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REPORT OF THE

WORKING GROUP ON

RESEARCH IN CORONARY HEART DISEASE IN BLACKS

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Foreword

Despite impressive progress over the past several decades, diseases of the heart remain the leading cause of death for American men and women, and coronary heart disease (CHD) accounts for the largest share of these deaths. CHD is particularly important in blacks due to the higher prevalence of major CHD risk factors such as hypertension, diabetes, obesity, and left ventricular hypertrophy.

Recent technological advances in the basic sciences provide unprecedented opportunities for new research to elucidate the pathogenesis of CHD in blacks, to improve management and treatment, and, ultimately, to develop effective preventive strategies.

To identify these new opportunities and chart a course for future research efforts, in 1992, the NHLBI convened the Working Group on Research in Coronary Heart Disease in Blacks. Comprising national experts in basic, clinical, population-based, and behavior and prevention research, the working group was charged to:

- Review the state of knowledge over the past 5 years
- Explore the pathophysiological mechanisms that underlie CHD in blacks
- Identify opportunities for developing and assessing new and improved approaches for clinical interventions and preventive and educational measures
- Develop a specific plan, including scientific priorities, for NHLBI support of research on CHD in blacks for the next several years.

During four meetings held over the course of more than a year, the working group members developed the report published herein. Organized according to four categories—basic research, clinical research, population-based research, and behavior and prevention research—it provides a detailed summary of accomplishments to date and identifies specific recommendations for future research.

We are very pleased to have this document to guide research activities with respect to CHD in blacks, and we are grateful to the working group members for this valuable contribution.

CLAUDE LENFANT, M.D.
Director

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Executive Summary

I. Executive Summary

Research on coronary heart disease (CHD) has contributed to the decline in cardiovascular disease morbidity and mortality that has occurred during the past three decades in the United States. However, life expectancy and rates of illness and death from CHD have not improved as much for blacks as for whites. Blacks have not experienced the full benefit of research advancements for a variety of reasons, including insufficient scientific data, lack of research focused on minority populations, and limited access to health care resources and technology. Consistent and universally accepted racial and ethnic categories have not been established, and definitions may vary according to the social and scientific context. The limited data base currently available leaves a number of paradoxes unresolved. Controversy remains, in particular, regarding both chest pain and sudden death. Available data indicate that the probability of dying from CHD is greater in black Americans than in white Americans and that there is a higher prevalence of smoking, hypertension, diabetes, obesity, and left ventricular hypertrophy (LVH) in blacks. Blacks are also less likely to receive coronary angiography or coronary revascularization.

In order to address these and other disparities in prevention, diagnosis, treatment, and outcomes of CHD in blacks, the NHLBI convened a Working Group on Research in Coronary Heart Disease in Blacks. This working group assessed the state of the science and identified research opportunities in four main areas of CHD in blacks: pathogenesis and pathophysiological mechanisms, clinical expression, diagnosis, and treatment; disease patterns and risk factors; and behavioral variables and strategies for education and prevention. In its deliberations, the working group identified 10 priority research areas, which are, in order of research priority:

- Treatment
- Epidemiology (data collection and analysis)
- Evaluation of chest pain and diagnosis of CHD
- Prevention and behavior
- Risk factors
- Genetics
- Vascular biology
- Left ventricular hypertrophy
- Coronary microvasculature
- Sudden cardiac death.

These research priorities are considered in four chapters of the report: basic research, clinical research, population-based research, and behavior and prevention research. Each chapter reviews the state of the science and identifies opportunities and recommendations for future research directions.

Although most studies show that there is little difference in the nature of the atherosclerotic process leading to CHD in blacks, it has become evident that there are important differences in the social and economic context in which CHD develops in blacks. It is difficult to determine whether phenotypic characteristics common in blacks, such as high blood pressure and LVH, play a primary role in the pathogenesis of CHD in blacks or are merely markers for more fundamental differences in mechanisms of disease. It is not clear whether differences in the biology of CHD or in the clinical expression of common pathogenetic processes account for reported racial differences. Differences in access to cardiovascular care, the impact of risk factors, or variations in clinical therapeutic responsiveness may be as responsible for the well-documented disparities in health outcomes and resource utilization as any genetic or biological mechanisms.

Research Accomplishments and Opportunities

Treatment

Although major advances in therapy for CHD have occurred in recent years, few data are available on the clinical value, effectiveness, and efficacy of newer therapeutic modalities in blacks. Innovative therapeutic approaches to CHD have been based on data obtained primarily in white male populations. Blacks, especially women, are at greater CHD risk. Therapeutic algorithms focused primarily on the relief of chest pain have been refined in majority populations, but other algorithms may be more efficacious in populations with higher prevalence of hypertension, diabetes, and differing clinical presentations. Although information regarding the interactions of LVH, hypertension, and CHD has increased, there are few data in blacks.

The development of pharmacological agents that stimulate regression of LVH, modulate insulin sensitivity, alter lipid metabolism, and control vascular tone provide new avenues for research on the treatment of CHD in blacks. Thrombolysis and coronary revascularization procedures, such as coronary artery bypass grafting (CABG) and percutaneous transluminal coronary angioplasty (PTCA), have been significant therapeutic innovations. Studies of CABG surgery indicate better survival rates, but less favorable functional outcomes, for blacks treated surgically than for those treated medically. Relatively little is known about the use of PTCA in blacks. Limited studies of thrombolytic therapy in blacks show higher patency rates for infarct-related arteries compared with whites and a higher risk of bleeding complications, although survival to hospital discharge and other clinical outcomes are similar. There are minimal data on the value of coronary atherectomy in blacks.

Epidemiology (Data Collection and Analysis)

Since the late 1960s, CHD mortality for all four major gender-racial groups has declined; however, since 1980, CHD rates have declined faster in whites than in blacks, particularly for men. Attempts to explain the disparities between blacks and whites in CHD morbidity and mortality, as well as differences in the use of clinical, diagnostic, and therapeutic resources, have been limited by the scarcity of comprehensive data on CHD in blacks.

Relationships between risk factors and CHD have been clarified in recent years and appear to be universally applicable, although data from specific ethnic subpopulations have not been consistent with findings in whites. Prospective epidemiological studies indicate that CHD rates are similar in black men and white men, but higher in black women than in white women. Local and regional data suggest that blacks have higher out-of-hospital deaths, fewer hospitalizations for acute myocardial infarction (MI), higher death rates from cardiovascular disease, and utilize cardiac diagnostic procedures and revascularization procedures less than whites. National surveys and clinical trial data provide valuable information, but have not been thoroughly analyzed for clinical comparisons of subpopulations. Racial and ethnic identifiers are often variable or absent in existing large data sets. Ongoing observational studies may be informative in the future.

Data from many of these studies could be collected and analyzed to provide a more comprehensive overview of CHD in blacks. Other than Medicare data, which are confined to the population over 65 years old, there is no national data base that contains comprehensive clinical information on blacks. National data on clinical characteristics, risk factor profiles, therapies received, health care providers, patient preferences, and long-term health outcomes are not available in blacks. An additional important issue in data analysis relates to the interpretation of exposure (i.e., outcome relationships in blacks compared with whites). In the complex, causal pathway linking risk factors to disease outcomes, available analysis procedures may not be adequate to define differences between blacks and whites.

Evaluation of Chest Pain and Diagnosis of CHD

Clinical evaluation of chest pain and establishment of the diagnosis of CHD in blacks is often difficult. Electrocardiographic (ECG) changes long accepted as common “normal variants” in blacks may have greater clinical significance when the increased prevalence of out-of-hospital death, LVH, and hypertension in blacks is taken into account. Coronary spasm and silent ischemia have become established clinical entities. Preliminary findings suggest that there may be racial or ethnic differences in the occurrence and manifestations of these clinical syndromes. The advent of ambulatory ECG and blood pressure monitoring has facilitated greater understanding of these syndromes and circadian variation in coronary syndromes in general.

Clinical studies suggest that the sensitivity and specificity of tests established in the white population may differ for blacks. Cardiac diagnostic accuracy and reliability have not been validated in blacks to the same extent as in whites with respect to risk assessment, therapeutic responses, prognosis, natural history, and long-term health outcomes. For example, echocardiography has provided a link between structural and functional measurements and epidemiological data, but its value in assessing the risk and prognosis of CHD, independent of LVH, has not been fully elucidated in blacks.

Limited available data show higher rates of normal coronary angiograms in blacks with chest pain than in whites, raising the possibility of abnormalities in the coronary microcirculation or in vascular tone. However, existing angiographic data on blacks may

not be representative because blacks are known to have reduced access to cardiac diagnostic procedures. In addition, newer imaging techniques, such as perfusion scintigraphy, intravascular ultrasound, nuclear magnetic resonance (NMR), and positron-emission tomography (PET), have not been adequately studied in blacks.

Prevention and Behavior

Prevention of CHD necessarily involves behavior change, since modification of risk factors for CHD is influenced primarily by individual choice and the decision to change one's lifestyle. Although behavior change is fundamental to the prevention of CHD by reducing risk factors, differences in health care seeking behavior between blacks and whites may also contribute to racial differences in CHD mortality and morbidity. For example, blacks delay longer than whites in seeking care for general medical problems, as well as for acute CHD symptoms, including acute MI.

Studies suggest that less tangible social support may be associated with stroke mortality and hypertension. The effects of diminished social supports on CHD in blacks appear to be particularly strong. Since it is likely that stress related to racial prejudice, economic disadvantage, and social disintegration is more common in blacks, understanding their relationship to CHD in blacks is likely to be helpful in elucidating strategies for lowering CHD rates. Studies also suggest that there may be differences between blacks and whites in symptom perception and symptom attribution. These factors may affect adherence to treatment recommendations and play a role in the utilization of cardiac procedures and ultimate health outcomes.

Until the roles of access to care, knowledge and beliefs concerning CHD, coping styles and the social environment, as well as biological variables, such as cardiovascular reactivity, are clarified, understanding racial differences will be difficult. Culturally and ethnically appropriate techniques for individual and community behavior modification and lifestyle change, which would affect primary and secondary prevention of CHD, have not been developed specifically for blacks.

Risk Factors

The decline in CHD mortality and morbidity that began several decades ago, and continues to the present, has been coincident with widespread acceptance of the effectiveness of risk-factor reduction in preventing CHD. The significant change in lifestyle and secular trends in risk factors that has occurred in the majority population has been less dramatic in blacks. Because prevalence rates of modifiable CHD risk factors, such as hypertension, cigarette smoking, physical inactivity, and obesity, have been documented to be greater in blacks than in whites, the opportunities for prevention may be greater for blacks.

Smoking rates in persons 18 years of age and older have declined in the general population, but remain higher in blacks. Studies of leisure-time physical activity suggest that blacks are more sedentary and less fit than whites, independent of income and education. Obesity, which is associated with hypertension, hyperlipidemia, hyperinsulinemia, and glucose intolerance, may be more common in blacks. The prevalence of obesity appears to be higher in black women than in white women or black men, but racial differences are less apparent between black and white men. Dietary patterns may differ slightly between blacks and whites, but foods selected by blacks and whites do not differ substantially in nutritional composition. Data in blacks are conflicting about the relationship of elevated levels of lipoprotein (a) [Lp(a)], a genetically determined lipoprotein associated with CHD, to CHD risk. Increased left ventricular (LV) wall thickness is more common in blacks, even in the absence of hypertension. The contribution of LVH to risk of sudden death and out-of-hospital death in blacks is not clear.

Both individual and community-based interventions have been successful in modifying CHD risk factors in blacks, although individual approaches may be less effective in blacks than in the general population. Local church and community-wide education programs have been particularly effective in the control of hypertension and smoking in some black communities.

Genetics

The recent, unprecedented progress over the past decade in genetics and molecular and vascular biology has enhanced understanding of the pathogenesis of human disease. Although initial progress was

made in diseases resulting from mutations of a single gene, methods are now available that allow investigation of complex diseases, such as atherosclerosis, hypertension, and disorders of coagulation. One prerequisite for studying complex diseases is identification of aggregates of patients or families with relevant phenotypic characteristics.

Family history comparisons between blacks and whites demonstrate a higher prevalence of positive family history of hypertension, stroke, diabetes, or obesity in black families. However, family history of CHD is similar among black and other populations. Black families also appear to be similar to other populations in having strong correlations for major CHD risk factors between biological relatives, but not with unrelated persons living in the same household.

Complex diseases, such as atherosclerosis, are typified by etiological heterogeneity, in which a variety of physiological systems interact to produce a clinical disease entity. Identification of a gene that occurs frequently in a population with a specific disease may not establish linkage to the disease. For example, although Lp(a) is found more commonly in blacks, it has only been established as a risk factor for whites. Similarly, polymorphisms of the angiotensinogen gene have been associated with increased risk of hypertension and preeclampsia in selected populations, and there are some interesting new findings at the angiotensinogen locus that deserve further attention.

Evidence suggests that pedigrees with a complex disease demonstrate genetic heterogeneity and that different individuals with a disease may be influenced by "non-overlapping genetic components." As differences in the distributions of alleles are identified between affected and unaffected pedigrees, more precise phenotypic characterization becomes essential, regardless of whether the investigative strategy primarily involves linkage analysis, identification of candidate genes, or detection of mutations of candidate genes.

Vascular Biology

Significant advances in understanding the mechanisms active in the development of atherosclerotic lesions and pathogenesis of macrovascular and microvascular disease now offer greater opportunities for acquiring knowledge on the clinical presentation, natural history, and outcomes of CHD in blacks. Studies of the biology of the arterial wall have led to significant advances in understanding endothelial function and structure, cell-cell interaction, growth factors, connective tissue, and lipoprotein metabolism. There has been dramatic progress in understanding gene regulation of lipoprotein metabolism, biosynthesis, and mechanisms of action of lipoproteins. It is now possible to study the fibrous plaque and the fatty streak directly in the human artery using biopsy tissue, transplant tissue, and vascular rings or strips obtained during surgery or at autopsy. The growth in the clinical application of coronary atherectomy has provided an additional source of tissue for studying a wide array of pathogenetic mechanisms in atherosclerosis.

Greater understanding has been gained of the interaction of the vascular endothelium and the vessel wall with specific cellular elements in blood; the function and composition of specific lipoproteins, enzymes, hormones, and receptors; the contribution of genetic and immunological factors; the impact of alterations in the autonomic nervous system; and the role of coagulation and thrombosis in atherogenesis and the coronary syndromes. It is not known, however, whether there are significant racial differences in the cellular and molecular mechanisms of atherogenesis.

Left Ventricular Hypertrophy

Research on CHD in blacks presents a unique challenge because of the increased prevalence of LVH and hypertension in the black population. In studying CHD in blacks, LVH and hypertension may be confounding factors, challenging investigators to identify the separate and common pathogenetic mechanisms of atherosclerosis, hypertension, and LVH and to explain their interaction. LVH has been shown to be an important risk factor for CHD, sudden death, and congestive heart failure, and it confers significant risk for future cardiovascular events, independent of atherosclerotic disease in the epicardial coronary vessels. Many of the pathogenetic features of LVH, such as endocrine, paracrine, and autocrine factors, can now be studied in humans.

Because hypertension is common in blacks, the increased prevalence of LVH in blacks is often attributed to concurrent hypertension, but young blacks tend to have increased LV wall thickness, compared with whites, even in the absence of increased blood pressure. Cardiac myocytes constitute 75 percent of the heart mass, and the interstitium comprises 25 percent. Hypertension is the

major stimulus to myocyte hypertrophy. Studies of the cellular response and remodeling of the interstitium in hypertension suggest that blacks have a tendency toward increased muscle cell mass.

It is not clear whether there are racial differences in systolic and diastolic function in the ventricle with LVH alone, with CHD and LVH, or with isolated CHD. Selected pharmacological agents have now been widely shown to cause regression of LVH. The impact of LVH regression on the course of CHD, hypertension, congestive heart failure, and sudden death in blacks needs further exploration.

Coronary Microvasculature

Blacks demonstrate high rates of angiographically normal epicardial coronary arteries despite a higher prevalence of multiple CHD risk factors and disproportionate morbidity and mortality from CHD. This paradox has led investigators to seek explanations in the microvasculature of the heart. However, because of the small size of the vessels which compose the microvasculature, gross examination has been difficult and histological studies have been limited primarily to microscopic examination at autopsy.

Still, much has been learned from studies of microvascular functional responses to physiological and pharmacological interventions. The microvasculature may respond differently to pharmacological agents than do large muscular arteries and veins. Endothelial dysfunction may play a role in microcirculatory disease and may occur in atherosclerosis, diabetes, low-renin states, coronary vasospasm, and reperfusion injury. Increased sensitivity to the vasoconstrictive effects of catecholamines may also occur with endothelial dysfunction.

Clinical diagnosis of abnormal microcirculation has been based largely on the demonstration of reduced coronary reserve. Abnormal coronary reserve is implicated if coronary blood flow does not increase when coronary resistance is lowered, usually in response to the administration of a potent coronary vasodilator, such as dipyridamole or papaverine, or to exercise. Numerous reports note the frequent occurrence of the syndrome in hypertensive patients with and without LVH or with hypercholesterolemia.

Microvascular disease, or nonatherosclerotic CHD (the clinical syndrome of angina-like chest pain and angiographically normal coronary arteries), may occur in up to 20 percent of patients undergoing coronary angiography. In some studies of blacks, however, nearly half of those with angina-like chest pain have normal coronary angiograms. Black women, in particular, have a higher incidence of chest pain with normal coronary arteries. Abnormal coronary microvascular function may limit appropriate flow response to stress, possibly due to endothelial dysfunction.

Pharmacological probes and provocative testing with agents such as acetylcholine may be helpful in determining whether there are physiological differences in the microvasculature between blacks and whites. The relative role of microvascular disease versus macrovascular disease in the pathogenesis of myocardial ischemia and vascular disease of the heart has not been studied extensively in blacks.

Sudden Cardiac Death

Death certificates and autopsy data indicate that more blacks than whites die out of the hospital or experience out-of-hospital cardiac arrest. Studies have not confirmed a relationship between race and access to emergency cardiac care or outcome of cardiac resuscitation. Out-of-hospital deaths may also be related to delay in the prehospital phase of acute MI care. LVH may be associated with increased atrial and ventricular arrhythmogenesis and, potentially, sudden death.

It is not clear whether there are racial differences in the electrophysiological substrate in blacks related to the increased prevalence of LVH and hypertension. Diminished coronary reserve may also be more common in blacks and predispose to life-threatening arrhythmias. The value of newer electrophysiological monitoring techniques in predicting risk of sudden death is also not clear, and the value of signal-averaged ECG in predicting arrhythmias has not been well studied in blacks.

Smoking may also increase the risk of sudden death in some individuals, most likely through enhanced platelet adhesion and attendant thrombogenicity, increased vasomotor reactivity, and reduced threshold for sustained ventricular arrhythmias. The contribution of smoking to differences in sudden death and out-of-hospital deaths in blacks has not been studied extensively.

RESEARCH RECOMMENDATIONS

For many years, evidence has been accumulating that blacks, compared with whites, in the United States suffer disproportionate rates of death and illness due to cardiovascular disease. Recently, the documentation of disparities in access to care, utilization of medical resources, and health outcomes has accelerated. Now is an opportune time for intensifying research efforts on coronary disease in blacks.

Clinical management of CHD has advanced dramatically with the advent of CABG surgery, thrombolysis, and PTCA. Despite extensive research on the efficacy of these therapeutic modalities, clinical data on their value and effectiveness in blacks are limited. More rapid progress in reducing the burden of CHD in blacks has been thwarted by lack of detailed information on the phenotypes of CHD in blacks. The increased availability of sophisticated diagnostic and therapeutic modalities offers an opportunity for studying the applicability of these techniques to blacks.

Development of new pharmacological therapies for CHD also affords greater possibilities for identifying and understanding racial differences in the pathogenesis of CHD and the therapeutic efficacy and effectiveness of these therapies, and to relate any differences observed to short- and long-term clinical outcomes. The expanded application of computer technology and informatics to the collection and analysis of medical data will facilitate analysis of existing data sets as well as collection and analysis of prospective data on CHD in blacks.

Significant progress has been made in understanding the mechanisms of CHD and the control of atherosclerosis, as well as nonatherosclerotic coronary disease, blood pressure regulation, LVH, and arrhythmogenesis. Unprecedented advances in molecular genetics and vascular biology have enhanced opportunities for research, at the cellular and molecular level, on the mechanisms of CHD in blacks. When considering CHD in blacks, however, research on the interaction of environmental, biological, and genetic factors is especially important.

Basic research has contributed substantially to the progress already made in reducing death rates from cardiovascular disease in the white community. Population-based studies and behavioral research may provide crucial insights that will allow similar improvement in the rates of death and disease due to CHD in blacks living in the United States. In reviewing the state of science on CHD in blacks, it is clear that existing knowledge is incomplete and fragmentary. As clinical paradoxes in CHD in blacks are resolved and new questions at the cellular and molecular level are answered, opportunities for developing innovative and improved methods of preventing, halting, reversing, and treating CHD will be expanded, not just for blacks, but for all Americans.

The research recommendations proposed by the working group are described in detail in the four main sections of this report. In developing these recommendations, the working group identified an overriding need in all areas of research on CHD in blacks for a comprehensive data base of information and a coordinated network of clinical researchers. Therefore, the working group strongly recommends the establishment of a centralized data base of *existing* data on CHD in blacks. Such a data base will be an important resource for planning and conducting future research studies of acute and chronic coronary syndromes in blacks. The working group also strongly recommends support for a comprehensive, multidisciplinary, national network of investigators in community-based clinical centers. Through this national network, clinical researchers will be able to collect and coordinate *prospective* data on environmental and behavioral determinants of CHD in blacks; clinical characteristics, disease course, and epidemiology of acute and chronic CHD syndromes in blacks; variations in cardiac care; and the extent and causes of differences between black and nonblack populations in the use of cardiac procedures.

Implementation of these two major recommendations of the working group will accelerate research on CHD in blacks and research findings that will be relevant to all U.S. populations. The data base and clinical network are necessary steps to the future, integrating existing fragmentary and incomplete data and encouraging coordinated research in pursuit of well-planned hypotheses.

The working group's recommendations for each of the 10 research areas, listed in priority order, are summarized below.

Treatment

Disparities in health outcomes of CHD in blacks, compared with whites, may result from differences in risk factor profiles, utilization of diagnostic tools,

management of acute and chronic CHD syndromes, and access to revascularization procedures. Research should be expanded to identify the most effective means of increasing awareness about the value of reducing risk factors and treating symptoms and signs of CHD in black populations. The causes of differences in clinical characteristics and outcomes of CHD between blacks and whites also need to be determined.

