cent of the causes of occlusion, with the remaining 8 per cent distributed among embolism, inflammation, and syphilis.[6]

The arteries are metabolically active structures that may be altered even in the absence of atherosclerosis. They participate, as do other tissues, in the aging process. The media, initially made up of circular, smooth muscle and elastic fibers, and the adventitia, a meshwork of connective tissue containing elastic fibers, both lose elastic fibers with age. These changes are most rapid in the left anterior descending artery and slowest in the right coronary artery. Fibroelastic changes occur in the intima and media, atrophy of the smooth muscle is seen in the media, and irregular patches of connective tissue develop.