Whereas reduction in the development of stroke attributable to control of hypertension has exceeded that predicted from epidemiological studies, reduction in CHD related to antihypertensive treatment has been much less striking. Given that hypertension is more common in blacks than in whites, studies should be conducted to define the possible contribution of antihypertensive therapy to mortality from CHD in blacks. Out-of-hospital CHD deaths also are more common in blacks. Methodologies for identifying individuals at risk of acute coronary events, especially sudden death, should be evaluated further. Identification and evaluation of antiarrhythmic agents designed to reduce the risk of life-threatening arrhythmias have been difficult in the past; however, development of effective therapies for patients at high risk (e.g., blacks and other patients with documented CHD, hypertension, LVH, normal coronary arteries with poor coronary reserve) should continue to be a goal of research.

Use of pharmacological therapy for ischemic heart disease has been influenced by recent major advances in coronary revascularization and thrombolysis. However, innovative research on the pathogenesis of atherosclerosis and greater understanding of the role of the endothelium, vascular smooth muscle, and vascular reactivity have led to renewed enthusiasm for established, as well as newer, therapeutic agents.

Clinical trials are needed, particularly related to CHD in blacks. These should address the efficacy of pharmacological agents (e.g., antioxidants, anti-inflammatory substances, growth factor inhibitors) in modifying vascular and ventricular remodeling processes, as well as the impact of pharmaceuticals (e.g., angiotensin-converting enzyme inhibitors, calcium-channel blockers, estrogens) on the course of atherosclerotic and nonatherosclerotic CHD.

The prevalence of heart failure related to CHD is increasing as more patients survive acute coronary syndromes. Heart failure due to CHD or ischemic cardiomyopathy is now one of the most common diagnoses prompting hospital admission. Heart failure is more prevalent in blacks, perhaps because of coincident hypertension or diabetes mellitus. Research comparing ventricular dysfunction due to macrovascular versus microvascular disease and atherosclerotic versus nonatherosclerotic disease is needed, especially in blacks.

Ischemic cardiomyopathy is one of the major contributors to heart failure leading to cardiac transplantation. Studies are needed to determine more effective drug therapy for both systolic and diastolic dysfunction. The appropriateness and value of CABG surgery, PTCA, and thrombolysis, compared with conventional medical therapy, also need to be assessed. For this effort, existing data from multicenter interventional trials should be pooled as appropriate, and prospective clinical trials of various revascularization approaches should be conducted in blacks and compared with existing data in whites.

Epidemiology (Data Collection and Analysis)

The fundamental obstacle in studying CHD in blacks is the absence of sufficient data for resolving many of the questions related to racial comparisons. Because information is limited for specific racial and ethnic groups, determining whether differences and inconsistencies are due to chance findings, artifacts in reporting, or important genetic and biological factors is a difficult, but not insurmountable, problem.

Data collected previously from large clinical trials, national surveys, and vital statistics sources have not been analyzed collectively. When integrated, they may contain valuable information on CHD in blacks. By merging national and regional data on CHD in blacks, it will be possible to obtain a more complete picture of the effectiveness of therapeutic interventions, determinants in the utilization of cardiological care and resources, medical practice patterns, and outcomes of hospital and ambulatory services. Based on these data, research needs and information gaps can be further clarified, and plans for future analyses of prospectively collected data can be formulated.

In conducting research on CHD in blacks, it is important to distinguish health-related consequences of social and economic factors from biological or genetic processes that may be active in

the pathogenesis, clinical expression, and outcomes of CHD in blacks. The appropriate use of racial categories in biomedical research should be defined and the limitations of these categories well understood. Studies of the magnitude of between-group genetic differences, and within-group heterogeneity, should be given high priority. Caution must be exercised in interpreting differences between population subgroups so that the contribution of genetic factors, such as race, is not overemphasized. The distinctive roles of environmental forces, such as socioeconomic status and stress related to minority status, and the genetics and biological aspects of race should be clarified.

Evaluation of Chest Pain and Diagnosis of CHD

The clinical evaluation of chest pain continues to challenge the diagnostic acumen of many clinicians. Accurate diagnosis of CHD in blacks may be more demanding because of the more common concurrence of hypertension, LVH, or both. How this information affects the diagnostic approaches of clinicians is not clear. It is known, however, that blacks receive cardiac procedures, both diagnostic coronary angiography and revascularization, less commonly than whites.

It is not clear whether this disparity between blacks and whites is a function of physician factors, limited access to health care, or individual health care seeking behavior. Providers may vary in their ability to convey educational messages to culturally diverse patient populations. Research on the roles of these factors is recommended.

Studies are also needed to compare the decision-making process by health care providers for ordering diagnostic procedures in blacks and whites and the role of patient preferences in choosing to accept recommended procedures. The relative roles of risk factors, disease severity, and other variables should be compared with the impact of race and socioeconomic status on the use of cardiac procedures in blacks.

Additional new and improved noninvasive techniques for monitoring the development, progression, and regression of CHD and LVH in blacks need to be developed. The implications of ECG findings considered to be normal in blacks should be reassessed, given the data indicating that out-of-hospital deaths and sudden death may be more common in blacks. Comparison of the relative value of imaging techniques for assessing CHD risk in blacks with signal-averaged ECG and other evolving noninvasive techniques should be undertaken. Also important is comparison of the relative value, reliability, accuracy, sensitivity, and specificity of noninvasive diagnostic techniques, such as ECG, echocardiography, stress testing (in conjunction with ECG, echocardiographic, or radionuclide imaging), NMR, and PET, in blacks and whites. The applicability of these tests to individuals with atherosclerotic and nonatherosclerotic CHD, and with hypertension and/or LVH, should be compared in blacks and whites.

Research establishing the role of genetics in some forms of LVH suggests the need to determine the value of echocardiography and other imaging techniques, compared with genetic testing, in diagnosing individuals with genetically determined LVH or hypertrophic cardiomyopathy. Clinical trials will be important in evaluating the value of new and improved noninvasive diagnostic tools, such as intravascular ultrasound and three-dimensional echocardiography, in assessing ventricular structure and function and the physiology of the macrovasculature in blacks and whites.

The reason(s) for the paradoxically high rates of normal coronary angiographic findings in blacks with angina-like chest pain need to be elucidated. Also, given that individuals who enter angiographic trials may not be representative of the general black population, methods need to be developed to assess and control for selection bias in angiographic studies of blacks. Investigators are encouraged to assess the relationship of coronary angiographic findings to the site of coronary occlusion, extent and severity of myocardial damage, and recurrence and outcomes of CHD events in blacks compared to whites.

Prevention and Behavior

Although a reduction in traditional risk factors has been shown to be an effective prevention strategy for the general population, data on the efficacy of prevention efforts in blacks are minimal. Collection of prevention data in blacks has been limited by the lack of culturally validated instruments for data collection and reliable methods for establishing risk factor profiles in minority communities. Still, even though existing data are not sufficient for making generalizations about the impact of behavioral risk factors on CHD in blacks, effective strategies can be developed based on these data.

New and improved tools for measuring risk factors in blacks, both in individuals and in populations, need to be developed and culturally validated. Data should be collected prospectively to allow assessment of the relative risk of factors that preferentially affect blacks as compared with those that have been studied most in whites. Identification and treatment of behavioral risk factors of special significance to black populations should be a high priority.

Research on health care seeking behaviors is another priority area. These behaviors may be determined by a wide array of factors, most of which are functions of social and economic forces. Limited data are available on the impact of social supports, income, stress, acculturation, or personality on CHD risk in blacks. Studies are needed of the psychosocial predictors of CHD mortality and morbidity in blacks, interaction of psychosocial and biological factors and their effect on CHD outcomes, as well as the effectiveness of programs targeted to individuals and communities.

Adherence to medical recommendations, acceptance of diagnostic testing procedures, and interactions with the health care system may be influenced by social and environmental forces. Educational strategies to improve adherence to prevention and treatment recommendations need to be developed, implemented, and evaluated. Innovative and effective research programs to increase long-term adherence to lifestyle modification programs are especially warranted.

Risk Factors

Prevention efforts in the general population have concentrated on identifying risk factors for CHD and treating specific risk factors in at-risk individuals. Differences in patterns of clinical CHD and short- and long-term outcomes of CHD may be related to differential effects of traditional risk factors in blacks and whites and/or the presence of factors in blacks that may not confer similar risk in whites. Increased prevalence of CHD risk factors, such as hypertension, diabetes, increased LV wall thickness, cigarette smoking, and obesity have been documented in blacks. However, other features, also common in blacks, such as enhanced thrombogenicity, increased vascular reactivity, and greater potential for ventricular arrhythmias, may also be significant in explaining racial differences in CHD.

If the mechanisms of CHD differ in blacks, the role of different risk factors may also vary. Smoking, for example, is more prevalent among blacks than whites. Yet, there are few data on the determinants of smoking habits in blacks. Valid and reliable instruments need to be developed for assessing the determinants of smoking topography and the contribution of smoking to the clinical manifestations and outcomes of CHD in blacks. Research also is needed to define the social, cultural, and environmental prerequisites for successful smoking cessation and to develop culturally relevant cessation programs. With regard to other risk factors, valid and culturally appropriate instruments need to be developed to assess nutrition, physical activity, and social supports.

Genetics

In order to demonstrate population-specific genetic susceptibility, it will be necessary to show that there are differential frequencies of genes that condition risk in similar ways in both black and white populations. Studies of possible gene-environment interactions are also recommended. A very large number of black sibships or families will have to be identified to study family-risk syndromes and to understand the interaction of cultural and genetic heritability. This research includes identification of major gene segregation and detection of linkage and susceptibility loci.

Trials of family prevention strategies will be important. Such trials should include identification of large numbers of high-risk families and longitudinal monitoring of the effect of risk factor reduction on CHD clinical expression and health outcomes. Detailed phenotypic data (e.g., on blood pressure, diabetes, obesity, insulin levels, LVH, and other variables) need to be collected and correlated with genetic data obtained from stored white cells from sibships and families. Studies that correlate genotype and phenotype should be given high priority.

Studies of candidate genes and identification of specific genetic traits leading to pathophysiological processes and CHD are encouraged. Also recommended is research on the frequencies of gene variants in black populations and assessment of possible associations with features of CHD in other populations with CHD.

Vascular Biology

Basic research has enhanced understanding of the mechanisms of atherosclerotic CHD. In recent years, there has been an increase in the rate of progress in research on the endothelium, cell-cell interaction, signal transduction, receptors, ion channels, growth factors, and vasoactive substances. Today, research on CHD in blacks should take advantage of modern techniques to study potential histopathological differences in coronary atheroma between blacks and whites. Investigations of necropsy, surgical, or explanted cardiac vascular tissue should be undertaken to define potential racial differences in lesion structure and the mechanism of transition from a stable lesion of chronic CHD to an active lesion of acute CHD. Studies of microvascular coronary artery function, using provocative pharmacological testing, are recommended for elucidating physiological differences between lesions in blacks and whites.

Left Ventricular Hypertrophy

The increased prevalence of LVH in blacks makes knowledge of its pathogenetic role critical to understanding CHD in blacks. Research on LVH will be greatly advanced by development of techniques that will yield better understanding of the cellular and biochemical basis of abnormal myocardial contraction and relaxation, and the role of the interstitium, in myocardial hypertrophy. The differential effects of hemodynamic loading conditions and of hormonal, dietary, and other nonhemodynamic factors in development of myocardial hypertrophy need to be clarified in blacks and whites.

LVH may also predispose to ventricular arrhythmias in blacks. The role of intracellular ionic and metabolic changes in initiating and maintaining a reduced threshold for ventricular fibrillation and complex ventricular tachyarrhythmias needs to be determined, and studies of the racial differences in these factors are recommended. Researchers are encouraged to utilize human biopsy specimens to delineate subcellular changes in the sarcolemma, sarcoplasmic reticulum, and contractile apparatus which may account for changes in intracellular calcium handling and excitation-contraction coupling that occur in LVH.

Valid and reliable noninvasive techniques should be developed for assessing the regression of LVH and its impact on the course of CHD in blacks. Experimental models are also needed for studying the role of hemodynamic, nonhemodynamic, and growth factors in development of LVH.

Coronary Microvasculature

Abnormalities of the coronary microvasculature have been proposed to explain the paradoxically high prevalence of normal-appearing epicardial vessels on angiography in patients with angina-like chest pain. However, the nature and pathogenesis of coronary microvascular disease have not been studied extensively in humans, and data in animals are relatively sparse compared with research data on the macrovasculature.

Investigations of the mechanisms that control microvascular function and structure, including endothelial function, intracellular ions, and vascular reactivity, are recommended. Interactions among endothelial, neural, and hormonal control of microvascular tone and coronary blood flow should be clarified using both animal and human vessels. The relative importance of the various control mechanisms in blacks and whites should be determined in in vitro microvascular reactivity profiles and how they are affected by CHD and hypertensive LVH. Studies of coronary vasodilator reserve in animal models (e.g., the pig model) using PET, NMR, or other imaging technologies may also be useful in assessing the determinants of microvascular function.

New and improved techniques are needed for human studies of the microvasculature and measurement of coronary reserve and microcirculatory flow in blacks with atherosclerotic and nonatherosclerotic CHD. The influence of inflammation, vasculitis, or immune complex disease on abnormal coronary reserve, microvascular function, and chest pain syndromes in blacks should be assessed. Also needed are investigations of the impact of controlling CHD risk factors, such as hyperlipidemia, LVH, diabetes, and smoking, on chest pain and the natural history of microvascular disease.

Further studies are recommended on the impact of microvascular disease on ventricular function and heart failure in blacks with angina-like chest pain and normal coronary arteries. Microvascular function should be compared in different vascular beds (i.e., forearm versus heart), and studies are needed on

the relationship of abnormal microvasculature in different vascular beds to the signs and symptoms of CHD.

Sudden Cardiac Death

Although recent data suggest that out-of-hospital and sudden death rates are higher in blacks, much of these data are derived from local studies and have not been confirmed in broader populations. The incidence and prevalence of life-threatening arrhythmias need to be determined in blacks with chest pain syndromes related to nonatherosclerotic and atherosclerotic CHD. The relationship of differences in cardiovascular reactivity to racial variations in sudden death and case-fatality rates in blacks and whites also should be explored.

Studies of diurnal variation in sudden death and other cardiac events are needed to identify the endocrine, paracrine, or autocrine factors that are most important in the pathogenesis of these events. Criteria for identifying individuals at high risk of arrhythmias and sudden death should be validated in blacks. Investigations are also needed on the relationship of traditional risk factors (e.g., LVH, hypertension, hyperlipidemia), and behavioral and environmental factors to the risk of sudden death and life-threatening ventricular arrhythmias.

Basic Research

II. Basic Research

The working group addressed four areas of basic research on coronary heart disease (CHD) in blacks:

- Pathogenesis of CHD
- Pathogenesis of coronary microvascular disease
- Left ventricular hypertrophy
- Genetics.

Advances, opportunities, and recommendations in each area are presented below.

PATHOGENESIS OF CHD

State of the Science

Atherogenesis

Although CHD is the leading cause of death in blacks and whites in the United States, little is known about the possible differences between these races in the anatomical substrates underlying CHD. Autopsy studies to evaluate the distribution and characteristics of atherosclerotic lesions have been performed in South Africa and the United States. Most of these studies conclude that there is little difference in the distribution or nature of atherosclerotic lesions between blacks and whites.

However, there are virtually no comparative data on the detailed histopathological appearance of coronary arterial lesions in blacks and whites. Tools of modern cell biology, recently applied to atherosclerotic lesions, generally also have not been used to analyze possible racial differences in cell types, markers of activation, or the content of markers of thrombosis or hemorrhage in established lesions.

Nonetheless, interesting data on aortic atherosclerotic changes suggest subtle differences in the evolution of lesions which may not be reflected when fixed or established atheroma are examined in adults. Anatomical observations show that young black men, as compared with young white men, have greater involvement of the aortic surface, with fatty streak lesions. Yet, in later life, fibrofatty lesions are more prominent in whites. This discrepancy suggests that the evolution of fatty streaks into fibrous plaques may differ between the races.

Although CHD appears to cause fewer deaths in black men than in matched white male cohorts, black women may actually be at greater risk of mortality due to CHD than white women. Such complexities in the biology of atherogenesis between races and genders must be considered when comparing the pathogenesis of CHD in black and white individuals. In many large angiographic studies, investigators have compared coronary anatomy between black and white individuals, but no consistent differences in the angiographic distribution of coronary lesions have emerged from these analyses.

Increasingly, it is recognized that coronary arteriography is a rudimentary way of assessing coronary lesions. This technique defines the lumen, but not the arterial wall where lesions reside. Furthermore, only structural, rather than physiological, luminal data are obtained from standard coronary arteriography. Recently, provocative pharmacological or physiological testing has been used to evaluate the function of endothelial vasodilator capacity in normal and diseased coronary arteries. Although these modern approaches to evaluating vasomotor reactivity and vascular function have yielded significant new insights into the pathogenesis of coronary syndromes, they have not yet focused on black and white differences in this context.

Pathogenesis and Evolution of Coronary Syndromes

Large angiographic studies have disclosed an interesting dissociation between chest pain syndromes and angiographically demonstrated CHD in blacks and whites. There is a higher incidence among blacks, than among whites, of coronary arteries that appear normal angiographically despite symptoms of chest discomfort that resemble angina pectoris. This interesting difference could be due to a number of physiological factors. The neural pathways for perception of ischemic discomfort could vary between the races. The absence of macrovascular CHD does not exclude the possibility of small-vessel arteriosclerosis or other dysfunction that could account for subendocardial ischemia in the absence of obstructive lesions of the epicardial coronary arteries. Indeed, one recurrent theme from analysis of the published literature about CHD in blacks is the higher incidence of hypertensive heart disease in this population. The myocardium in blacks may thus have different oxygen requirements, particularly in the subendocardium, as a

result of left ventricular hypertrophy (LVH). This situation would alter the balance between myocardial oxygen supply and demand so that the threshold for ischemia could be reached with a lower degree of coronary arterial obstruction in the presence of LVH. This situation could resemble that in aortic stenosis with angiographically normal coronary arteries in which patients may develop chest pain because of increased oxygen demand rather than reduced supply.

Black patients with acute myocardial infarction (MI) may have a worse prognosis than their white counterparts. This possibly increased morbidity and mortality does not appear to result from a greater burden of CHD in the black population, but could be attributable to differences in the biology of the lesions, comorbid states, or the seeking or availability of post-MI care.

LVH as a consequence of the higher prevalence of hypertensive heart disease is a likely comorbid factor that could explain a worse outcome in black patients with CHD. For example, the hypertrophied myocardium may be more prone to lethal ventricular arrhythmias that result in sudden death when ischemia due to CHD is superimposed on the existing condition.

Effect of Risk Factors on Pathogenesis

The literature is replete with studies which examine the effect of risk factors on CHD events between black and white patients. Comparison of most of the data indicates that the usual risk factors, which are well established in the population at large, apply to blacks as well. Although many individual studies support or refute associations of specific risk factors for CHD in black and white populations (see below), most studies show that hypertension, glucose intolerance, and obesity may contribute disproportionately to CHD risk in the black population.

A major paradox is the unexpectedly equal or lower prevalence of angiographically significant CHD despite increased numbers of risk factors in blacks compared with whites. A plausible explanation for this difference is that black patients die prematurely at a higher rate than whites as a consequence of the risk factors. Thus, by the time blacks reach the age when CHD becomes manifest, some individuals with risk factors common to heart failure or cerebral vascular accident may have already succumbed due to noncoronary consequences of their risk factors. This phenomenon is known as morbidity selection. Based on this explanation, age-specific death rates would be expected to be higher in blacks, as is reported from analysis of the National Hospital Discharge Survey data base.

Review of the literature comparing CHD in blacks and whites yields one major area of consensus: Hypertensive heart disease creates a different substrate for coronary atherosclerosis in blacks than in whites. This concept suggests that one way to reduce coronary morbidity and mortality in the black population would be early and intensive screening and therapy for hypertension. This effort would have to be based on race-specific investigations of the treatment of hypertension, an effort that is currently under way.

Another black/white difference in the pathogenesis of CHD is the time-dependent changes in risk factor profiles. It is well recognized that CHD risk factors have changed over time in the U.S. population. The effect of these secular trends on CHD outcomes became evident from the analysis of the Multiple Risk Factor Intervention Trial (MRFIT). Analyses of the National Health and Nutrition Examination Survey (NHANES) I and II indicate that smoking has declined in the black population over time. Anatomical evidence of aortic atherosclerosis has also declined over time in both black and white populations. Thus, CHD in blacks is constantly evolving—another factor that must be taken into account when designing future public health approaches.

Research Opportunities

The current use of atherectomy affords an unusual opportunity for obtaining atherosclerotic tissue from black and white populations. In conjunction with classical necropsy studies applying modern technology, it would be of interest to determine whether there are differences in the structure, cell types, or expression of activation markers in coronary artery lesions from black and white patients.

Newer imaging modalities enable investigators to evaluate the chemical composition of plaques, including their lipid content and degree of calcification. The use of these technologies may also provide information on the structure of the intima, media, and adventitia of coronary arteries, which will enable researchers to make deductions about vascular remodeling and compensatory responses to atheroma. Such observations will be descriptive, but may provide insight into how profiles of risk factors

in the black population influence these pathophysiological mechanisms. Through anatomical analyses, investigators have identified plaque rupture and acute thrombosis as major substrates for acute coronary syndromes in the general population. However, it is not known whether current concepts about lipid content and structure of the fibrous cap of atheroma are directly applicable to blacks or whether these characteristics have a more pronounced influence on the development of acute coronary syndromes owing to the high prevalence of hypertension and thrombotic diathesis related to lipoprotein (a) [Lp(a)] in blacks.

Provocative testing of coronary artery function (for example, using pharmacological probes such as acetylcholine) is another technique that may help increase understanding of CHD in blacks. Use of this approach could help define physiological differences between coronary lesions that are anatomically indistinguishable in black and white patients. Such information may be crucial to understanding differences in the manifestations of CHD in black and white populations. Specifically, the vasodilatory reserve of the microcirculation could be studied directly in blacks and whites to determine whether changes in small-vessel function, hypothesized on the basis of clinical and epidemiological data, actually occur.

Genetically modified animal models are needed for studying the molecular bases of potential black and white differences in atherogenesis and CHD. Such studies will require sufficient research data on the differences in structure and function of coronary artery lesions between blacks and whites. This type of information will be important for designing experimental approaches for studying racial differences in CHD. One strategy would be to create transgenic animals that express candidate genes for enhanced susceptibility to or complications of atherosclerosis identified by positional cloning or other methods. This strategy would enable investigators to conduct pathophysiological studies of specific genes that are implicated in atherogenesis in a particular population. Suitable mouse models for atherogenesis are currently available. Transgenic technology enables the breeding of compound mutant mice that would introduce candidate genes into atherosclerosis-susceptible backgrounds.

Recommendations

Specific recommendations for basic research on the pathogenesis of CHD are:

1. Apply modern techniques to explore potential histopathological differences in coronary atheroma between blacks and whites; design angiographic, intravascular ultrasound, nuclear magnetic resonance (NMR), atherectomy, and necropsy studies to define potential racial differences in the structure of coronary artery lesions and the mechanism of transition from chronic to acute CHD.

2. Develop appropriate genetically modified animal models for studies of the molecular bases of potential differences between blacks and whites in atherogenesis and CHD.

PATHOGENESIS OF CORONARY MICROVASCULAR DISEASE

State of the Science

Normal Coronary Microvasculature and Flow Assessment

Microvasculature Structure

The structure of individual vessels and their location in interconnecting series and parallel circuits are important factors that define the anatomy of microvessels. Individual vessels consist largely of endothelial, smooth muscle, and pericyte cells, and connective tissue elements such as elastin, collagen, matrix, and fibroblasts. The specific types of vessels and the relative distribution of their various components differ.

The microvasculature can be subdivided into at least seven different microvessel types which include small muscular arteries, arterioles, terminal arterioles, precapillary sphincter vessels, collecting venules, muscular venules, and small veins. The classification of these types is based on their function and anatomical parameters such as luminal diameter, amount of smooth muscle and connective tissue in the wall, and position within the vascular network. The diameters of these vessels are generally in the micron range, with venous capillaries, for example, ranging from 5 to 8 μm, progressing to 100 to 300 μm in small veins. Because of the small

size of these vessels, gross examination in human myocardium is difficult and evaluation of microvascular anatomy and innervation has depended on microscopic histological examination at autopsy. The network structure is determined by the interconnecting pattern of vessels, beginning with right and left coronary arteries and branching into smaller arteries that course over the epicardial surface of the heart. Penetrating branches course through the myocardial wall and diverge into arterial, arteriolar, and capillary vessels which subsequently converge into venules and veins, many of which drain into the coronary sinus.

Flow Assessment

Blood pressure and flow patterns are typically different for various branching levels of the coronary vascular tree. These patterns are controlled by the activity of endothelial and smooth muscle cells. Accordingly, smooth muscle and endothelial responsiveness to endogenous and exogenous vasoactive agents (catecholamines, angiotensin, adenosine, prostaglandins, vasopressin), sympathetic neural control, and cardiomyocyte metabolic activity (state of oxygenation and pH) are important determinants of pressure and flow in the coronary network. Because of the small size of the microvessels, it is difficult to assess their physiological functions in human tissues. There has been evidence for some time that the microvasculature exerts primary (autoregulatory) control over the flow of blood through organs such as the heart. Direct measurement of changes in vessel diameter in response to physiological and pharmacological interventions, however, has been feasible only in special areas of the body where the microvessels can be visualized clearly, such as the skin and mesenteric viscera in animals. Application of servo-null micropressure techniques has enabled investigators to measure intravascular micropressures.

In human studies, flow has been assessed by a combination of Doppler, radionuclide, and metabolic-based techniques such as positron-emission tomography (PET). Intracoronary Doppler has been used to determine the velocity of coronary blood flow at rest and after a hyperemic stimulus such as atrial pacing, or intracoronary dipyridamole or papaverine, as a way of estimating flow reserve. Flow reserve may be decreased in hypertensive individuals because the arterioles lose some of their vasodilator capacity under chronic high pressure. One important result of the various studies conducted has been demonstration that the responsiveness of microvessels to a variety of different pharmacological agents may differ markedly from that of large muscular arteries and veins. Moreover, microcirculatory responsiveness may be significantly altered by disease states and even dietary manipulations.

Abnormal Coronary Microvasculature

Microscopic and Angiographic Findings at Autopsy

Abnormal structural changes in the coronary microvasculature can involve plaque formation, which affects the pattern of blood flow through the segments affected, or vascular hypertrophy, which occurs in hypertension and affects flow by increasing the resistance of the segments affected. Microscopic findings of arteriolar hypertrophy, plaque formation, or decreased vascularization may correlate with functional angiographic findings of ischemia. In previously ischemic myocardium, subendocardial plexus vessels may be enlarged and, thus, contain large amounts of angiographic contrast material. In dogs, enlargement of the collateral vessels has been demonstrated after chronic ischemia. In the past, autopsy data obtained from perfusion of the coronary microvasculature with casting material has been used to estimate vascular supply (i.e., vessel sizes and numbers, degree of branching, branching angles, and capillarization), although it is difficult to ensure that all capillaries fill with the casting material because of its high viscosity. Using histological techniques, the sites of stenosis and degree of vascular closure also can be determined in autopsy material. These changes have been correlated with patient history and data obtained from angiograms of the coronary vasculature.

A number of studies indicate that some patients with chest pain and angiographically normal coronary arteries, and no evidence of large-vessel spasm, demonstrate an abnormally reduced capacity for decreasing coronary resistance and increasing coronary flow in response to atrial pacing. This abnormality appears to reflect dysfunction of the small resistance vessels that are not visible angiographically, although the large conductance vessels appear to function normally. An abnormal vasodilator reserve may be associated with exercise-induced regional wall motion abnormalities as well as abnormalities in diastolic relaxation. Similar abnormalities can be demonstrated by PET scanning of the heart. These abnormalities have been identified in patients with hypertension and LVH who complain of chest pain syndromes and in patients with dilated cardiomyopathy. Other patients with angina and normal coronary arteries have been found to have hypertrophic

or dilated hearts in which decreased subendocardial flow was documented as the possible etiology. These in vivo findings are of interest and appear to correlate with autopsy observations of arteriolar wall thickening.

Functional Findings (Vasoconstriction)

Coronary vasoconstriction can result from direct stimulation of the vascular smooth muscle cells by active neural and humoral agents; increased release of endothelin and other endothelial-dependent constrictor agents from endothelial cells, which then stimulate adjacent smooth muscle cells; or decreased release or increased inactivation of endothelial-derived relaxing factors (EDRFs) from endothelium, which also results in an increase in vascular tone. In both atherosclerosis and hypertension, patients have been shown to have decreased EDRF activity in peripheral vessels, which may be related to the development of vascular tone or vasospasm.

Abnormal microvascular function can best be assessed in vivo by challenging patients or animals with vasoconstrictors or vasodilators. A diminished response to vasodilators, or an enhanced response to vasoconstrictors, provides evidence of diminished vasodilator reserve and microvascular dysfunction.

Plasma from low-renin hypertensive patients has been shown to contain elevated levels of a digitalis-like factor that inhibits cellular uptake of potassium and extrusion of sodium (the sodium-potassium ATPase pump). Under such circumstances, sodium tends to accumulate intracellularly. This factor is thought to have a hypertensinogenic (vasoconstrictor) effect by indirectly causing a rise in the cytosolic free calcium concentration in vascular cells (i.e., the rise in intracellular sodium causes a subsequent rise in intracellular calcium due to increased activity of the sodium-calcium exchange mechanism). Increased cytosolic free calcium enhances vasoconstriction. Chronically increased cytosolic calcium may also enhance collagen secretion and promote development of hypertrophic or hyperplastic vessels. Sodium pump inhibition decreases catecholamine uptake by nerve endings, so that the synaptic norepinephrine concentration remains high and effective in maintaining vasoconstriction. Because blacks tend to have low-renin hypertension, and sodium pump inhibition has been identified with low-renin hypertension, these mechanisms may play a greater role in the pathogenesis of hypertension and CHD in blacks than in whites.

Factors Related To Pathogenesis

Hypertension and LVH

The frequency of salt-sensitive hypertension is greater in blacks than in whites, and blacks tend to retain more sodium than whites. About 80 percent of black patients with CHD also have hypertension. Hypertension promotes hypertrophy and fibrosis of the myocardium as well as atherosclerosis of the coronary vessels. Longstanding, severe hypertension results in cardiac failure. Before that point, however, function may be preserved at rest, but cardiac reserve may be damaged. Hypertension with secondary LVH is associated with a high incidence of angina and false-positive electrocardiograms (ECGs) in blacks. Many of these patients are evaluated by coronary angiography which reveals, in a significant number of the patients, normal coronary artery anatomy. It is believed that, in many of these patients, microvascular dysfunction leads to myocardial ischemia. These findings would be expected to correlate with the presence of inadequate vasodilator reserve, hyperresponsiveness of the coronary microcirculation to vasoconstrictors, and an abnormal response to exercise.

Endothelial Factors

In recent years, it has become clear not only that the large and small coronary vessels are under the control of the autonomic nervous system, but also that their function is modulated in an important way by autacoids released locally from endothelial cells. A number of different factors have been identified, including relaxing factors such as EDRF (nitric oxide), prostacyclin, and endothelium-derived hyperpolarizing factor, and constricting factors, such as endothelin and superoxide anions, which play an important role in modulating the tone and proliferation of smooth muscle cells. Some endothelial factors may also affect the proliferation of smooth muscle cells. The endothelial cell responds to changes in sheer stress, hypoxia, and receptor-operated mechanisms and to mediators released from blood cells, including polymorphonuclear neutrophils and platelets. The endothelial cell also responds to vasoactive substances such as thrombin, substance P, vasopressin, bradykinin, serotonin, adenosine triphosphate, adenosine diphosphate, and leukotriene C_4. There is evidence that endothelial cells in the coronary circulation may also elaborate angiotensin II.

Under normal physiological conditions, a balance is present between endothelium-derived relaxing and contracting substances, both of which contribute to maintaining optimal vessel caliber and adequate tissue perfusion. However, in certain diseases, the endothelium cannot perform its physiological function, resulting in an imbalance between these substances. Endothelial dysfunction has been demonstrated in a variety of cardiovascular disease (CVD) states, including thrombosis and coagulopathies, diabetic angiopathies, hyperlipidemia, atherosclerosis, peripheral artery disease, reperfusion injury, hypertension, and coronary vasospasm. The exact mechanism responsible for endothelial dysfunction in each of these states has not been fully defined and probably varies considerably from case to case. With regard to hypercholesterolemia, it appears that oxidation products may inactivate EDRF, allowing vasoconstriction to predominate. Oxidatively modified low density lipoprotein (LDL) may interfere with signal transduction pathways within endothelial cells, resulting in diminished nitric oxide production.

Diabetes

The incidence of end-stage renal disease resulting from diabetes is 2.6-fold higher in blacks than in whites, especially among type II diabetics. Insulin is atherogenic via several metabolic pathways. It has been suggested that, in an individual who is insulin resistant, the body attempts to maintain normal glucose tolerance by augmenting the secretion of insulin, causing hyperinsulinemia and atherosclerosis. It also has been suggested that the hyperinsulinemia and insulin resistance commonly observed in type II diabetes might increase the risk of renal hypertension owing to salt and water retention and increased microvascular reactivity to angiotensin II and norepinephrine. Blacks appear to have an increased risk for both diabetic and hypertensive renal disease.

Renin-Angiotensin System

The renin-angiotensin system is important in cardiovascular homeostasis. Myocardial injury may initiate local or systemic release of renin from the kidney, brain, and other tissues, thereby producing a subsequent increase in the release of angiotensin II. Angiotensin's overall cardiovascular effects are due to its stimulatory effects on a wide array of systems, including the thirst mechanism, central and peripheral sympathetic outflow, aldosterone synthesis and release, renal excretion of sodium, and contraction of vascular smooth muscle. The pressor response elicited by angiotensin is complicated and depends not only on angiotensin's direct effect on vascular smooth muscle, but also on angiotensin's enhancement of norepinephrine release from sympathetic nerves (or inhibition of norepinephrine uptake into nerves) and its release of eicosanoids in coronary, mesenteric, and other vascular beds.

Thus, the level of circulating renin is an important determinant of many cardiovascular functions that are affected by local or systemic concentrations of angiotensin II. Blacks tend to have a distinct plasma renin profile. That is, black men are more likely than white men to have a low level of plasma renin activity and a high level of plasma prorenin. In addition, the action of prorenin in coronary vascular tissue may differ between the two groups, especially in the ability of prorenin to release angiotensin from coronary vascular endothelium.

Neurogenic Factors

The density of adrenergic innervation in different segments of the microvascular bed appears to vary widely, with the greatest concentration of nerve endings occurring in the more proximal segments. The precapillary sphincters and collecting venules appear to be sparsely innervated, if at all. Hypertensive rats have been shown to have an increased density of sympathetic nerve endings on arteriolar vessels. Endothelial cells may play an important role in modulating the effects of catecholamines in human coronary arteries under normal and pathophysiological circumstances. This action may occur by several mechanisms. Stimulation of alpha-2 adrenergic receptors on endothelial cells can lead to the release of EDRF. It is now well known that removal of endothelium from rings of large arteries markedly increases the sensitivity of these arteries to constriction by phenylephrine and cholinergic agonists such as acetylcholine.

CHD conditions, including atherosclerosis, may result in endothelial dysfunction and a marked shift in the sensitivity of the coronary vasculature (both large and small vessels) to catecholamines. For example, studies in which cardiac catheterization of segments with evidence of endothelial dysfunction, as assessed by acetylcholine-induced vasoconstriction, was used showed a constrictor response to phenylephrine at a 100-fold lower concentration than segments with normal endothelial function. These results suggest that the endothelial dysfunction that characterizes early and advanced atherosclerosis is associated with a marked increase in sensitivity to the constrictor effects of catecholamines.

One may reasonably assume that similar abnormalities may be present in the microvasculature, as has been documented in patients with dilated cardiomyopathy in whom endothelial-dependent vasodilator function was abnormal.

As stated above, certain kinds of hypertension exhibit an inhibition of sodium-potassium ATPase, resulting in an increase in intracellular sodium which, in turn, tends to decrease the activity of the sodium-calcium exchange mechanism and cause accumulation of intracellular calcium. Sympathetic neurons may release more norepinephrine in low-renin hypertension, which is common in blacks, triggered by the rise in intracellular calcium. This effect may decrease the re-uptake mechanism so that the released norepinephrine has a longer time of action. This calcium transport effect on catecholamine activity should be investigated to determine whether it occurs to a greater degree in black hypertensives than in white hypertensives.

Research Opportunities

Microvascular Disease: In Vivo Assessment

The methodology is available for making important progress in assessing microvascular function in vivo in humans and animals. Routine evaluation of the function of epicardial coronary arteries by cardiac catheterization can be correlated with Doppler flow probes and newer noninvasive imaging techniques, such as echocardiography, thallium, PET, and NMR, to assess regional flow. These techniques have already been used to demonstrate microvascular dysfunction in patients with angina-like chest pain and normal coronary arteries. The same techniques could be applied effectively in evaluating blacks with coronary artery syndromes and with normal coronary function.

In animal studies, coronary flow can be assessed using fluorescent or radioactive microsphere techniques, in addition to the PET and NMR scanning used in human studies. With these methods, resting blood flow in humans or animal CVD models, including normotensive, hypertensive (genetic, renal, and high salt-sensitive), high cholesterol-fed, and diabetic individuals, can be compared with flow states after vasodilation to demonstrate relative ischemic coronary conditions in these disease states. During the past several years, it has become clear that the vasodilator reserve can be adequately assessed by infusing vasoconstrictors (such as ergonovine) or administering drugs that are normally vasodilators (such as cholinergic agonists) directly into the coronary circulation. Patients and animals with low coronary flow reserves may exhibit abnormal flow responses on PET. These techniques could be applied in evaluating black patients with chest pain syndromes who do not have clearly demonstrable anatomical changes in their epicardial coronary arteries.

Vascular Studies Using Biopsy and Necropsy Tissue

Vascular studies have been conducted successfully on pig coronary microvessels. Because human and pig hearts are of comparable size, it is feasible that human microvessels, readily obtained from coronary artery bypass graft (CABG) surgery, necropsy, or transplantation, can be used in pharmacological (vascular strips or rings), physiological (transport), and biochemical (second messenger systems) studies or as a source for cell culture studies to evaluate similar processes in individual cells. In human and animal pharmacological studies, the reactivity profile of microvessels to agents such as catecholamines, endothelin, EDRF, vasopressin, angiotensin, and prostaglandins can be assessed. Physiological function (contraction/relaxation) of intact, pressurized microvessels can be readily studied using an in vitro myograph that accommodates small vessel segments about 2 mm long, sectioned between branches to allow pressurization. The responses of vessels from atherosclerosis patients, especially to EDRF and endothelin, in both normal and plaque regions, can be investigated in vessels from necropsy or diseased hearts that have been removed for transplantation. Such studies may provide information on the extent of alterations in the control mechanisms during the disease process. Microvascular segments distal to plaque regions in larger vessels can be studied and compared with normal vessels distal to nonplaque-containing large vessels.

Vessels can be classified according to the extent and location of intimal lesions determined by microscopic image analysis. Transport studies can be performed on isolated vascular (both endothelial and smooth muscle) and blood cells to determine tracer fluxes of sodium, calcium, and potassium, before and after physiologically important perturbations such as hypoxia or acidification of cells. Red blood cells have been shown to exhibit altered transport properties in essential hypertension. The lithium-sodium countertransport and sodium-potassium cotransport systems have been studied extensively.

Although there may be racial differences in the results obtained in hypertensive patients, these differences are not yet clear and should be further studied. Thus, by assessing the various exchange mechanisms for controlling intracellular pH, sodium, and calcium, investigators may be able to evaluate, in various types of CHD patients, the capacity of vascular and blood cells to activate transport mechanisms important for controlling the intracellular environment. Such assessments may also enable researchers to compare mechanisms and processes between blacks and whites with the same disease. In addition, cell and molecular biology techniques can be used to assess the presence and structure of specific receptor and transport proteins.

Endothelial Function/Microvascular Dysfunction

The effects of coronary vasodilators and constrictors on the microcirculation of the left ventricle (LV) have been studied in animal models such as rats, cats, and rabbits using in vivo microscopic techniques (servo-null micropressure, videomicroscopic measurement of vascular diameters) as well as in vitro techniques to assess force generation in ring segments or pressurized microvessels in response to pharmacological interventions. The responses of cultured endothelial and smooth muscle cells to physiological agonists such as endothelin, EDRF, angiotensin, serotonin, or catecholamines have been evaluated to determine the receptor mechanisms and second messenger systems by which these cells exert their actions in normal tissues.

Studies show that hypercholesterolemia affects vascular responsiveness to many agents and is particularly associated with marked endothelial dysfunction. The relative importance of endothelial mechanisms (relaxing versus constricting) for controlling coronary blood flow, compared with endothelial-independent mechanisms, has not been investigated fully in the normal state or in CHD. Rabbits and monkeys on high cholesterol diets develop atherosclerosis. The effects of plaque on the physiology of coronary arteries in these animals can be studied effectively using in vivo and in vitro techniques. Physiological changes in blood flow through these vessels and pharmacological properties of vascular cells from plaque- and nonplaque-containing regions can be correlated.

In addition to these studies of hypercholesterolemia, other studies show that endothelial mechanisms of vascular control are also changed in vascular conditions such as hypertension, diabetes, reperfusion injury, and coronary vasospasm. Most in vitro pharmacological studies have used vascular segments; however, functional studies of isolated human vascular cells also need to be developed more fully. Most studies of isolated cells have used cells from larger vessels such as rat aorta; recently, techniques have been described for isolating cells from human coronary microvessels.

It is not known whether blacks and whites differ in endothelial control of vascular tone in normal or diseased vasculature, or whether this form of vascular control in the coronary microvascular system is important. The degree to which endothelial cell mechanisms control vascular tone in the coronary vascular circuit and the manner in which they interact with neural and hormonal control mechanisms need to be determined in animal and human studies.

Coronary Versus Systemic Microvascular Disease: Association With Hypertension and Other Risk Factors

It is clear that microvascular dysfunction occurs not only in patients with CHD, but also in patients with significant secondary LVH, due to hypertension, who appear to have a normal coronary artery anatomy. Although both types of patients exhibit microvascular dysfunction, it is not clear whether the mechanisms responsible are similar. Investigation of physiological mechanisms relating to sodium-potassium ion transport and the receptor mechanisms for cardiovascular drugs in tissues of patients with either or both of these two major clinical conditions is important. Moreover, it would be valuable to determine the effect of environmental factors such as diet, alcohol, and cigarette smoking, singly or in combination, on microvascular structure and function in patients susceptible to microvascular dysfunction. The availability of a variety of molecular biology techniques, such as polymerase chain reaction (PCR) technology, may enable investigators to amplify and express nucleic acids in small quantities of genetic material obtained from human biopsy samples in order to assess the structure and function of various cellular entities present in patients exhibiting these syndromes.

Animal Models: Large Species

Only one model of microvascular spasm has been developed in large animal species. Created in the pig, this model provides a useful tool for evaluating coronary artery spasm in both large and small vessels. The advantage of using the pig model is that the animal's heart can be assessed using the usual

clinical modalities, including Doppler flow catheters, imaging techniques, and PET scanning. Studies of this model indicate that it appears to mimic microvascular disease in humans and share many of the risk factors related to development of microvascular dysfunction. Since LVH is a common feature in hypertensive CHD in blacks, the hypertensive pig model may be useful for delineating the adequacy of myocardial flow and long-term changes in capillary/myocyte ratios. It may be possible to use the pig model to explore capillary growth (i.e., angiogenesis). Assessment of angiogenic factors could provide a new approach for reversing the abnormal capillary/myocyte cell ratio that appears to characterize the hypertrophic myocardium.

Recommendations

Specific recommendations for basic research on the pathogenesis of coronary microvascular disease are:

1. Investigate membrane transport mechanisms responsible for regulating the intracellular ionic environment in coronary microvascular cells (endothelial and smooth muscle) and red blood cells, particularly with regard to calcium, sodium, potassium, and hydrogen, and the mechanisms for controlling cell volume, pH, and vascular reactivity in both animals and humans. Determine, in human vessels, whether these parameters are qualitatively and quantitatively similar in blacks and whites.
2. Clarify the interactions among endothelial, neural, and hormonal control of microvascular tone and coronary blood flow using both animal and human vessels, determine the relative importance of the various control mechanisms in blacks and whites, and determine in vitro microvascular reactivity profiles and how they are affected by CHD and hypertensive LVH.
3. Determine the extent of coronary vasodilator reserve in the pig model using PET or NMR, and assess the effects of risk factors such as hypertension, diabetes, and smoking.

Left Ventricular Hypertrophy

State of the Science

Definition, Prevalence, Consequences

Left ventricular hypertrophy, defined as either thickened heart wall muscle or increased cavity volume, occurs in 15 to 20 percent of adult hypertensives. Hypertrophy confers a significant risk factor burden for future cardiovascular events independent of the degree of obstructive epicardial CHD. Studies over the past three decades suggest that, for equal levels of hypertension, blacks have thicker LV walls than whites. Furthermore, even in the absence of hypertension, young adult blacks tend to have greater wall thickness compared with whites, suggesting that there may be inherent differences in ventricular structure between blacks and whites which may account for the excess incidence of cardiovascular events in blacks compared with whites.

Cardiac Cell Hypertrophy

The heart is composed of several different cell types each of which participates in normal and pathological myocardial growth processes. Based on direct morphological and biochemical estimates, the diameter and volume of myocytes may increase two- to threefold. In addition, important changes may occur in the myosin isoform composition of the heart and in the density and function of important subcellular structural proteins, including sodium-potassium ATPase of the sarcolemma; calcium ATPase in the sarcoplasmic reticulum and, perhaps, the L-type calcium channels; and sodium-hydrogen and sodium-calcium exchangers located in the sarcolemma. Increased load may result in the activation of stretch-dependent channels which, in turn, leads to a change in the intracellular milieu, thereby providing a stimulus in development of hypertrophy. A rise in intracellular calcium concentrations may act through a calmodulin-dependent process to activate the enzyme protein kinase C, which, in turn, may phosphorylate cellular sites that elaborate transacting factors that may facilitate the expression of genes mediating development of hypertrophy. The response of stretch-sensitive ionic channels may be more pronounced in blacks than in whites, which may lead to greater protein synthesis for a similar degree of wall tension. Similarly, induction of the protooncogenes c-myc and c-fos in response to wall stress, catecholamines, or angiotensin II may be more pronounced in blacks than in whites.

Although myocardial cells constitute most of the heart mass, the cardiac interstitium, composed of endothelial cells, vascular smooth muscle cells, cardiac fibroblasts, macrophages, and mast cells, constitutes approximately 25 percent. Fibroblasts, which produce interstitial collagens, have the capacity to divide, as do coronary artery vascular smooth muscle cells. In hypertension, the interstitium remodels and becomes more prominent. There is evidence that coronary smooth muscle cells in blacks may hypertrophy more than in whites. This development may occur at a very young age, as suggested by preliminary research information which demonstrates that, independent of blood pressure, the total coronary artery medial thickness is much greater in blacks than in whites even in 15-year-old black normotensives. This propensity for an increased smooth muscle cell mass in blacks than whites may be analogous to keloid development, which is much more prominent among blacks than whites in response to dermal injury, and suggests that smooth muscle cells in blacks are hyperresponsive to growth stimuli.

Pathogenesis of LVH

Both hemodynamic and nonhemodynamic factors may account for the differences in myocardial structure between blacks and whites.

Hemodynamic Factors

Blood Pressure. Blood pressure is the predominant factor leading to muscle hypertrophy, and it is likely that the LV in blacks is chronically exposed to higher blood pressure levels. Several studies in adolescents and young adults demonstrate that, in response to physical or psychological stress, blacks have a significantly greater increase in blood pressure than whites. For example, blacks may have greater stress at work, which raises diastolic blood pressure and is associated with increased LV mass. Nighttime blood pressure in black male adolescents is significantly higher than in white adolescents, and elevated nocturnal blood pressure is associated with increased LV mass. Thus, the lack of a nocturnal fall in blood pressure, as well as increased blood pressure in response to stress, could account for the increased LV mass seen in blacks.

LV Volume and Contractility. LV mass is directly related to LV volume and inversely related to intrinsic myocardial contractility. Blood volume in black hypertensives is higher than in white hypertensives, but there is no compelling evidence to suggest that black hypertensives have either increased LV end-diastolic volume or decreased contractility.

Anemia and Blood Viscosity. Sickle cell anemia and microvascular disease secondary to microvascular coagulopathy can exacerbate the cardiac effects of hypertension in some patients. Moreover, by producing microvascular infarction, which can become confluent and lead to significant overall depression of global LV function, compensatory ventricular hypertrophy may develop. In almost all patients with sickle cell anemia, the heart becomes markedly enlarged.

Valvular Disease. Valvular disease can produce left and/or right ventricular hypertrophy through a combination of pressure and volume overload. However, it is not clear whether there are any true differences in susceptibility based on gender, race, or ethnicity.

Concomitant CHD. Myocardial hypertrophy can occur in patients with CHD, even in the absence of hypertension. It is possible that, for a given level of ischemic damage, the degree of compensatory hypertrophy that develops in blacks is greater than in whites. Increased ischemia among blacks may be explained by preliminary evidence which suggests that coronary flow reserve (see below) is depressed in blacks compared with whites.

Nonhemodynamic Factors

Weight and Age. Obesity, which contributes to LV mass, is more prevalent among blacks than among whites. Owing to the higher incidence of untreated hypertension among blacks, the number of elderly blacks with significant LVH may represent a greater percentage of the elderly population than their white counterparts.

Dietary (Sodium and Alcohol Intake) and Ionic Factors. Blood pressure in blacks is more sensitive to sodium than in whites. Studies in the red blood cell suggest that blacks have higher levels of intracellular sodium; this may be a signal for myocardial hypertrophy. An abnormality in the modulation of intracellular sodium is suggested by the finding that sodium-potassium ATPase activity may be decreased in various types of cells from blacks compared with whites. Paradoxically, blacks have lower intracellular levels of calcium. Intracellular calcium is probably a mediator of hypertrophy, and, hence, the relationship between intracellular calcium and hypertrophy may be shifted among blacks. Alcohol

has been associated with LVH in the Framingham Heart Study, which predominantly consists of white participants. In one study, in which 20 percent of the population was black, no relationship was found between alcohol consumption and LV mass.

Hormonal Differences. Activation of the renin-angiotensin axis differs between blacks and whites, with blacks tending toward a low-renin form of hypertension and whites tending toward a high-renin form. There is no clear evidence that variation in renin levels (and thus, presumably, angiotensin and aldosterone levels) affects LV mass in hypertensives. Furthermore, because renin levels in blacks decline in early adolescence, it is hard to invoke this hormonal system as a cause of increased LV mass in blacks. However, it is possible that the local renin-angiotensin system is more active in blacks than in whites.

Insulin, a hormone associated with macrosomia, is higher in blacks than in whites owing to a greater incidence of insulin resistance among blacks beginning in adolescence. Black adolescents with marginally elevated blood pressure are more insulin resistant and hyperinsulinemic compared with normotensive black adolescents. Hyperinsulinemia and insulin resistance may be related to the development of LVH.

Increased sympathetic tone may stimulate hypertrophy. It is known that norepinephrine stimulates hypertrophy in cultured neonatal myocytes through the stimulation of alpha-1 adrenoreceptors. However, there appears to be a similar incidence of thyroid heart disease in both black and nonblack populations.

Renal Disease. Renal disease is far more prevalent among blacks than whites, leading to a significantly greater prevalence among blacks of end-stage disease requiring hemodialysis. Hypertensive end-stage renal disease is about 10-fold more common nationwide in blacks than in whites and 17-fold higher for blacks in some sections of the United States. Some investigators have proposed that abnormal adaptation of the medial smooth muscle cells to the increase in renal arterial pressure is responsible for the changes that develop. Nephron loss begins at an early age, and uremia can depress LV function. Since LV function is inversely related to LV mass, early subtle changes in renal function may contribute to increased incidence of hypertrophy among young blacks.

Pathophysiological Consequences Associated with LVH

Abnormal Coronary Flow Reserve

Coronary flow reserve is the difference between coronary blood flow at baseline and flow that occurs after maximal vasodilation induced by exercise or pharmacological intervention. Abnormal coronary flow reserve can result in perfusion defects, as shown on thallium perfusion scans, even when no epicardial coronary disease is present. This observation strongly suggests that abnormalities cause myocardial ischemia and may become more pronounced when obstructive epicardial disease is present. Because blacks have increased LVH as well as increased medial thickness of the coronary arteries, compared with whites, it is very likely that they also have more abnormal coronary flow reserve.

Animal studies suggest that abnormalities of coronary perfusion associated with hypertension and LVH are reversible. Improvement may require regression of LV muscle mass and collagen regression; a reduction in blood pressure without a regression in LV mass may further decrease the coronary flow reserve. More studies are needed to determine the optimal treatment for these abnormalities.

Diastolic Function in Hypertension

Abnormalities of LV diastolic function are more common in the hypertrophied ventricle, where they can manifest as clinically significant congestive heart failure. These abnormalities may be due to fibrosis and increased myocardial stiffness or may reflect abnormalities of LV relaxation. Diastolic abnormalities may occur early in the course of hypertension and precede detectable hypertrophy. Factors that lead to these abnormalities may be inherited. Preliminary evidence suggests that, in the absence of hypertrophy, blacks do not have an increased incidence of diastolic dysfunction compared with whites.

Arrhythmias

LVH is associated with an increased incidence of nonsustained ventricular tachycardia and atrial arrhythmias. Data also suggest that there may be an increased incidence of sudden death in individuals with LVH. Hypertrophy may be associated with an increase in arrhythmogenesis due to a variety of reasons, including an increased propensity for developing reentry phenomenon and triggered ventricular responses from a relative state of

calcium overload. However, it is difficult to induce ventricular tachycardia in hypertensives with LVH, and signal-averaged electrocardiography in these patients is rarely abnormal. Further study of individuals with myocardial ischemia might be useful. A number of studies comparing racial differences and the risk of sudden cardiac death in whites and blacks have yielded inconclusive data, although evidence suggests that an interplay between race and environmental factors may be important in determining outcomes.

Regression of LV Mass

Pharmacological Interventions in Animals

In animal studies, the hypertrophied heart appears to respond differently to different antihypertensive agents. Treatment of hypertensive rats with pure vasodilators may actually increase LV mass despite a profound reduction in blood pressure, whereas treatment with methyl dopa decreases both LV mass and blood pressure. The response of hypertensive rats to beta-adrenergic blockade has been shown to vary from undetectable or minimal change in ventricular weight to sizable regression of hypertrophy. This variation probably relates to a combination of factors, including the efficacy of the blockade of adrenergic influence on the myocardium under different conditions. It may also relate, in an important way, to the relative resistance of black hypertensives to therapy with beta-adrenergic agents compared with other drugs such as calcium channel-blockers and diuretics. Different etiologies also may respond differently to therapy. For example, the cardiac response of renovascular hypertensive rats, in contrast to that of spontaneously hypertensive rats, appears to correlate closely with a reduction in blood pressure and a reversal of ventricular mass regardless of whether the antihypertensive treatment is medical or surgical. This observation emphasizes the inhomogeneity of cardiac responses to different types of hypertension and, therefore, therapy.

Pharmacological Interventions in Humans

Meta-analysis of more than 100 human studies suggests that beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, and calcium-channel blockers are almost equally effective in producing regression of LVH, whereas diuretics reduce the dimensions of the chamber but may not lead to regression of the hypertrophied muscle. The findings from a recently completed controlled trial of mild hypertension suggest that all classes of antihypertensive agents are equally effective in reducing LV mass.

Lifestyle Modification

Modifying risk factors for hypertension would minimize the occurrence of hypertension and secondary hypertrophy in the black population. These lifestyle changes include moderating the ingestion of alcohol and sodium, maintaining ideal body weight, and eliminating cigarette smoking.

Effect on Morbidity and Mortality

A reduction in blood pressure has been associated with reduced cardiovascular morbidity and mortality. Reduced blood pressure is also associated with regression of LVH. Because of the intimate relationship between blood pressure and LVH, it is difficult to distinguish the relative contributions of a reduction in blood pressure versus regression of LV mass to the observed decreases in morbidity and mortality. Preliminary evidence suggests that patients in whom regression or stabilization of LVH is successfully induced experience a threefold reduction in cardiovascular morbidity and mortality compared with patients whose LV mass increases despite treatment.

Research Opportunities

Important changes may occur in the responsiveness of myocardial cells, the structure of various tissue components, and the growth of cell types. Improved techniques need to be developed to study these phenomena (e.g., myocardial relaxation and the influence of cellular and biochemical changes associated with LVH and interstitial fibrosis). Cellular, biochemical, and imaging approaches need to be combined in studies of interstitial and other tissue abnormalities in LVH. It is also important to identify growth factors associated with LVH and to determine whether they differ between blacks and whites. Hemodynamic and nonhemodynamic mechanisms that may be responsible for differences in myocardial structure between blacks and whites are also important areas for research, the results of which will provide valuable information for improving the prevention and management of CHD.

Studies of the electrical properties of hypertrophied myocardium are needed to clarify the apparent association of LVH with increased arrhythmogenesis. Research should focus on racial differences and other factors that may be involved in various outcomes, especially sudden death. These data will be important for developing improved approaches for preventing, detecting, and managing CHD events in blacks.

It is likely that blacks have more abnormal coronary flow reserve than whites, which may explain their high death rates from CHD even though their epicardial coronary arteries may be normal. The role of LVH and subcellular changes related to calcium and high-energy phosphates are important areas for future research.

Animal models can be used to investigate topics such as abnormal coronary perfusion associated with hypertension and LVH and with MI and compensatory hypertrophy. Information from such studies is needed for developing optimal treatment approaches for these conditions. The influence of hemodynamic, nonhemodynamic, and growth factors in the development of LVH can also be evaluated in animals. Models with specific defects, such as in sodium-potassium ATPase, will be useful for studies of drug efficacy.

Recommendations

Specific recommendations for basic research on LVH are:

Myocardial Cell Responsiveness, Tissue Characterization, and Cell Growth

1. Develop techniques to understand better the cellular and biochemical basis of abnormal myocardial contraction and relaxation associated with myocardial hypertrophy and interstitial fibrosis.

2. Develop combined cellular, biochemical, and imaging studies to understand better the role of the interstitium in the pathophysiology of myocardial hypertrophy.

3. Identify the growth factors responsible for myocardial hypertrophy.

4. Clarify the mechanism by which hemodynamic load stimulates myocardial protein synthesis.

5. Clarify the role of hormonal, dietary, and other nonhemodynamic factors in the development of myocardial hypertrophy.

6. Determine whether growth factors, hemodynamic variables, and nonhemodynamic factors responsible for myocardial hypertrophy differ between blacks and whites.

Electrophysiological Studies of Hypertrophied Hearts and Myocardial Cells

1. Assess the role of intracellular ionic and metabolic changes on cellular electrophysiology by utilizing newer techniques such as (a) patch clamp to evaluate the effects of stretch-activated channels on ionic currents; and (b) artificial membranes to study ion channels and pharmacological agents under precisely controlled conditions in the hypertrophied heart.

Ischemia and Energy Metabolism in the Hypertrophied Heart

1. Utilize human biopsy specimens to delineate subcellular changes in the sarcolemma, sarcoplasmic reticulum, and contractile apparatus which may account for changes in intracellular calcium handling and excitation-contraction coupling that occur in LVH.

2. Pursue metabolic studies of mitochondrial activity and high-energy phosphate metabolism using currently available imaging technology coupled with appropriate indicators.

Animal Model Development

1. Develop experimental models and conduct further studies to clarify the role of hemodynamic, nonhemodynamic, and growth factors in the development of LVH.

GENETICS

State of the Science

Definitions and Methodology

When a specific disorder such as CHD or hypertension occurs in a family more often than expected among persons of the same age and gender in the general population, this family is said to have a "positive family history" for the disorder. A quantitative scoring system has been developed for assessing the strength of familial aggregation. The age and gender distribution of persons in a given family is determined and the number of observed events in this family is compared with the number expected

in the general population with the same age and gender distribution. Persons who have a strong positive family history can then be indexed for more detailed studies such as segregation analysis or linkage studies. Care must be taken to record exactly how the families were identified to allow for "ascertainment" correction in determining genetic mechanisms with statistical analyses.

Several methods have been used to detect genetic and cultural familiarity. All require collection of basic physiological and biochemical data in families of specific composition. In twin studies, identical versus nonidentical twin comparisons allow estimates to be made of the proportion of overall variance attributable to genetic factors, given the assumption that identical twins share all of their genes in common, whereas nonidentical twins share half of their genes in common. Adoption studies compare measurements between adopted offspring and biological or adoptive parents. Strong correlations between adopted children and their natural parents indicate genetic determinants, although strong correlations with their adoptive parents indicate the effect of a shared family environment.

Correlations are calculated between specific family members who are related (i.e., parents with natural offspring, siblings with each other) and between persons living in the same household who are not biologically related (spouse pair, adoptive children versus nonblood relative siblings or parents). Using certain mathematical models, one can estimate the proportion of overall variance in a physiological trait, such as cholesterol level or blood pressure, that can be attributable to genetic heritability (H^2) or cultural heritability (C^2).

When quantitative variables have been collected in multiple members of nuclear families or extended pedigrees, mathematical analysis using complex segregation analysis allows one to infer possible monogenic and polygenic effects and even combine these effects with shared family environment components. In such analyses, well-defined mathematical models of specific types of genetic effects (penetrant dominant traits versus additive traits of variable penetrance) are constructed under varying circumstances such as different gene frequencies, different effects of environmental factors that affect penetrance of traits, different effects of age and gender, genetic models (additive, dominant, recessive), and different amounts of polygenic effect. Once multiple genetic models have been carefully constructed mathematically, the observed data are tested to see how well they fit each of the different models of genetic influence and transmission. The degree to which a defined model of genetic and environmental factors fits the observed data better than another specific model is quantitatively assessed using maximum likelihood segregation analysis. This approach has been very useful and is applied to many quantitative traits in CVD (different types of blood pressure, types of lipid level measurements, insulin levels, multiple indices of obesity).

The mathematical methods mentioned above are helpful, but have limitations. Genetic heterogeneity for common disorders such as hypertension, CHD, or hypercholesterolemia makes it difficult to find genetic models that fit precisely for single-gene traits. Even when specific traits have been found (i.e., segregating urinary kallikrein excretion in families with hypertension), mathematical analyses cannot verify whether the trait being examined plays a causal role or is simply an indirect reflection of some other underlying causal factor.

The most powerful and convincing methods for defining genetic factors employ recently developed molecular markers of genetic traits. The molecular tools for identifying differences in genes carried at specific loci between different individuals have advanced dramatically. Methods for identifying genetic polymorphisms include restriction fragment length polymorphisms, oligonucleotide hybridization in conjunction with PCR amplification of DNA, and detection of single-stranded DNA conformational polymorphisms. In each case, DNA itself is examined for variability rather than distant genetic markers, such as blood types or protein polymorphisms, which were used prior to the new discoveries in molecular biology over the past 15 years.

These new DNA marker technologies can be applied in several settings. One test is for "genetic association." In this test, the frequencies of particular genetic variants are compared between cases with a specific disease, such as hypertension, and comparable controls (e.g., of the same age and race). When a particular genetic variant is found to be consistently more common in disease cases compared with controls, it suggests that this genetic variant is either the causal locus or in linkage disequilibrium with the causal locus (i.e., located very close to the causal gene on the human genome).

In another test, genetic linkage in pedigrees, the cosegregation of a particular physiological trait, such as high cholesterol or high blood pressure, is compared with specific genetic variants or polymorphisms. For example, genetic polymorphisms at the

LDL receptor locus on the short arm of chromosome 19 consistently cosegregate with very high LDL-cholesterol levels observed in families with familial hypercholesterolemia. This identifies the genetic location (at the LDL receptor locus) for genes causing the observed phenotypes (very high LDL-cholesterol levels). Next, one must identify the specific causal mutation, using direct DNA sequencing at this locus or "positional cloning" in which refinement of genetic linkage is carried out to find the exact location of a causal gene. Once a particular gene has been identified, it can then be expressed in vitro to learn about the gene products and pathophysiological mechanisms by which it contributes to disease.

Genetic heterogeneity has been a major challenge in identifying specific gene loci using traditional genetic linkage and cosegregation in pedigrees. This method requires a well-segregating trait from segregation analysis before the DNA marker can be tested for cosegregation. Linkage in sibships has recently been used to overcome this problem. In this case, multiple siblings with a disorder and other siblings in the same sibship who do not have the disorder, such as hypertension, are tested for the sharing of specific alleles. If a particular gene is linked with hypertension, the hypertensive siblings will share a particular gene variant or polymorphism more often than the nonhypertensive siblings. If the number of sibships sampled is large enough, even considerable heterogeneity will not prevent a "statistically significant" detection of genetic linkage using this method. The keys to success are having highly polymorphic genetic markers and large numbers of sibships with multiple affected and nonaffected siblings. The parents are also tested to identify the expected frequencies of the genetic variants, and then the observations in affected versus nonaffected siblings can be tested using "identify by descent." If parents are unavailable, expected allele frequencies are estimated from population data with some loss in power ("identity by state"). Once a particular locus has been identified as linked to a particular variant using sibship linkage studies, further progress can be made using the DNA sequencing or positional cloning methods mentioned above. The final goal is always the same: A specific causal locus is identified, expressed in vitro, and investigated regarding a particular pathophysiological chain of events leading from a particular gene locus to the disease of interest.

Family History and Genetic Analyses

Careful quantitative family history studies show very high familial risk in a small percentage of the general population. For example, about 2 to 4 percent of families in the general population have a strong positive family history of CHD, defined as having two or more first-degree relatives with coronary events before the age of 55. Young adults in these families have an approximately 12-fold risk of CHD compared with persons with usual risk in the general population. For hypertension, about 15 percent of families in the population have two or more first-degree relatives with hypertension before the age of 55. Young adults in these families have an approximately fourfold increased risk of hypertension. Because of the higher prevalence of hypertension, diabetes, stroke, and obesity among blacks in the general population, these conditions are also seen more frequently in black families. The frequency of a positive family history for CHD appears to be about the same in black populations as in others.

Twin, adoption, and family studies all indicate that major CHD risk factors, such as blood cholesterol, high density lipoprotein (HDL) cholesterol, and systolic and diastolic blood pressures, correlate strongly between biological relatives and very weakly between persons living in the same household who are not blood relatives. Estimates of genetic heritability range from 25 to 60 percent for these characteristics, whereas estimates of cultural heritability are generally below 20 percent. The few data available in black families suggest similar estimates of heritability and correlation.

One of the most heritable CHD risk factors is Lp(a), which shows approximately 90 percent genetic heritability. Interestingly, Lp(a) levels, on average, are about 1.7 times higher in blacks than in whites. Lp(a) is somewhat controversial: It has been suggested as a major CHD risk factor in several, but not all, white populations studied, but has not yet been studied well enough to establish it as a risk factor in the black population.

HDL cholesterol shows one of the highest cultural heritabilities (approximately 25 percent) as well as genetic heritability (about 35 to 50 percent). It is also one of the variables shown to have higher familial correlation in blacks than in whites and higher levels in blacks than in whites. Thus, there may be genetic and environmental factors in black families that help explain the tendency for blacks to have more protective levels of HDL cholesterol.

The recent use of new DNA techniques is producing results from genetic linkage and association studies of CHD risk factors. Polymorphisms of the angiotensinogen locus on chromosome 1 have been found genetically linked to essential hypertension in sibships in Utah and Paris. A specific genetic variant of the angiotensinogen locus has been found genetically associated with a higher risk of hypertension in Utah and Paris, and with pregnancy-induced hypertension and preeclampsia in Utah and Japan. This locus, and others involved in the renin-angiotensin system, may be a profitable area of physiological research. The frequency of the renin-angiotensin genetic variant predisposing to hypertension in whites is much more common in blacks. Further research will be required to define any potential role for the angiotensinogen locus in hypertension in blacks.

A genetic variant at the ACE locus is associated with increased risk of CHD in France. The presence of this locus in persons with and without CHD is now being explored in other populations, including some black participants in NHLBI-supported population studies of CHD.

Several recent studies have shown that homocysteine is consistently higher, on average, in persons with CHD compared with controls. This association correlates strongly in sibling pairs and more weakly in spouse pairs. The exact genetic cause of these levels is not yet known. One hypothesis suggests that several genes known to cause homocysteinuria in homozygous carriers may cause the less severe elevations observed, in more recent studies, in the heterozygous state. Of special interest, some studies suggest that there may be significant differences in homocysteine levels between blacks and whites.

Research Opportunities

Few data are published regarding genetic studies of CHD risk factors in black populations and families. Established methods need to be followed for the collection and analysis of detailed family history data. For a cohort of probands or study participants, family history data should include the following:

- Enumeration of all first-degree relatives with gender, vital status, year of birth, and current age, if alive, or age at death, if deceased.
- Presence or absence of any medical conditions of interest (MI or CHD death, hypertension, diabetes, stroke) recorded for each relative enumerated.
- Age at first diagnosis for medical conditions of interest present in any relative enumerated.
- A response of “yes” or “no” to the question “Blood relative of proband?” for each relative. This determination allows separate analyses for family risk score based on only biological relationships (genetic risk) or shared family risk (includes nonblood relatives in the family).
- Presence or absence (and semiquantitative level, if desired) of environmental risk factors in relatives (e.g., smoking, obesity, exercise level).
- Current location or place of death for each relative (to facilitate data validation and family studies).
- Validation, whenever possible, of key medical data from medical family history questionnaires or interviews using followup contacts with relatives enumerated or their next of kin if deceased. Copies of death certificates and hospital discharge summaries should be obtained to validate causes of death or important medical events such as MI or CABG surgery. Collected medical family history data should be edited in the computer to reflect validated medical information.
- Classification of persons as having, or not having, a strong positive history using standardized definitions of family risk derived from these data. The following examples can serve as simple category definitions:
  - Two or more first-degree relatives affected with CHD before age 55 in males or age 65 in females
  - Two or more first-degree relatives affected with stroke before age 70
  - Two or more first-degree relatives diagnosed with hypertension before age 60.

- Calculation of a quantitative Family Risk Score (FRS) for more quantitative family history assessment. For multivariate statistical analyses, a quantitative FRS can be calculated using the formula:

$$FRS = \frac{(|O-E| - 1/2)\,|O-E|}{\sqrt{E}\,(O-E)}$$

if: $|O-E| \leq 1/2$, then FRS = 0,

where:

O is the OBSERVED number of relatives with the disease of interest, and

E is the number of relatives EXPECTED to have the disease of interest.

The EXPECTED is based on the number of enumerated relatives in age-gender specific categories applied to the age-gender specific population rates for the disease (which can be estimated from the whole population of relatives in a large collection of family history questionnaires for a given study).

These standardized methods for collection and analysis of detailed family history data are being used in the NHLBI-supported Family Heart Study, a large, population-based study of CHD in families, which includes data on blacks. The results of other studies that use this same family history methodology can be directly compared with the results of the Family Heart Study.

Gene frequencies of variants and disease associations that need to be evaluated in blacks include, but are not limited to, the following loci or segregating traits:

Angiotensinogen
ACE
Angiotensin-II receptors
Nitric oxide synthase
Renin (structural gene)
Sodium lithium countertransport and sodium hydrogen exchange
Insulin (structural gene)
Insulin receptors
Renal kallikrein
LDL Receptors
Apolipoprotein B (several variants of the structural gene)
Lp(a)
Hepatic triglyceride lipase
Apolipoprotein E variants (E2, E3, E4)
Apolipoprotein AI-CIII-AIV locus
HLA
LPL (lipoprotein lipase)
LDL Subfractions

Many CHD mechanisms still need to be studied using genetic techniques. These mechanisms include measures of thrombogenesis and atherogenesis, determinants of LVH or microvascular disease, and arrhythmogenic factors contributing to sudden death. For some risk factors, such as Lp(a), homocysteine, HDL cholesterol, and angiotensinogen, there may be significant differences between blacks and whites that suggest opportunities for important genetic studies in black populations in the future.

Recommendations

Specific recommendations for basic research on the genetics of CHD are:

1. Apply standardized and detailed family medical history questionnaires and quantitative methods for assessing family history risk to black populations being studied for CHD.

   – Computerize family medical history data for large numbers of individuals.

   – Include quantitative family risk scores in multivariate analyses of CHD risk, testing for independent and interactive effects.

2. Identify large numbers of black sibships or families with strongly positive family histories (e.g., high family risk score, as defined above, or two or more affected individuals at an early age with disorders of major interest, such as hypertension, CHD, and diabetes).

   – Study these high-risk families for familial risk syndromes, cultural and genetic heritability, major gene segregation, and linkage and detection of susceptibility loci.

   – Recruit high-risk families for focused, family-oriented prevention trials (i.e., smoking, diet, obesity).

3. Obtain and store white blood cells collected from single individuals (useful for future

association studies), sibships (for sibship linkage studies), or multigenerational families (classical linkage studies) for DNA analysis in any CHD studies.

- Collect detailed phenotype data (blood pressure, indices of obesity, insulin levels, and other variables including Lp(a) and homocysteine) in black families, including sibships or nuclear families.
- Perform statistical genetic analysis of phenotypes, and test for correlation of phenotype data with genotypes from polymorphisms in DNA extracted from white blood cells.

4. Evaluate black populations for frequencies of gene variants and disease associations found in other studies of CHD.

CLINICAL RESEARCH

III. Clinical Research

Although age-adjusted death rates and hospital mortality from CVD in both blacks and whites has declined steadily since the 1960s, CVD remains the major cause of death and illness in the United States. Blacks still lag behind whites in overall life expectancy, and they exceed whites in deaths and morbidity related to heart and vascular disease. CVD death rates for black men continue to exceed those for white men. Although some data on the incidence of CHD—a major component of CVD—are conflicting, studies consistently report a poor survival in blacks with symptomatic CHD.

In patients who have had an MI, annual mortality rates are about 50 percent higher in blacks than in whites, and angiographic analyses show that mortality in blacks is 35 percent higher than in whites. In the mid-1980s, 5-year survival in blacks with multivessel CHD at a large urban medical center was only 70 percent. Although the reason this survival differential is not certain, more severe CHD at baseline and an increased rate of coexisting hypertension, diabetes, and congestive heart failure may be contributing factors.

Particularly notable is the high CHD mortality in black women. They have been reported to experience a 48 percent mortality in the 32 months following an acute MI, compared with 32 percent for white women. In angiographic analyses of CHD, black women tend to be older and have more diabetes and hypertension. However, LV function tends to be better and the extent of disease tends to be less severe than in white women. Diabetes doubles the mortality risk for black and white women with CHD, but has a much smaller effect on men. After multivariate adjustment, black women with normal coronary arteries at cardiac catheterization have mortality rates that are less than half those experienced by black men with comparable angiographic findings. In the presence of significant CHD, the gender advantage is eliminated, with black women having greater CHD death rates than white women.

Rapidly accumulating documentation of the wide disparities in health outcomes of blacks with hypertension and CHD has generated a diverse array of untested hypotheses concerning the observed differences. Because blacks in the United States have experienced differences in environmental influences, socioeconomic and psychological factors, and access to care, the relative roles of these forces, in addition to genetic and biological determinants of clinical disease, remain an area of great interest. As disparities in the health status of blacks continue to grow, the need for more thorough understanding of all aspects of CHD in blacks becomes more compelling.

Greater understanding of the mechanisms of disease and the factors that contribute to differences in clinical expression of disease will lead to greater opportunities for curing or preventing CHD in blacks and in the entire U.S. population. Although associations may be detected, determination of a causative relationship may be difficult. For example, although high blood pressure is more common in blacks, it has been shown to be a major risk factor for CHD primarily in whites. This association indicates that risk factors may not act similarly in all groups. Assessment of the relative influences of genetic factors, biological differences, data deficiencies, effects of racial bias, and the impact of social and cultural determinants on the seeking of health care and access to care presents a formidable challenge to researchers who study racial differences in clinical disease.

In this chapter, the working group focuses on seven areas of clinical research:

- Clinical characteristics of CHD
- Clinical ischemic syndromes
- Detection and quantification of CHD
- Therapeutic interventions for macrovascular disease
- Small-vessel (microvascular) CHD
- Arrhythmias and sudden death
- Heart failure and CHD.

Advances, opportunities, and recommendations in each area are presented below.

Clinical Characteristics of CHD

State of the Science

Phenotypic Features

The recent dramatic and rapid advances in molecular genetics and cellular biology offer an unprecedented opportunity for exploring the relative influences of genetic, physiological, and environmental factors in the pathogenesis and clinical expression of complex diseases which disproportionately affect blacks, such as hypertension, CHD, stroke, obesity, and diabetes mellitus. Unraveling the interaction of cultural, behavioral, and biological forces that account for racial differences in the presentation, natural history, and outcome of CHD may provide insight into the multiple mechanisms that determine the expression of CHD in the general population. Moreover, the concept of race as a research paradigm can be questioned, particularly when considering diseases in which environmental factors, lifestyles, and socioeconomic factors may be at least as important as biological and genetic factors.

Because of the complexity of CHD, it is likely that its clinical expression in blacks involves the interaction of several different genes as well as multiple environmental influences. It is important, therefore, to establish the phenotypic expression of the disease accurately, especially in a particular group such as blacks. In CHD, phenotypic measurements include a wide array of clinical, diagnostic, and therapeutic characteristics as well as many biochemical, physiological, and biological parameters.

Numerous studies document that blacks have worse outcomes from CHD, excess deaths, and lower rates of use of cardiological procedures. These studies, however, do not present enough clinical information to determine whether disparities in mortality or resource utilization are a function of differences in biology, variable expression of clinical disease, the health care system, or patient or provider traits. To understand the differences in use of cardiological procedures, it will be necessary to obtain detailed clinical profiles, descriptions of patient and physician characteristics, and features of the health care system. In addition, the roles of patient preferences and physician attitudes must be compared with such factors as clinical features, presence of risk factors, coronary anatomy, LV function, and insurance status.

Research Opportunities

The overriding limiting aspect of attempts to resolve apparent inconsistencies in clinical and epidemiological studies of CHD in blacks is the lack of sufficient data to determine whether there are differences in the clinical manifestations of CHD between blacks and whites. Since there is no comprehensive data base of information on CHD in blacks, it is necessary to develop and maintain a system of data collection that will measure clinical and functional outcomes. Much of the data previously collected have been limited geographically or are narrowly focused (i.e., on the utilization of cardiac procedures). Because of the heterogeneity and multiplicative gene interactions inherent in a condition as complex as CHD, effective research will require development of a data base that includes environmental factors as well as biological data. It is unlikely that any one research facility will have access to a sufficiently large cohort of blacks and also have the necessary expertise in such disciplines as clinical evaluation, physiology, biochemistry, molecular genetics, statistics, and epidemiology, to be able to define intermediate phenotypes and subphenotypes. A comprehensive, multidisciplinary approach involving a number of centers and investigators will be required to define phenotypes sufficient to establish a data base that will have long-term importance as a shared source of comprehensive data on CHD in blacks.

Although multiple CVD data bases in blacks are maintained (e.g., NHANES, National Hospital Discharge Survey), national and regional data bases need to be merged to obtain a complete picture of therapeutic interventions, utilization of cardiological care and resources, practice patterns, outcomes of hospital and ambulatory care of CHD, and long-term outcomes in blacks. Development of clinical profiles or diagnostic parameters will help resolve questions regarding differences between blacks and whites in clinical manifestations, natural history, therapy, and prognosis, as well as primary and secondary prevention strategies.

Available data on phenotypic expression of CHD in blacks need to be expanded. One approach may be to establish a retrospective clinical data base. Interested investigators and staff from Federal agencies (e.g., NHLBI, National Center for Health Statistics) could review existing data bases and develop common formats, definitions, and criteria for merging data sets. In addition to collecting and evaluating existing data bases, analysis of available data from population-based studies with information on CHD in blacks could be undertaken. Data could

then be collated, edited, reviewed, and formatted into a resource document of retrospective clinical data for use in identifying research needs and information gaps. The data base could establish the actual frequency of acute and chronic CHD syndromes in blacks (e.g., classic angina, unstable angina, variant angina, mixed angina, silent ischemia, angina-like chest pain with normal coronary arteries). It may also provide information regarding the predisposition to coronary spasm, incidence and prevalence of silent ischemia, and relationship of silent ischemia to arrhythmias.

A clinical network of community-based clinical research centers, located in geographically and socioeconomically diverse black communities and involving minority investigators, is needed to assess the clinical characteristics, natural history, and epidemiology of acute and chronic CHD syndromes; variations in cardiac care; and extent and causes of differences in the use of cardiac procedures. Information could be collected on chest pain in black patients with normal coronary angiography and in patients with significant atherosclerotic coronary stenoses in order to establish correlations with the clinical presentation, signs, symptoms, and coronary anatomy and physiology.

The network and data base would use a common format and definitions for identifying target groups for interventions, clarifying gaps in information, and defining needs for further data.

A data and coordinating center would be needed to support the network. It would serve as a resource and coordinate the efforts of scientists in multiple disciplines who would prospectively define the clinical, physiological, biochemical, cellular, molecular, and biological phenotypes of CHD in blacks. Optimizing the use of informatics technology, the center could provide information management and long-term collection, storage, processing, retrieval, and analysis of population, family and genetic, and clinical and laboratory data.

Recommendations

Specific recommendations for research on the clinical characteristics of CHD in blacks are:

1. Establish a retrospective data base on CHD in blacks for use as a resource to identify knowledge gaps and research opportunities and to provide information on acute and chronic coronary syndromes.
2. Establish a community-based clinical network to assess the clinical characteristics and epidemiology of acute and chronic CHD syndromes; variations in cardiac care; and extent and causes of differences in the use of cardiac procedures. A computerized data base and coordinating center should support the network.

Clinical Ischemic Syndromes

State of the Science

Acute CHD

Although angina pectoris is the classic manifestation of CHD in whites, many questions have yet to be answered about chest pain related to CHD in blacks. In whites, CHD and atherosclerosis are often considered synonymous. Indeed, atherosclerotic obstruction of epicardial coronary vessels is the proximate cause of the vast majority of CHD morbidity and mortality in the United States. However, increasing evidence that blacks have a higher mortality from CHD but less coronary atherosclerosis, at least angiographically, conflicts with the common understanding of the pathophysiology of CHD and the genesis of clinical manifestations in whites.

In the Coronary Artery Surgery Study (CASS), in which angina was the major inclusion criterion for angiography and study participation, “probable or definite angina” was significantly more common in whites than in blacks. There was no racial difference in severity of angina according to gender. Unstable angina was also comparable between race and gender groups. Moreover, even though chest pain was the presenting complaint in most patients in CASS, nearly half of the black men and two-thirds of the black women had no significant CHD on angiography. Other studies in blacks with angina-like chest pain have reported less severe angiographic CHD than in whites. In a study of black and white patients admitted with symptoms suggesting acute MI, no significant CHD was found on angiography in 48 percent of blacks and 17 percent of whites. Blacks were also less likely to have a final diagnosis of acute CHD. The paradox of disproportionately high rates of angiographically normal coronary arteries combined with a high prevalence of CHD risk factors and excess CVD morbidity and mortality presents many research challenges.

Chronic CHD

National and regional statistical data indicate that chronic CHD is the leading cause of death for blacks, as it is for whites. Several studies using hospital discharge data suggest, however, that blacks have lower rates of acute CHD and MI. The reasons for the disparity between data derived from death certificates, hospital discharge, and clinical experience have not been thoroughly investigated. Possible explanations for these inconsistencies range from differences in clinical expression of CHD between whites and blacks to fundamental differences in vascular biology or molecular genetics. It has been reported that blacks are less likely to be admitted to the hospital or triaged to the coronary care unit after presenting with chest pain. Other studies indicate that blacks are also less likely to have cardiac catheterization or CABG surgery.

In the limited number of studies in which angina has been specifically studied in blacks, its prevalence in black men has been found to be comparable to that in white men. In black women, however, angina, or at least chest pain consistent with angina, occurs more commonly than in white women. In NHANES, age-adjusted prevalence rates of angina using the Rose Questionnaire were similar in black, white, and Mexican-American women. However, the reliability and validity of the Rose Questionnaire continue to be questioned by clinicians who treat large numbers of black patients. Because a diagnosis of chronic CHD depends on the ability of patients to communicate the nature of their symptoms and the provider asking the right question in the right way, further validation of the Rose Questionnaire in geographically and socioeconomically diverse black populations is necessary.

Atypical Angina and Abnormal Vasomotion

Anecdotal reports from clinical practices with large numbers of blacks suggest that the proportion of blacks with classical symptoms of chronic CHD is less than that of whites. Some studies suggest that blacks present more commonly with atypical angina (i.e., chest discomfort with aberrant characteristics, precipitants, or accompanying clinical symptoms or signs). For many clinicians, it is difficult to distinguish cardiac chest pain syndromes in blacks from other causes of chest pain. Although typical angina is attributed to increased oxygen demand, most commonly associated with increased physical activity and evidence of excess sympathetic nervous system discharge, chest pain in blacks often occurs at rest, at varying thresholds of activity, and with diverse precipitants. As evidence has accumulated that angina may also be due to inadequate supplies of oxygen, as well as increased demand for oxygen, the role of disordered vasoreactivity has become an important research question in studies of blacks. Because blacks have increased rates of hypertension compared with whites, the vasodilatory capacity of the large and small coronary arteries may be affected. Studies of the interaction of factors that control blood pressure and other CHD risk factors, such as diabetes mellitus and hypercholesterolemia, are particularly important.

Silent Ischemia

Silent ischemia, the syndrome in which significant evidence of myocardial ischemia occurs on the ECG in the absence of chest pain, may also occur more commonly in blacks. It may occur in conjunction with fixed atherosclerotic lesions and may be associated with coronary spasm. The syndrome may occur in patients who have symptomatic clinical angina or in patients with no clinical angina pectoris. Silent ischemia is usually detected by ambulatory blood pressure monitoring. The availability of ambulatory ECG monitoring in some clinical environments has facilitated diagnosis of silent ischemia and led to greater understanding of the mechanisms of this syndrome. Although some studies suggest that silent ischemia occurs more commonly in blacks, its extent and severity have not been well studied. It is not clear whether an increased prevalence of silent ischemia in blacks accounts for the perception among many clinicians of a reduced prevalence of angina in blacks. The possibility that blacks have a predisposition to coronary spasm and may experience silent ischemia with increased frequency, especially associated with LVH, hypertension, excess catecholamine stimulation, psychological stress, and autonomic dysfunction, should be explored. Several studies have raised the possibility that patients with silent ischemia may have less ischemia and, therefore, no angina pectoris or a reduced pain threshold due to increased endorphin levels or altered autonomic function similar to that in diabetics. A patient's denial of symptoms may also be important.

Myocardial Infarction

The high prevalence of CHD in blacks has been documented using vital statistics, death certificate sources, surveys of hospital discharges, and smaller nonpopulation-based clinical reports. Data from observational studies, however, suggest that blacks have fewer hospitalizations for acute MI relative to the rates of out-of-hospital events. Few data are

available that compare the prevalence of transmural and nontransmural MI in blacks. Data regarding differences in presentation and clinical manifestations of acute MI are conflicting. Several studies show significant differences between whites and blacks in presenting signs and symptoms of MI, although other studies report no significant differences in clinical characteristics. For example, data from the National Hospital Discharge Survey indicate that blacks and whites have comparable rates of hospital admissions for acute MI. Blacks, however, particularly women, have MI at younger ages and higher mortality rates than whites, especially before age 50. Death rates for MI have been found to be decreased in black men over 50 years old. In view of the higher prevalence of MI in young blacks, the lower rates of mortality from MI in older blacks is paradoxical: One would expect that higher MI rates in young blacks would yield higher death rates from MI in older blacks.

Differences in the clinical features of MI in blacks, particularly urban blacks, have been reported in several studies. Mortality rates with MI have generally been noted to be increased in blacks, possibly due to an increased prevalence of prior MI on the ECG, elevated blood pressure, diabetes mellitus, and congestive heart failure. Several studies show that blacks may have higher in-hospital mortality rates as well as higher post-discharge mortality rates, although these findings have not been consistent across all studies. One study of inner-city residents suggests that blacks with MI present without chest pain more commonly than whites and more often with pulmonary edema, elevated blood pressure, or a history of congestive heart failure. Black patients with MI admitted to coronary care units tend to be younger and have more prior hypertension but less prior CABG surgery. Most studies report that whites have more coronary artery angioplasty and CABG surgery, although the rates of thrombolytic therapy and cardiac catheterization vary.

Complicating Factors

Prehospital and Hospital Delay

Among the clinical CHD syndromes, the outcome from MI is most affected by delays in seeking care. The time from onset of symptoms to admission to a coronary care unit or other special CHD treatment facility constitutes the prehospital period in the management of acute MI. Prehospital delay is an important determinant of out-of-hospital mortality and may play a major role in short- and long-term outcomes. Prehospital delay may be divided into three phases. Phase I involves patient recognition and action: The patient or other persons in the environment must recognize the signs and symptoms of a possible heart attack, avoid denial, and seek emergency treatment immediately. Phase II usually involves the use of emergency medical services and includes the time to dispatch of transportation and provision of life-sustaining measures in the field. Phase III refers to actions in the hospital emergency room (e.g., time required to take the ECG, establish the diagnosis, begin definitive treatment, and transfer the patient to the coronary care unit). Delay in any of these phases of care is a problem because of the need to begin thrombolytic therapy as soon as possible (optimally, within 6 hours of the onset of pain). Factors contributing to prolonged prehospital delay may be related to a patient's health care seeking behavior; deficiencies in the emergency medical system; or inadequacies in the emergency room, hospital, or provision of care.

For inner-city patients, prehospital delay is an especially severe problem. Studies of urban blacks suggest that they are more likely to delay seeking care for potentially serious symptoms such as chest pain. An analysis that examined the duration of chest pain and determinants of prehospital delay in inner-city patients in Brooklyn, New York, found that the average prehospital delay was 11.9 ± 25 hours. Mean delays were longer for blacks and Hispanics. Most of the delay was due to failure to recognize MI symptoms, failure to attribute symptoms to heart disease, or a belated decision to seek medical help. Other studies also suggest that a major contributor to delays by black patients may be lack of knowledge about the warning signs of acute MI. Still other studies of inner-city patients with MI have found not only prolonged prehospital delays, but also significant delays in transferring patients from emergency rooms to coronary care units. Delay also may be related to inappropriate prehospital medical consultation, slow progression of symptoms, female gender, advanced age, race, and low income. Psychological factors, such as somatic and emotional awareness, may also determine the length of prehospital delay. It has been postulated that U.S. blacks tend to wait longer because of the historical precedent of slavery in which only the most disabling conditions justified an interruption of one's duties in order to seek care. There is little direct evidence, however, that the different hospitalization rates for acute MI in blacks result from differences in the health care seeking behavior of blacks and whites.

With the advent of thrombolytic therapy, the delay of which can have a major impact on clinical outcome, prehospital delays have significant prognostic implication. For low-income blacks who reside in the inner city, as well as rural blacks, the logistics of communicating with the emergency medical system, securing transportation, and achieving access to emergency care is often limited by financial resources and competing life conditions. Adding to the problem of access to emergency medical systems is the lack of standardization among these systems across the nation. In some cities, emergency medical transportation is provided only by private ambulance companies; otherwise, patients must take public transportation, private automobiles, or taxis. Procedures for obtaining emergency services and the availability of "911" emergency calls vary widely between cities and between communities. The availability of sufficiently trained staff (e.g., paramedics, emergency medical technicians) and "field-based" electrocardiography, defibrillators, or thrombolytic therapy varies even more. These resources are often in short supply in the underfunded urban and rural public health care systems that many blacks use.

Circadian Variation

Circadian variation in CHD events has been recognized for some time. Many patients with variant angina, silent ischemia, and MI have more disease activity during early morning hours when blood pressure and pulse rate are increased prior to arising. Several studies of ambulatory blood pressure show that more blacks tend to have higher blood pressures during the night, compared with whites. Whether this continuation of daytime levels of elevated blood pressure during the night is also linked to increased prevalence of ischemia and MI in the early morning hours in blacks has not been thoroughly investigated. A relationship between circadian variation and sudden death and arrhythmias has also been suggested, but data are limited in blacks.

Research Opportunities

Apparent differences in the clinical characteristics of exertional angina in blacks and the suggestion in several studies that atypical angina and silent ischemia are more prevalent in blacks has led clinicians to consider whether the pathogenetic mechanisms described in whites are the same as those producing chest pain in blacks. This concern has fostered a need to reexamine the clinical definition of angina pectoris as applied to blacks.

Some of the questions about the clinical aspects of angina pectoris and angina-like chest pain in blacks are: What is the prevalence of atypical angina and silent ischemia? Why do blacks have more chest pain than whites despite having normal coronary arteriograms? Do the quality and characteristics of chest discomfort related to epicardial disease differ between blacks and whites? Do the quality and characteristics of chest pain due to epicardial CHD disease differ from that due to microvascular disease? Is the threshold for angina different in blacks than in whites? Are the precipitants of angina in blacks different than those in whites (e.g., emotion, exercise, eating, environment)? Is the chest pain of different quality, character, and radiation? What is the distribution of noncardiac causes (e.g., gastrointestinal, pulmonary, musculoskeletal, neurogenic) of chest pain in blacks with normal coronary arteriograms? Is coronary artery spasm a factor in the chest pain syndrome in blacks?

There are also many research questions concerning MI, prehospital delay in seeking care, and hospital delays in initiating care. Is the time from symptom onset to hospital arrival longer for black patients than for white patients? What is the clinical course for black patients admitted to coronary care units? Is there a marker in the postinfarction period for identifying patients who would benefit from efforts to reduce expansion of the infarct? Do differences in the quality of emergency medical systems account for differences in survival after MI in blacks?

Understanding why the hospital-discharge diagnosis of MI in blacks occurs dramatically less often than the diagnosis of MI on out-of-hospital autopsies or death certificates is one of the greatest challenges facing researchers today. Answers to this complex question may be obtained from a variety of research approaches involving multiple disciplines. Studies of the pathogenesis of atherosclerosis, mechanisms of coronary occlusion, or differences in clinical expression of pathological processes common to multiple racial and other subgroups are likely to provide answers. Studies of the factors associated with prehospital delay, such as health care seeking behavior, availability of health insurance, knowledge about CHD, characteristics of the symptoms, physician attitudes, or emergency medical systems, also may yield answers. Technological advances in early detection and quantification of vascular disease, innovative cardiac imaging techniques, and new methods of identifying patients at risk of MI or sudden death will also be useful. Previous studies in blacks in each of these areas have been limited by small sample sizes and scant clinical, laboratory, and outcome data.

Recommendations

Specific recommendations for research on clinical ischemic syndromes associated with CHD in blacks are:

1. Study the effects of race and sociocultural environment on clinical presentation, natural history, and treatment of MI and unstable angina.

2. Determine the most effective means (e.g., public education programs) for increasing awareness of MI, including warning signs and the appropriate response to possible symptoms of acute ischemia, in geographically and socioeconomically diverse black populations.

3. Assess the impact of variations in emergency medical systems in urban and rural black communities, and determine the relative value of improving these systems in different environments.

4. Develop reliable methodology to identify subgroups of blacks at high risk of MI and sudden death for evaluation of clinical interventions.

5. Expand studies of the significance of differences in diurnal blood pressure, neurogenic activity, hormonal function, and other physiological factors on the incidence and prevalence of MI, sudden death, and arrhythmias.

6. Determine whether the response to ischemia and infarction and the incidence of myocardial reperfusion abnormalities, myocardial stunning, and ventricular remodeling differ between racial groups.

DETECTION AND QUANTIFICATION OF CHD

State of the Science

Utilization and Validation of Diagnostic Tools

Diagnosis of CHD in blacks is viewed by many clinicians as more difficult and complex than in whites. The unproved reduced prevalence of CHD and the apparent difficulty clinicians have in establishing the etiology of chest pain in black patients may account for some of the disparities in the use of resources. The impression that CHD is uncommon in blacks and that diagnostic testing is, therefore, not indicated because of low yield may affect a clinician's decision to order specific diagnostic procedures. Reluctance of black patients to undergo cardiac procedures because of lack of confidence in the physician or health care system, unfamiliarity with the proposed procedure or its value, or financial factors may also influence the decision making of physicians and patients.

More knowledge is needed regarding the value of standard diagnostic tools in distinguishing atherosclerotic and coronary symptoms from nonatherosclerotic and noncoronary symptoms. In contrast to techniques that require excision of tissue, either during atherectomy or surgery, innovative approaches, such as intravascular ultrasound and radiolabeled monoclonal antibodies, need to be applied to assess vascular lesions in vivo in blacks. Pharmacological probes to assess vascular reactivity and function are available for testing in clinical trials and may help elucidate mechanisms of progression and regression of lesions in multiple racial and other subgroups. Although much is known about the value of more established diagnostic techniques in whites, many common diagnostic parameters and assumptions related to risk assessment, prognosis, and natural history have not been validated in blacks.

Standard Techniques

Echocardiography

Echocardiography has proved to be of critical importance in understanding CHD in blacks because of the possible contribution of LVH and hypertension to clinical manifestations and natural history of CHD in blacks. Although earlier epidemiological studies established the increased prevalence of hypertension in blacks, echocardiography enabled investigators to link structural and functional information to epidemiological data. However, questions regarding the usefulness of echocardiography in repetitive long-term measurements of LVH have led to its reassessment for longitudinal evaluation of CHD in blacks, as well as the general population. Echocardiography continues to be the most commonly used tool for measuring LVH and, more recently, has gained favor for the assessment of regional wall motion and other parameters of structural and functional change related to CHD. The insights gained on the interactive

roles of hypertension and LVH in the genesis of structural and functional changes associated with vascular disease have not been applied in studies of CHD in blacks.

The efficacy of dobutamine, two-dimensional stress echocardiography and perfusion scintigraphy [i.e., technetium-99m methoxy isobutyl nitrile (sestamibi) single-photon emission computed tomography] for detecting CHD has been shown to have equivalent accuracy in some studies, but has not been compared in blacks. In patients with LVH, studies suggest that the test of choice should be echocardiography. Scintigraphy with sestamibi or similar agents appears to be preferable in patients with a negative submaximal echocardiogram and enhances the accuracy of stress echocardiography alone.

Development of intravascular ultrasound holds great potential for quantifying and evaluating atherosclerotic lesions and their progression and regression. As intravascular echocardiography matures and new and innovative techniques are developed, it is likely that clinicians will have a tool to monitor the effects of advanced therapeutic agents on vascular biological processes. Application of intravascular echocardiographic techniques in blacks will help distinguish between nonatherosclerotic and atherosclerotic CHD. Studies of the new technique of three-dimensional echocardiography suggest that it may provide an accurate method for directly measuring global and regional myocardial surface areas postinfarction. Application of newer noninvasive techniques for evaluating vascular and ventricular remodeling, as well as changes in ventricular morphology following MI, will permit clinicians to assess treatment effects in more detail and may be useful for studying CHD in blacks.

Electrocardiography

Much confusion remains concerning interpretation of ECG "normal variants" in blacks. Understanding the fundamental mechanisms responsible for producing ECG normal variants in blacks enables evaluation of the electrophysiology of repolarization and surface ECG. For example, nondiagnostic ST- and T-wave changes and early repolarization occur more commonly in young black men. These findings may be markers for unique electrophysiological, structural, or functional characteristics of the LV and may indicate special electrophysiological "traits" in blacks that predispose to arrhythmias and sudden death. Similarly, increased R-wave voltage is more common in young black men than in young white men. It is not clear whether this occurrence is a function of increased LVH, enhanced conduction, or another, as yet undiscovered, factor. Renewed interest is being given to the surface ECG because of evidence that LVH can be diagnosed as effectively and more reproducibly from the scalar tracing as from the ECG.

The clinical usefulness of the signal-averaged ECG in predicting potential arrhythmias has not been studied specifically in blacks. The technique has proved to be useful in identifying individuals with a propensity for arrhythmias after MI and may also be useful in evaluating black patients because of their increased rates of sudden death and ventricular dysfunction related to CHD and hypertension.

Exercise ECG Testing. The limitations of exercise ECG in diagnosing CHD have been studied extensively. Indeed, the value of diagnostic tests, as measured by Bayes' theorem, is particularly relevant to exercise ECG stress testing. That the diagnostic accuracy of a diagnostic test depends on the pretest likelihood of disease is a maxim that has become widely accepted. Bayes' theorem, as it relates to exercise stress testing, has not specifically been tested in blacks. High rates of ST-segment and T-wave changes and of LVH on ECG make it difficult to interpret changes. The increased prevalence of hypertension and LVH in blacks and their accompanying ECG changes are well known to most practitioners. These changes may be confused with ECG changes associated with CHD. Since LVH that is evident on echocardiography may not be detected by routine ECG in black patients with chest pain, the clinician is faced with a dilemma in evaluating chest pain in blacks. Chest pain is often characterized as atypical in blacks, and the exercise ECG stress test is judged to be equivocal or nondiagnostic. Moreover, in patients with angina pectoris, the exercise ECG may not be substantially better at predicting coronary anatomy or 3-year survival than the initial physician's history and physical examinations. A history of congestive heart failure, digoxin use, ST depression, change in systolic blood pressure, and reduced exercise capacity has been shown to predict time until CVD death. The role of psychological factors, such as denial, deception, anger, and depression, and of marital adjustment and external stress in determining the results of exercise stress testing has also been investigated. The perception of physical symptoms, in addition to ischemic threshold and exercise tolerance, may be independently associated with chest pain during exercise ECG testing. The influences of these factors may add to the severity of coronary artery obstruction.

Exercise stress testing is less reliable in middle-aged women, particularly black women. Black women, however, have higher rates of MI and more severe CHD morbidity and mortality. The roles and mechanisms of action of psychological and behavioral factors on electrophysiology are not clear. Changes in catecholamine levels and adrenergic function may be related to stress and may be reflected on the ECG.

Myocardial Imaging

Because many blacks often have less access than whites to the newest diagnostic technologies, there is little population-based information about the value and applicability of the technologies to evaluating the special problems of black patients with chest pain. The value of modalities such as PET, NMR, gated computerized tomography, B-mode ultrasonography, and intravascular ultrasound has not been delineated according to race. It is likely, however, that by evaluating the influence of hypertension and LVH on the results obtained from newer diagnostic techniques, insights will be gained on the usefulness of these techniques for evaluating possible CHD in blacks.

Imaging of the myocardium with radionuclide agents such as thallium-201 has gained wide acceptance in the assessment of myocardial perfusion. The ability of these imaging techniques to assess ischemic as well as infarcted myocardium has proved useful in assessing CHD. The recent development of new radionuclide agents, such as sestamibi, which have kinetics and distributions different from thallium, offers the prospect of even more precise timing and quantification of ischemic events and myocardial injury. Experience with the use of these imaging techniques in blacks, however, has not been separately reported. Data are needed on the value of these agents in CHD, hypertension, and LVH in blacks.

Abnormalities may occur with thallium stress testing in hypertensive patients who have a low likelihood of CHD, suggesting that the false-positive rate in hypertensives may be significant. Studies show, however, that a negative thallium scan (with or without dipyridamole) in hypertensives virtually excludes significant abnormalities of myocardial perfusion. For hypertensive patients with chest pain or ECG criteria for myocardial ischemia, the high sensitivity, negative predictive value, and low false-negative rate of thallium stress testing support its role, with or without dipyridamole, as an exclusion test for significant CHD. The reliability of thallium testing for diagnosis of CHD in the presence of LVH and hypertension has not been thoroughly evaluated. Abnormalities on thallium scanning have also been reported in patients with normal coronary arteries and chest pain or microvascular angina. The significance of a positive thallium perfusion scan, however, is not certain, given that abnormal scans may occur in patients who have a low likelihood of CHD. New techniques, such as radiolabeled monoclonal antibody probes for imaging atherosclerotic lesions, offer additional research opportunities regarding the diagnosis of CHD.

Coronary Angiography

In CASS, normal or minimally diseased vessels were significantly more common in blacks than in whites. Review of angiographic comparisons of blacks and whites also shows that blacks with chest pain have a higher proportion of normal coronary angiographic studies than whites. The clinical implications of these data are not clear, however, because of the small size of the black cohorts, selection bias, or the retrospective and nonconsecutive nature of the observations. Much of the uncertainty regarding CHD in blacks has evolved from the apparent discrepancy between the statistically high prevalence of CHD, excess morbidity and mortality related to MI and congestive heart failure, and the high rate of normal coronary angiograms in blacks enrolled in studies of cardiac surgery or catheterization. Angiographic morphology of coronary stenoses in acute coronary syndromes helped establish the role of intracoronary thrombosis in the pathogenesis of unstable angina and MI. Recent examination of angiographic findings in patients presenting with a first ischemic episode compared with those in patients with chronic angina suggests that the severity of angiographic narrowing is more severe in the chronic state. Chronic angina, acute coronary syndromes, and angiographic information (e.g., lesion severity, morphology, lesion distribution, evidence of thrombus, plaque rupture) do not differ significantly between blacks and whites. In large clinical trials, coronary angiographic findings have been similar in blacks and whites. Few studies have compared the results of coronary angiography in blacks and whites in acute coronary syndromes, chronic stable angina, or ischemic cardiomyopathy.

Access to Coronary Angiography. Factors that determine whether or not a patient with chest pain undergoes diagnostic cardiac catheterization and coronary angiography are not well understood, especially in blacks. Multiple studies consistently demonstrate that blacks are only half as likely as

whites to receive cardiac catheterization and subsequent revascularization. Studies show that, compared with whites, blacks have less access to cardiac catheterization, percutaneous transluminal coronary angioplasty (PTCA), and CABG surgery. Even after controlling for indicators of disease severity, these differences persist in such populations as Medicare recipients and patients in Veterans Administration hospitals, where reimbursement should not be an obstacle. The reasons for these differences in the provision of cardiac care have not been elucidated. It is not clear how the interplay between patient factors (e.g., denial, mistrust of the medical system, lack of medical information) and physician factors (e.g., poor communication skills, inconsistent referral patterns, racial bias that affects decisions for discretionary care) influence the utilization of these resources. This disparity in access appears to be independent of case mix, payor mix, disease severity, and socioeconomic status (SES). The role of variations in insurance coverage, inconsistent availability of health system resources, practice differences, and lack of subspecialists and providers of primary care in minority communities has not been completely assessed. Available data indicate that race is a major independent determinant of access to many cardiac procedures. Because of lack of access, it is possible that the published studies of angiographic findings in blacks are subject to selection bias and may not be representative of the spectrum of angiographic findings in blacks.

Research Opportunities

Echocardiography, as the most commonly used tool for measuring LVH, can now be used for assessing regional wall motion and other parameters of structural and functional change related to CHD. Research on the interactive effects of hypertension and LVH on structural and functional changes associated with CHD needs to be pursued in blacks. In addition, the efficacy of dobutamine, two-dimensional stress echocardiography and perfusion scintigraphy in detecting CHD should be investigated in blacks. Intravascular echocardiographic techniques offer opportunities for differentiating nonatherosclerotic and atherosclerotic CHD in blacks. Newer techniques, such as three-dimensional echocardiography, may enhance the evaluation of CHD in blacks, particularly global and regional myocardial surface areas after MI.

Among the possible areas of future research that have potential for improving the detection and quantification of CHD in blacks is interpretation of the ECG in blacks. Some of the questions to be answered are: What are the causes of ECG variants seen in many blacks? How do these changes relate to hypertension, LVH, and CHD in blacks? How should the clinician view the well-known ECG normal variants that occur more commonly in blacks? Why is the false-positive rate for stress testing high in blacks, especially black women? Is Bayes' theorem appropriate for blacks with a different pretest likelihood of CHD and higher rates of chest pain with normal coronary arteries? How do patients and physicians decide which diagnostic tests to perform and what to do with the results? What does a positive test mean in blacks compared with whites?

Studies of the angiographic morphology of coronary lesions in unstable angina and MI have enhanced our understanding of the pathogenesis of acute coronary syndromes. It has been suggested that the location of coronary lesions, as well as the severity and extent of atherosclerotic involvement, may be useful in predicting future events. Some studies, however, note that the site of subsequent infarction often is unrelated to the site of maximum stenosis and often occurs in a less diseased arterial segment. In addition, the value of angiographic findings in predicting in-hospital and long-term outcomes has not been studied in blacks. It would be of value to review existing angiographic data on blacks to identify a cohort of individuals with chest pain and normal coronary arteriography stratified on the basis of the presence or absence of LVH on the echocardiogram or the presence of abnormal stress test results. A study of the natural history of this angiographically defined group might prove informative. Study of the clinical correlates of angiographic findings in blacks may provide a unique opportunity for understanding the mechanisms of myocardial ischemia in nonatherosclerotic and atherosclerotic CHD.

Several questions concerning coronary angiography in blacks need to be investigated: What can be learned from the discrepancy between the low incidence of abnormal angiograms and the common occurrence of angina-like chest pain in blacks? Are the numbers of procedures in blacks inappropriately low or the rates in whites inappropriately high?

Efforts to monitor the quality and appropriateness of coronary angiography and cardiac catheterization have led to the establishment of minimal standards for quality that have not been directed at this second important question. One of the commonly used measures of appropriateness is the number of normal angiograms performed in a given catheterization laboratory. In the white population, such measures would, presumably, limit the number of inappropriate

procedures. However, in a laboratory serving a predominately black population, those who determine appropriateness may need to consider the pretest likelihood of disease and the value of finding a normal test in diagnosis. Because noninvasive tests have been shown to have high false-positive rates in some black populations, the decision to proceed to coronary angiography in black patients may be the most efficient means of determining whether symptoms are due to atherosclerotic CHD.

How much time and money should be spent on noninvasive testing before proceeding to coronary angiography? Concern about studying too many "normals" may serve as a disincentive to performing angiography in black patients. Perhaps the minimum criteria for the number of normal studies allowed in a laboratory should include the prevalence of significant disease in the population served. It is unclear whether new standards of quality are necessary for catheterization laboratories that serve significant numbers of blacks and whether other noninvasive tests are more valuable in assessing chest pain.

Recommendations

Specific recommendations for research on the detection and quantification of CHD are:

Utilization and Validation of Diagnostic Tools

1. Compare the relative specificity and sensitivity of noninvasive tests (e.g., stress testing with ECG and echocardiography, transesophageal echocardiography, radionuclide imaging, cardiac ultrasound) in diagnosing atherosclerotic versus nonatherosclerotic heart disease in blacks compared with whites.

2. Compare the decision-making process by health care providers for ordering diagnostic procedures in blacks and whites and the decision-making process by patients in accepting recommended procedures.

3. Assess the role of race, SES, and access to care in the utilization of discretionary cardiac procedures such as diagnostic tests.

4. Utilize new and improved noninvasive techniques for monitoring the development, progression, and regression of atherosclerotic disease in the coronary arteries and other vascular systems.

Echocardiography

1. Determine the value of echocardiography and other imaging techniques in diagnosing individuals with genetically determined LVH or hypertrophic cardiomyopathy, and compare these results with those from genetic testing.

2. Compare the sensitivity and specificity of echocardiographic measurements with ECG techniques for assessing ventricular structure in patients with and without atherosclerotic vascular disease and/or LVH.

3. Determine the prognostic significance on outcomes, independent of blood pressure, of various echocardiographic measurements of ventricular function and CHD (e.g., three-dimensional echocardiography and intravascular ultrasound).

4. Develop new and innovative methods for analysis of echocardiograms that will accurately assess LVH and ventricular function, both global and regional, and structure (e.g., three-dimensional echocardiography).

Electrocardiography

1. Compare the diagnostic accuracy, reliability, sensitivity, and specificity of exercise stress testing in blacks with chest pain, with and without epicardial CHD, and with and without hypertension and/or LVH, as compared with whites.

2. Determine the impact of psychological and behavioral factors (e.g., anxiety, stress, beliefs, and attitudes) on the genesis of differences in ECG changes, both at rest and with exercise, in blacks and whites.

3. Determine the structural and functional mechanisms of ECG changes that are considered normal variants in blacks, assess the contribution of LVH and hypertension to these changes, and define the clinical significance of these changes in acute and chronic myocardial ischemia.

4. Elucidate the mechanisms in exercise-induced regional wall motion abnormalities and in systolic and diastolic functional abnormalities in black patients with normal and abnormal coronary angiograms.

Myocardial Imaging

1. Compare the value, accuracy, sensitivity, and specificity of myocardial imaging techniques in black and white hypertensives and nonhypertensives and individuals with and without LVH.

2. Determine the mechanism of abnormalities in stress tests using thallium, with and without dipyridamole, and other radionuclide perfusion imaging agents in patients with normal coronary angiograms, hypertension, and LVH.

Coronary Angiography

1. Develop methods for assessing and controlling for selection bias in angiographic studies in blacks with chest pain and possible CHD.

2. Assess the natural history of chronic CHD in blacks with normal and abnormal coronary angiography, acute and chronic CHD syndromes, and ischemic cardiomyopathy.

3. Determine the relationship of coronary angiographic findings to the site, severity, and outcome of subsequent MI and other cardiac events in patients with mild to moderate CHD, with and without LVH.

Therapeutic Interventions for Macrovascular Disease

State of the Science

New Approaches

The number of direct therapeutic approaches for treating atherosclerotic lesions continues to grow. Research on strategies to prevent and control clinical manifestations of CHD and to produce regression of atherosclerosis offers new and dramatic possibilities for the future. As innovative therapeutic modalities are developed, it is important that minorities, particularly blacks, be included in clinical trials of their efficacy. Blacks represent the second largest group of individuals (after women) for which there are only limited data on many aspects of CHD.

Many new interventions hold great promise for treating atherosclerotic CHD. For example, monoclonal antibodies tagged with radionuclides can be used not only to image lesions and monitor their regression, but also, with the addition of chimeric molecules, to bind to the surface of lesions and serve as messengers for delivering therapeutic agents such as antioxidants, anti-inflammatory substances, or antigrowth factors. A wide range of clinical questions could be addressed using this approach. Subpopulations in whom there is a high likelihood of variations in therapeutic range, dosage, and side effects could be studied if this approach proves to be feasible and cost effective. Pharmacological agents that modify endothelial function, alter smooth muscle growth and proliferation, control vascular reactivity, and manipulate cellular interactions could also be examined.

Pharmacological Therapy

The management of CHD and the choice of intervention in blacks may be affected by the likelihood of concurrent hypertension and LVH associated with vascular pathology, as well as the direct effect of the intervention on the circulation. There is no evidence as yet that the atherosclerotic process differs between blacks and whites. However, because of the more frequent possibility of a nonatherosclerotic etiology for chest pain in blacks, the nature of the coronary syndrome must be defined precisely in blacks in order to select effective therapy. Unlike the treatment of hypertension in blacks, in which the relative effectiveness of antihypertensives may differ among racial subgroups, traditional antianginal medications (e.g., nitrates, beta-blocker drugs, and calcium-channel blocking agents) control chest pain in both blacks and whites. The goals of antianginal therapy in blacks are often based on presumptions about the desirability and efficacy of a given intervention to reverse LVH or reduce elevated blood pressure. The data (e.g., on the control of angina, CHD morbidity and mortality, and prognosis) on the relative value of drugs in stimulating LVH regression are insufficient.

Percutaneous Transluminal Coronary Angioplasty

Few data are available on the effectiveness of PTCA in blacks. Several studies report that recanalization rates with PTCA in asymptomatic patients with

exercise-induced silent ischemia are comparable to rates in patients with chest pain and are accompanied by low cardiac event rates and no deaths during the followup period.

Coronary Artery Bypass Graft Surgery

Data published on CABG surgery in blacks are fragmented and limited. Information from CASS indicates that blacks have better survival rates with surgery than with medical management. Other short-term followup studies of CABG in blacks also show that survival is acceptable but functional outcomes are disappointing. Results indicate that 50 percent of blacks continue to experience angina after surgery and the percent of individuals working (employed) decreased, with 13 percent working postoperatively compared with 33 percent preoperatively.

Thrombolysis

Information on the use of thrombolysis for acute MI in blacks is extremely sparse. One study in which 24 of 352 patients were black reported patency (luminal opening) rates for the infarct-related artery of 91 percent in blacks compared with 72 percent in whites. Survival of patients until hospital discharge, and other clinical outcomes, did not differ between blacks and whites. Fewer blacks required PTCA to rescue ischemic myocardium in jeopardy for MI.

Research Opportunities

Examples of research questions regarding new therapeutic approaches for CHD in blacks include: How should genetically modified cells be used in altering vessel wall pathology? Which pharmacological agents are most effective in modifying smooth muscle growth and proliferation?

Given that classical atherosclerotic vascular disease has similar pathogenetic features and clinical manifestations in blacks and whites, the efficacy of traditional therapy is, as expected, similar. However, no large clinical comparison of the effectiveness of antianginal therapy has been performed between blacks and whites. Questions that need to be answered are: Is the response to antianginal therapy the same in blacks and whites? How does the presence of LVH, diabetes, smoking, or hypertension affect the response to antianginal drugs? Is the response to antianginal therapy linked to changes in blood pressure or LVH?

Multiple PTCA data bases should be merged to obtain a more complete population-based registry of PTCA data in blacks. This information could be used to assess aspects of care such as PTCA utilization and outcomes in hospitals that serve both black and white patients. The relative effectiveness of PTCA compared with CABG surgery in blacks is another important issue.

Recommendations

Specific recommendations for research on therapeutic interventions for macrovascular disease are:

1. Determine the efficacy of newer therapeutic agents, such as antioxidants, anti-inflammatory substances, growth factor inhibitors, ACE inhibitors, and hormone replacement, in modifying vascular and ventricular remodeling in blacks with atherosclerotic and nonatherosclerotic CHD.

2. Conduct clinical trials of newer therapeutic agents to assess their effects on vascular smooth muscle, control of vascular tone, the endothelium, and other components of the atherosclerotic process in blacks with CHD.

3. Pool data from existing multicenter, interventional trials and establish a prospective data base to determine the appropriateness and value of CABG surgery, PTCA, and thrombolysis compared with conventional medical therapy in blacks.

SMALL-VESSEL (MICROVASCULAR) CHD

State of the Science

Chest Pain: Diagnosis and Evaluation

Acute coronary syndromes and chronic myocardial ischemia are most commonly caused by stenoses of the coronary arteries due to arteriosclerosis. However, up to 20 percent of patients with angina-like chest pain do not have abnormalities on a coronary angiogram despite symptoms that may appear to be typical of classical coronary insufficiency, often with abnormal noninvasive stress testing. The syndrome of chest pain with normal epicardial coronary angiography, no coronary artery spasm, and an

ischemic-appearing ECG response to exercise has been referred to as "Syndrome X" in some studies. However, this term has also been applied to patients with hypertension, hypertriglyceridemia, and insulin resistance and therefore should be avoided when discussing coronary syndromes. Several studies suggest that abnormal coronary microvascular function may limit appropriate flow responses to stress, possibly due to endothelial dysfunction. However, convincing evidence of ischemia during stress has not been shown in many studies. Further, in many patients, chest pain may be due to heightened sensitivity to cardiac pain.

Research Opportunities

Investigations of cardiac microcirculation in humans have focused on indirect functional measurements of coronary reserve; techniques for directly assessing the function and structure of this microcirculation have not been developed. Mechanisms for controlling vascular reactivity play a major role in the development of abnormal coronary vascular reactivity and nonatherosclerotic vascular disease, including microvascular disease. Studies are needed on the differences between blacks and whites in the responsiveness of the microvasculature to physiological stresses (e.g., pacing) and pharmacological agents (e.g., acetylcholine). Research on vascular endothelium and smooth muscle should focus on the control of microvascular tone and reactivity in blacks. The relative roles of hypertension, LVH, hypercholesterolemia, diabetes, and smoking in the development of microvascular disease in blacks should be further elucidated.

Additional questions about the microvasculature in blacks include: What is the effect of vascular remodeling and LV remodeling on microvascular flow? Does nonhomogeneous epicardial atherosclerosis result in a microvascular "steal" phenomenon (i.e., diversion of blood flow)? What are the mechanisms responsible for the production of lactate in some patients with angina-like chest pain and normal coronary arteries on angiography? What is the mechanism of the increase in coronary flow coincident with myocardial lactate production and abnormal contraction pattern in patients with angina-like chest pain and normal coronary angiography? Studies of vasodilator reserve in blacks with and without these key factors would significantly improve understanding of nonatherosclerotic CHD in blacks.

Research shows that structural remodeling of the epicardial and intramyocardial coronary arterioles occurs with hypertension and that fibrillar collagen accumulates in the myocardium with hypertrophy. How do these factors contribute to a reduced dilatory capacity of the microcirculation in blacks? Studies of biopsies of the right and left septum show an increased medial wall area of arterioles and increased volume density of interstitial fibrosis. Are the structural changes in the microcirculation independent of loading conditions? Is the increase in angina-like chest pain with normal coronary arteries in blacks related to the prevalence of hypertension or another, as yet undiscovered, factor (e.g., genetic, hormonal)? How does myocardial ischemia associated with microvascular disease affect ventricular hemodynamics and function? How does LVH and regression of hypertrophy affect the clinical course of angina-like chest pain (e.g., pain frequency and severity, response to treatment) in patients with normal coronary arteries? Are there differences in the response of the epicardial and microcirculatory endothelium to CHD risk factors, diabetes, hypertension, and the extent of atherosclerosis?

Recommendations

Specific recommendations for clinical research on small-vessel (microvascular) CHD are:

1. Develop new and improved methodologies and techniques for studying the microvasculature and measuring coronary reserve and microcirculatory flow with Doppler, radionuclide, and metabolic-based techniques (e.g., PET, NMR) in blacks with atherosclerotic and nonatherosclerotic CHD.

2. Examine the relationship of structural changes in the arterial wall and arteriolar wall to vascular reactivity and coronary reserve, especially in the context of chest pain and hypertension in blacks.

3. Assess the influence of inflammation, vasculitis, or immune complex disease on abnormal coronary reserve and microvascular function and chest pain syndromes in blacks.

4. Determine the impact of controlling CHD risk factors such as hyperlipidemia, LVH, diabetes, and smoking on chest pain and the natural history of microvascular disease.

5. Determine the effect of myocardial ischemia resulting from microvascular abnormalities on ventricular function and heart failure in blacks with angina-like chest pain and normal coronary arteries.

6. Compare measurements of microvascular function in different vascular beds (i.e., forearm versus heart) and the relationship of these measurements to signs and symptoms of microvascular cardiac disease.

ARRHYTHMIAS AND SUDDEN DEATH

State of the Science

Role in CHD Morbidity and Mortality

Vital statistics show that morbidity and mortality from CHD are higher in blacks than in whites. Yet, clinical observational data, survey data, and anecdotes from health care providers who care for large numbers of black patients suggest that the numbers of blacks who seek care for CHD are fewer than would be expected, based on morbidity and mortality rates, and much fewer than in a comparable white population. Further, data obtained from death certificates and autopsy data indicate that more blacks with CHD die out of the hospital or from sudden death than in the health care system. Possible explanations for these data include socioeconomic and cultural factors, such as access to and utilization of health care services, as well as biological factors.

Although health statistics on the trends for sudden death and out-of-hospital deaths in blacks are limited, several studies suggest that there may be biological differences between blacks and whites that could account, in part, for some of these data. Early studies (e.g., New Orleans, Nashville) report that blacks have higher rates of cardiac arrest than whites. More recent data (from Chicago) document that the incidence of out-of-hospital cardiac arrest in persons of all ages is substantially higher in blacks than in whites. These data further show that the survival rate after cardiac arrest is lower in blacks than in whites, which is not explained by any difference in the quality of emergency medical services provided.

These data and findings support the need for additional research to document more precisely the risk of life-threatening arrhythmias and sudden death in blacks and to clarify biological differences between blacks and whites that may account for this risk.

Signal-Averaged ECG

Signal-averaged ECG has been shown to be useful in determining the risk of life-threatening arrhythmias and sudden death. Using this technique, investigators are able to detect areas of slowed conduction (i.e., late potentials) usually related to nonhomogeneity, MI, or cardiomyopathy. The technique may also be useful in predicting infarct expansion and ventricular dilatation. Infarct expansion results in the separation of myocytes by areas of fibrosis and may be related to the development of late potentials. It is also possible that LVH and collagen deposition may result in similar histological patterns. The predictive value of detecting late potentials in patients with LVH or ventricular dilatation, either due to ischemic cardiomyopathy or end-stage hypertensive heart disease, has not been assessed.

Research Opportunities

Prevalence data on arrhythmias and sudden death in blacks are scant. Appropriate questions that need to be addressed in future research include: What are the incidence and prevalence of potentially lethal arrhythmias in blacks? Is sudden death indeed more common in blacks? What are the clinical correlates of sudden death in blacks? Is the relationship of sudden death to atherosclerosis as close in blacks as it is in whites? What is the role of plaque rupture and intracoronary thrombosis in sudden death in blacks? What are the roles of silent ischemia and coronary vasospasm in sudden death in blacks?

LVH has been shown to be more prevalent in blacks; however, there are few data on the relationship of LVH and sudden death. Pertinent questions include: Does LVH predispose to sudden death in blacks and, if so, what is the mechanism? What is the role of the microvasculature, hypertension, and vasculitis in sudden death in blacks? Are there genetic determinants of arrhythmias? What is the best way to assess the risk of sudden death in blacks (e.g., Holter monitoring, stress testing)?

Other research questions relevant to understanding the mechanism for increased sudden death in blacks include: What are the incidence and prevalence of arrhythmias according to risk factor profile, family history, and other factors in blacks? Should asymptomatic individuals with angina-like chest pain and normal coronary arteries be screened to assess their risk for sudden death? What are the roles of silent

ischemia and coronary artery spasm as a cause of sudden death in blacks? What are the prevalence, severity, and extent of atherosclerosis in blacks who die suddenly? What is the correlation of atherosclerotic disease and LVH in blacks who die from sudden death? Are diurnal patterns of blood pressure in blacks related to patterns of sudden death?

Recommendations

Specific recommendations for clinical research on arrhythmias and sudden death are:

1. Determine the incidence and prevalence of life-threatening arrhythmias in blacks with chest pain syndromes related to nonatherosclerotic and atherosclerotic CHD.

2. Study the clinical electrophysiological characteristics of ischemic and hypertrophied myocardium in blacks, and develop criteria for detecting high risk of arrhythmias and sudden death in blacks.

3. Examine mechanisms of diurnal variation in sudden death and of differences in cardiovascular reactivity as possible explanations for higher rates of sudden death in blacks compared with whites.

4. Determine the role of antihypertensive therapy in sudden death.

HEART FAILURE AND CHD

Numerous studies have documented the increased prevalence of congestive heart failure in blacks. The reasons for the prominence of heart failure in the spectrum of CHD in blacks may be related to comorbid conditions such as cardiomyopathies (i.e., primary myocardial diseases) which, when combined with risk factors common in blacks, lead to significant ventricular dysfunction.

State of the Science

Ischemic Cardiomyopathy

Ischemic cardiomyopathy, or LV dysfunction from diffuse (multivessel) CHD, is often not considered nor vigorously pursued diagnostically. This condition may be worse when LVH and CHD occur simultaneously.

Compared with whites, blacks with CHD tend to have worse LV function that may lead to heart failure. Determination of the etiology of LV dysfunction may be challenging insofar as the differential diagnosis of the dysfunction may be influenced by preconceptions based on the increased prevalence of hypertension and LVH in blacks. High rates of alcoholism and drug abuse in some segments of the black population often prompt consideration of alcoholic cardiomyopathy or postviral or human immunodeficiency virus (HIV)-related cardiomyopathy. Uncertainty regarding the likelihood of CHD in blacks may lessen consideration of ischemic LV dysfunction. However, in whites, the most common cause of end-stage heart disease leading to heart transplantation is CHD. Why is ischemic cardiomyopathy so rarely diagnosed in blacks when mortality data indicate that CHD is as common in blacks as it is in whites?

Acute pulmonary edema without chest pain, a syndrome that may be of comparable clinical significance as unstable angina, may also be more common in blacks for several reasons. Studies of demographic and angiographic findings in patients presenting with acute pulmonary edema without accompanying chest pain reveal that these patients have rates of epicardial CHD comparable to patients with chest pain. The extent of coronary stenoses for this syndrome, demonstrated on coronary angiography, is the same for black and white patients. LV function is usually more compromised in patients presenting with pulmonary edema than in patients with chest pain but no pulmonary edema. Patients with pulmonary edema are more commonly blacks with diabetes and prior hypertension. The syndrome of "flash pulmonary edema," in which severe pulmonary congestion occurs paroxysmally in patients without chronic symptoms of congestive heart failure, may also be anginal-equivalent and occur more commonly in black hypertensive patients with LVH and concurrent, severe angiographic CHD.

Hypertrophic Cardiomyopathy

In some patients with hypertrophic cardiomyopathy, it may be difficult to ascertain whether the hypertrophy is secondary to the effects of hypertension or related to a primary hypertrophic cardiomyopathy. Studies suggest that there may be some overlap between primary and secondary forms of hypertrophy, particularly in blacks. In patients with hypertension, a substantial proportion may have the asymmetric pattern of hypertrophy, which is similar to the morphological spectrum of hypertrophic cardiomyopathy rather than the more common concentric form. The discovery that some forms of hypertrophic cardiomyopathy are due to mutations of the beta myosin heavy chain gene suggests that other forms of LVH may be genetically determined. If LVH in blacks is genetically linked, similar mechanisms may determine other phenotypic characteristics that are more common in some population subgroups.

Diabetic Cardiomyopathy

Diabetes mellitus, like LVH and hypertension, occurs more commonly in some racial groups. Blacks have diabetes more commonly than whites, but less commonly than Hispanics. Microvascular disease is the hallmark of diabetes mellitus and affects the retina, kidney, and neurovasculature. Cardiac involvement with diabetes appears to be related to a predisposition for atherosclerosis. However, the nature and mechanism of microvascular involvement of the heart in diabetes have not been well elucidated. Diabetic cardiomyopathy also occurs more commonly in individuals with other noncardiac, microvascular disease. Diabetes may lead to the development of ischemic cardiomyopathy through increased frequency of dyslipidemias, obesity, and associated atherosclerotic CHD. Hypertension also occurs more frequently in diabetics. The confluence of risk factors is more common in blacks, especially black women. The association of diabetes with cardiomyopathy may be independent of coronary atherosclerosis. Myocardial hypertrophy and cardiac fibrosis, as well as microvascular disease, may be related pathogenetically, but their relationship to clinical ischemic syndromes in blacks is not clear.

Research Opportunities

Several research questions need to be addressed: What is the relationship of the extent of epicardial and microvascular CHD and LV dysfunction in blacks? Do patients with normal coronary angiography but reduced coronary reserve have abnormal LV function? What are the incidence and prevalence of ischemic cardiomyopathy in blacks? Are there differences in systolic and diastolic function in patients with LVH only, CHD only, and both? Are there differences in the degree of LV function in patients with genetically determined LVH compared with LVH due to pressure or volume overload? What are the differences in microvascular and macrovascular CHD in ischemic, hypertrophic, and diabetic cardiomyopathy?

Recommendations

Two specific recommendations for clinical research on heart failure and CHD are:

1. Compare the relationship of macrovascular and microvascular CHD to systolic and diastolic ventricular function in blacks and whites.

2. Determine the most effective class of drugs for improving diastolic function in blacks with heart failure associated with CHD.

POPULATION-BASED RESEARCH

IV. Population-Based Research

The working group addressed three main topics in population-based research:

- Historical and social context of CHD
- Disease patterns
- Risk factors: distribution and effects.

Advances, opportunities, and recommendations in each topic area are presented below.

HISTORICAL AND SOCIAL CONTEXT OF CHD

State of the Science

Historical Trends

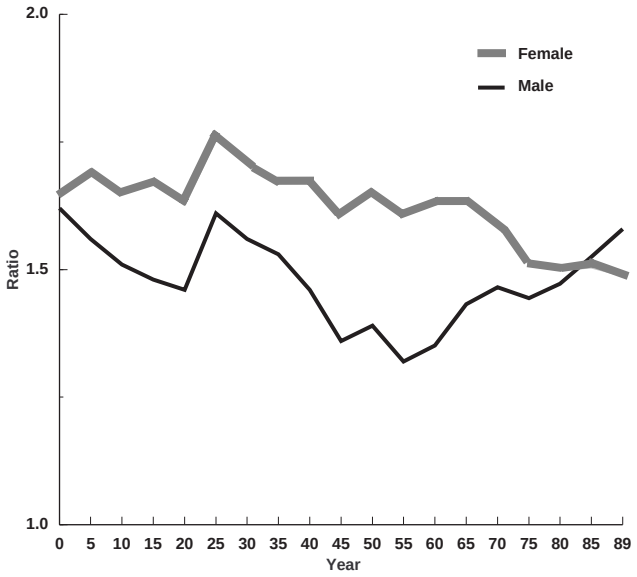
The health disadvantages experienced by blacks have been recognized since vital records were first collected early in this century. All-cause death rates for all ages combined were 60 percent higher in blacks than whites from 1900 through the end of World War II for both men and women (figure 1). In the 1940s, a rapid decline was observed in the ratio of black to white death rates, particularly for men; this corresponded in time with the migration of blacks to the North and economic advancement acquired through employment in industrial jobs. During this period, infectious diseases, particularly tuberculosis, were major contributors to mortality. By the mid-1950s, the disparity in death rates between the races had narrowed by almost 50 percent for men and 25 percent for women. For black men, however, this period of relative improvement came to an abrupt end around 1955 and, by the 1980s, the difference in death rates had returned to the level in 1900. The death rates for black women, in contrast, continued to improve modestly and gradually over the next three decades, again consistent with modest economic progress.

Although a number of conditions contribute to the health disadvantages of blacks, CVD has the greatest impact on mortality differentials in adults. In the rural South, hypertension was common and severe in black populations; however, low rates of smoking and low levels of serum cholesterol were protective against CHD. With migration to urban centers in the North and gradual economic progress in the South, the risk factor patterns in blacks changed to resemble those in whites.

The decade of the 1960s is the major starting point for evaluating recent trends in CHD (figure 2). At the beginning of this period, death rates from CHD were 25 percent lower in black men than in white men and comparable for both black and white women. Since 1960, the ratio of black to white death rates has increased (figure 3). By 1991, age-adjusted death rates from CHD were 3 percent higher in black men than in white men and 33 percent higher in black women than in white women. Death rates from all cardiac conditions, including the much higher rates from hypertensive heart disease, were one-third higher in black men than in white men and two-thirds higher in black women compared with white women (table 1).

Figure 1

Black to White Ratio of Age-Adjusted All Cause Mortality, United States, 1900-1989



Source: National Center for Health Statistics.

Within this context, life expectancy for black men declined during the second half of the 1980s and improved little for black women. Continued high mortality from heart disease, combined with recent increases in mortality from Acquired Immunodeficiency Syndrome (AIDS), violence, and other causes of death, has resulted in a significant deterioration in the health status of adult blacks for the first time in this century.

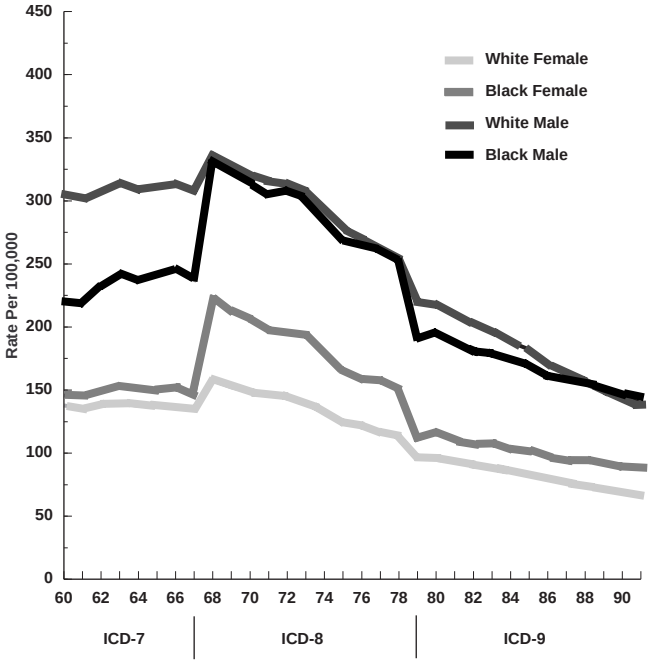
A Key Problem: Insufficient and Inconsistent Data

The search for causes of CHD and use of that knowledge to serve prevention is one of the great success stories in epidemiological research. Knowledge has now been advanced so that control of CHD over the course of the next one or two generations is a realistic possibility. An important paradox has emerged, however. On the one hand, investigators have acquired a rich and detailed understanding of the general relationships linking risk factors to CHD, and these relationships appear to be universally applicable. On the other hand, data from specific ethnic subpopulations are inconsistent in important aspects with certain findings in white men. Because of the limited data available for any particular ethnic group, it is often difficult to determine whether these inconsistencies are chance findings, artifacts of reporting, or important biological facts. Thus, although there is no doubt that the basic cause-and-effect relationships that underlie CHD are identical in blacks and whites, it is possible that some of the risk differentials could result from population-specific factors.

This dilemma will not be easy to resolve. From a statistical point of view, it is twice as difficult to determine whether cause-and-effect relationships are the same or different between two groups as it is to identify the existence of these relationships in any given group. The commitment of resources required to duplicate all research findings in separate populations is obviously prohibitive, and generalization across groups will always be required. Interpreting the importance of differences between groups, therefore, inherently demands judgment. Nonetheless, the fundamental problem in studying CHD in blacks is the absence of sufficient data to resolve many of the questions related to comparisons between blacks

Figure 2

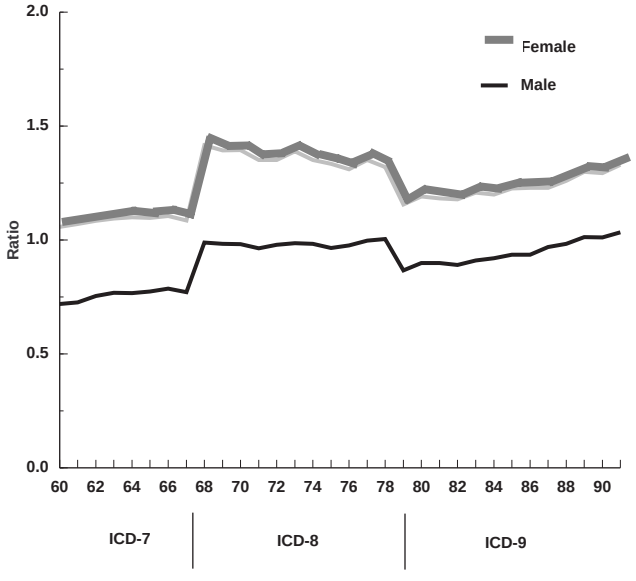
Age-Adjusted Coronary Heart Disease Mortality, United States, 1960-1991



Source: National Center for Health Statistics.
Rates reflect three revisions of the International Classification of Diseases.

Figure 3

Black to White Ratio of Age-Adjusted Coronary Heart Disease Mortality, United States, 1960-1991



Source: National Center for Health Statistics.
Rates reflect three revisions of the International Classification of Diseases.

and whites. An identical dilemma applies for comparisons between males and females.

Although judgment must be embraced as an essential ingredient of epidemiological research, its limitations must also be recognized. The debate over differences in CHD between blacks and whites, as for any racial comparisons of health status, is profoundly influenced by the intellectual construct of race. Since its introduction into the scientific literature in the 17th century, the concept of race has been highly controversial. Because such definitions are based on the social meaning given to biological traits and are, therefore, arbitrary in nature, it is not possible to define consistent and universally accepted racial categories. In the United States, blacks experience a different economic and social status than do whites, and the health-related consequences of these factors are difficult to separate from true biological or genetic processes.

The study of racial differences in health is, therefore, complicated by two deep-seated and interconnected problems that arise from the social context of science. First, the category of race cannot be defined. It is, therefore, difficult to perform many practical tasks such as maintaining a surveillance system that consistently and accurately assigns individuals to one or another group. Second, at the most general level, the meaning of race is fundamentally ambiguous. It is often not known whether racial differences are based on biological or social phenomena.

Research Opportunities

There are several clear challenges for the future. A detailed understanding of CHD trends since 1960 is urgently needed. Unless this long-term pattern is changed, the gap between blacks and whites in CHD mortality can be expected to widen for the foreseeable future. A number of general questions must be answered before an appropriate public health strategy can be devised:

- Why have blacks not experienced the same reduction in CHD rates as whites in the period since 1960?
- To what extent have the benefits of new knowledge gained through research on CHD prevention not been translated into practical benefit at the community level in blacks?
- To what extent do biological factors account for the observed differences in CHD between blacks and whites?
- Have the benefits achieved in treating CHD not been distributed equally across ethnic groups and, thereby, contributed to the growing disparity?

Related to these general questions is a series of specific research questions, which serve to frame future efforts in population research:

- What are the true death rates from CHD in blacks, and what are the current trends?
- Is the force of mortality (i.e., the average risk for an individual) for CHD similar in blacks

and whites given the distribution of risk factors?

- Do the key risk factors have a different impact in blacks and whites? Do secondary modifying factors play an important role?

- What are the relative contributions of different trends in risk factors, SES, and access to medical care to the widening gap in CHD rates?

- Why are survival rates of black patients with CHD worse than those of whites with comparable disease?

Within the limitations of the theoretical approach and measurement tools available, the state of knowledge about CHD at the population level should be reviewed. Although difficulties associated with using the concept of race in biological research have been recognized for many years, a particularly intense debate has taken place in recent years. In addition, advances in molecular biology may enable investigators to address specific genetic hypotheses directly. The combination of renewed attention to social factors related to race and the potential for direct studies of genetic effects has created considerable ferment in this field. A concerted effort to clarify the distinctive roles of social class and biological race could, therefore, be particularly productive at this time and should become a major priority for research in this area in the coming years.

A thorough evaluation of available CHD data on blacks is also needed. Similar to the Pooling Project of the American Heart Association, which combined data from the first generation of epidemiological studies on white men, this work would establish the most precise risk estimates possible given the current state of knowledge.

Recommendations

Two specific recommendations for research on the historical and social context of CHD are:

1. Conduct a coordinated and comprehensive assessment of data resources on CHD in blacks.

2. Define the appropriate use of racial categories in biomedical research, and describe the limitations imposed by these categories on studies of health disparities.

DISEASE PATTERNS

State of the Science

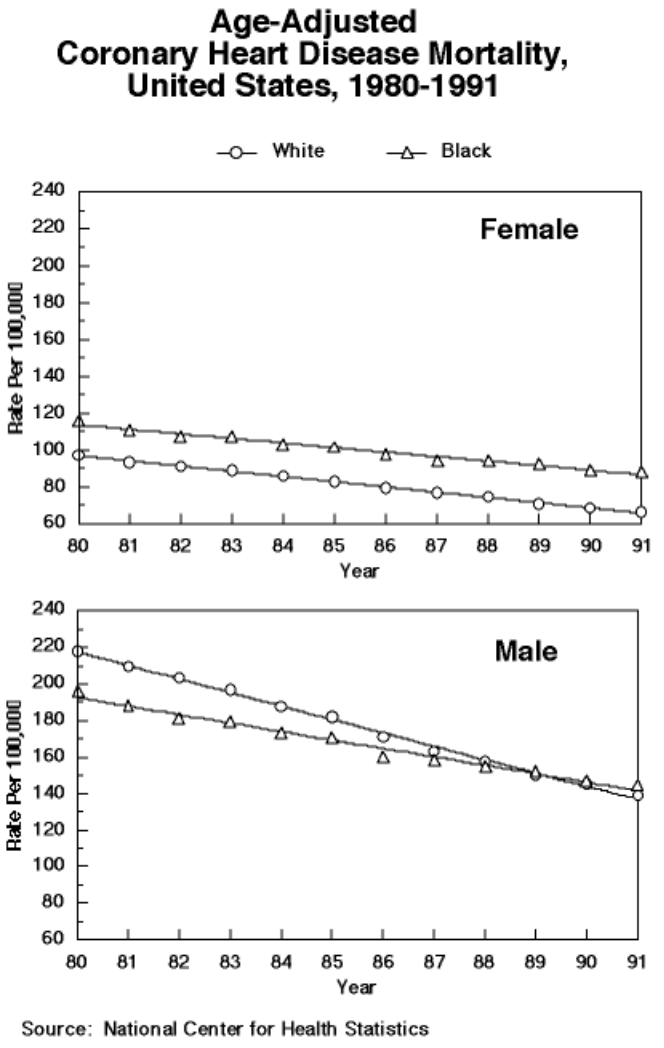
National Vital Statistics

William Farr, an 18th-century English public health official who developed the first vital records system, once remarked, “The death rate is a fact; anything beyond that is interpretation.” Unfortunately, even facts have been hard to identify with regard to CHD in blacks. It is well recognized that the designation of cause of death is an unreliable process. When a single rate is given, there is no standard by which to make a comparison. However, concern about reliability unavoidably arises when detailed comparisons are attempted between groups.

Over the past decade, considerable effort has been made to estimate the “true” death rate from CHD in blacks compared with whites. Although many contentious issues have been resolved, the findings are not simple. Because of twofold higher rates of hypertension among blacks, compared with whites, one would expect blacks to have significantly higher rates of CHD. Throughout the 1970s and 1980s, however, this was not the case. Lower than predicted rates of CHD were observed in relation to CHD risk at the population level. These paradoxically low rates motivated a persistent search for “protective factors,” which were conceived as primarily biological (i.e., genetic) in character. However, recent trends have clarified underlying patterns. As noted above, CHD rates have declined faster in whites than in blacks since 1980, particularly for men. In 1989, age-adjusted CHD death rates finally “crossed over” as the rates for black men surpassed those for white men. By this time, rates for black women were 30 percent higher than for white women (figure 4).

The vital statistics data clearly demonstrate one important additional difference in CHD between blacks and whites: CHD mortality occurs at an earlier age in blacks. Below age 50, death rates are 50 percent higher in black men and 100 percent higher in black women compared with their white counterparts. After age 60, a crossover occurs and, among the most elderly, the rates in blacks fall well below those in whites. Because of these patterns, the median age of death from CHD is 5 years earlier in blacks than in whites.

Figure 4



Why, then, are the differentials in the age-adjusted rates not larger? It is a common misperception that taking into account the age at death compensates fully for different age structures in two populations. Age-adjusted rates are weighted by diseases common in the elderly. Because many fewer blacks than whites survive into old age, the relative distribution of causes of death varies across the groups. In addition, some selection factors may exist. Hypertension, for example, may lead to other vascular diseases and thereby eliminate a subset of the coronary-prone population before the peak ages for CHD are reached. This issue requires an estimate of the force of mortality in each population. It provides an estimate of the average risk for an individual and cannot be calculated directly from vital statistics data. Although no specific estimate can be given for the force of mortality for CHD in blacks, compared with whites, it is clearly higher in blacks. In combination with the recent crossover in death rates for black men, this conclusion is entirely consistent with the risk factor profile.

Although the age-adjusted data before 1989 suggest that blacks are relatively protected from CHD, the age-*specific* data have always demonstrated a stronger force of mortality because of the earlier age of onset of CHD in blacks compared with whites. These two measures convey different views of the distribution of disease in populations. Age-*adjusted* rates provide information on the total population burden, whereas age-*specific* data provide information more pertinent to individuals (the force of mortality). Much of the confusion in the debate on disease burden derives from the failure to make this distinction clear. CHD age-adjusted rates in blacks are lower than might be anticipated from a prediction based on risk factor levels. Yet, CHD death rates are much higher in young and middle-aged black men and women. The only consistent explanation for this paradox is that, although blacks are exposed with greater intensity to CHD risk factors throughout life, they experience high mortality from other causes and do not survive in the same numbers to the age when CHD events (e.g., heart attacks) are most common.

Epidemiological Studies

Unfortunately, the vital statistics data alone cannot entirely resolve this paradox in mortality. Artifacts of reporting are unmeasurable in passive surveillance systems and may be of sufficient magnitude in this instance to bias the outcome. In addition, the impact of specific biological differences between the races cannot be determined from an analysis of vital records. Only detailed studies, based on defined population cohorts, can address these issues.

Epidemiological studies from the 1960s and 1970s, particularly those in the South, suggested that CHD was, indeed, less common in blacks than in whites. In addition, an early study from Baltimore demonstrated consistent misclassification of sudden death on vital records. Findings from the National Health Epidemiologic Follow-Up Study (NHEFS) of NHANES I, which spanned the years from 1972-74 through the mid-1980s, demonstrate similar CHD rates overall between blacks and whites. After adjusting for age, black men were found to have fewer nonfatal CHD events, primarily hospitalization for acute MI, but to experience slightly higher death rates. A similar trend was apparent in black women. The NHEFS provides an important data set because it is representative of the U.S. population.

Unfortunately, only 683 black men and 1,175 black women were followed in this study. Followup through 1987 yielded only 80 fatal CHD events in black men and 73 in black women. Preliminary data from the Atherosclerosis Risk in Communities (ARIC) study demonstrate similar age-adjusted rates of CHD in black men, with slightly higher rates in women. This study has enrolled 4,000 blacks between the ages of 45 and 64 years from Jackson, Mississippi, and Forsythe County, North Carolina. It will provide crucial information on CHD contrasts between blacks and whites in the coming years.

Thus, by the 1980s, prospective epidemiological studies, which included careful verification of end points, showed that CHD rates were similar in black and white men and higher in black women than in white women. These studies also consistently found higher rates of fatal events, particularly out-of-hospital deaths, among blacks compared with whites, and fewer hospitalizations of blacks for acute MI.

Because it is the only contemporary biracial sample available, the NHEFS is a unique resource. It also provides information on the role of the major CHD risk factors. Based on multivariate analysis, risk relationships in the two populations are very similar. Although there are substantial gender-specific, between-race differences, none of the differences are statistically significant. Without knowledge of the existence of other potential risk factors unique to either the black or white population, the aggregate population risk can be estimated based on the level of established risk factors. Indeed, national surveys have demonstrated that CHD risk is higher in blacks than in whites. In the NHANES II survey, the following percentages of adults had two or more CHD risk factors: black men, 20 percent; white men, 13 percent; black women, 15 percent; and white women, 10 percent. Hypertension accounted for these differences.

Epidemiologists frequently summarize the contribution of particular factors to disease outcome by calculating the population attributable risk (PAR). Expressed as a percentage, this statistic implies that disease rates would be reduced by a comparable amount if a specific factor were not present. Comparisons between blacks and whites for CHD are highly instructive in this regard. For whites, the PAR for hypertension is approximately 10 percent. For black men, the figure is 30 percent and, for black women, 20 percent. High levels of blood cholesterol contribute similarly in both races, but cigarette smoking is more important in whites. In recent years, the impact of diabetes has increased markedly in black women, to a PAR of 14 percent.

Although existing data do not offer precise answers, three major conclusions are apparent:

- The age-adjusted burden of CHD is similar in blacks and whites overall, with higher rates in black women than in white women.
- The major risk factors have a similar impact in both populations.
- The aggregate level of CHD risk is higher in blacks than in whites.

These findings are consistent with the higher force of mortality for atherosclerosis in blacks and higher rates of premature CHD.

CHD Mortality in Blacks: Recent Trends

Recent public health history demonstrates clearly that the disease burden from CHD is highly responsive to trends in risk factors and social processes at the population level. All four major gender-race groups (black and white men, black and white women) experienced the onset of a decline in CHD mortality almost simultaneously in the late 1960s. It is estimated that 450,000 fewer deaths from CHD were recorded in 1990 as a result of the decline in rates since 1966. This achievement offers great encouragement and suggests that the CHD epidemic is well on its way to being controlled.

As noted earlier, however, the success has been unequal: The death rate from CHD in blacks is now higher than in whites. Earlier, the reduction in death rates was similar in all groups. However, after 1978, the rate of decline continued on the same trajectory for white men, but slowed considerably for all other groups. For black men, the rate of decline through the late 1980s had slowed by one-third; for black women, it had slowed by two-thirds. As a result of these divergent trends, an estimated 9,300 excess deaths from CHD occurred in black men and women in 1991, which account for about 10 percent of all excess deaths. If the present pattern continues, by the year 2000, the mortality rate for CHD in blacks will be 60 percent higher in women and 40 percent higher in men than in whites of the same gender.

These differential trends cannot be explained quantitatively based on available information. The last data point for national prevalence estimates of risk factors is derived from the NHANES II survey completed in 1976-1980. Preliminary results from NHANES III do not show major ethnic differences in trends for the major CHD risk factors, although more detailed analyses will be necessary. Diabetes

is emerging as the next important risk factor, after hypertension, and cigarette smoking may be increasingly important as a cause of the different trends in men.

Research Opportunities

The momentum achieved in the pharmacological control of hypertension must be continued. New programs should be targeted to hard-to-reach segments of the population such as middle-aged men. Efforts to prevent the age-related increase in blood pressure are urgently needed. Attempts should be made to reduce fat and cholesterol intake in the black population, and vigorous antismoking campaigns should be implemented. The rapidly emerging epidemic of diabetes in blacks deserves great attention. Simultaneous with this broad public health approach, it will be important to resolve the existing contradictions and inconsistencies in the current understanding of CHD determinants in blacks.

Although ARIC includes a black community, the sample size is relatively small (4,000 persons, aged 45-64 years) and participants are drawn from the southeastern portion of the country. It will be important to develop a population-based research setting in which a series of coordinated observational and intervention studies can be conducted. The development of appropriate survey instruments and a positive relationship with a specific community would provide the basis for addressing many pressing questions.

Given the fragmented nature of existing data, it is often not attractive for a single group of investigators to devote the large amount of time needed to develop sophisticated strategies for analysis. Support for data sharing and statistical support to centers having access to primary data should be further encouraged.

Recommendations

Specific recommendations for population studies of CHD disease patterns are:

1. Determine the feasibility of developing a surveillance and intervention project in a community representative of more urbanized populations.
2. Apply sophisticated analysis techniques to clarify the mechanisms leading to the crossover of CHD mortality between blacks and whites over age 60.

Risk Factors: Distribution and Effects

State of the Science

Lipids and Lipoproteins

Over the past 30 years, survey research has consistently demonstrated that blacks have similar levels of total and LDL cholesterol as whites. However, the levels of HDL cholesterol are higher and triglycerides are lower in blacks than in whites, and these differences are more pronounced in black men than in black women. HDL-cholesterol levels in black men exceed those in white men by approximately 10 mg/dl, but by only 3 to 5 mg/dl in black women compared with white women. The determinants of these ethnic differences are generally considered to be genetic in origin, although there is some controversy. A large study of middle-aged male veterans found that adjustment for lifestyle factors eliminated the differences between blacks and whites. In most published reports, however, environmental covariates do not entirely explain the ethnic differences in HDL cholesterol. To date, there are no data from prospective studies that demonstrate the protective benefit of HDL cholesterol in blacks. If the same relationship holds as in whites, blacks should experience a substantially lower aggregate risk of CHD.

Lp(a) is an unusual lipoprotein that has potential thrombotic and atherosclerotic properties. The components of its molecular structure include the apolipoprotein B molecule and a covalently linked protein with sequence homology to plasminogen. Differences in Lp(a) between blacks and whites have recently attracted attention and represent a potentially interesting model for genetic studies of interethnic patterns of CHD. Although the physiological role of Lp(a) is not known, most, but not all, studies of persons of European descent show that Lp(a) confers increased risk of CHD. Serum levels of Lp(a) are two to three times as high in blacks as in whites, which suggests a considerably increased population risk of CHD. However, epidemiological evidence does not support this conclusion. Several recent studies fail to demonstrate an association

between increased Lp(a) and atherosclerosis in blacks. Preliminary data from ARIC show an association of Lp(a) both with carotid artery atherosclerosis and incidence of clinical CHD in blacks as well as whites.

Lp(a) is the most variable protein known to exist in humans; 34 isoforms have been identified. Isoforms vary in size depending on the number of "kringle" subunits, and the structural gene determining size has been cloned. The distribution of alleles coding the apolipoprotein (a) isoform varies between blacks and whites, as does the distribution of Lp(a) levels. Lp(a) levels are found in an approximately normal distribution in blacks, but the distribution is highly skewed in whites. Recent data confirm a pattern in Nigerians similar to that found in U.S. blacks. Although serum levels are generally correlated with isoform size, this relationship is not consistent between blacks and whites.

Lp(a) is a highly heritable trait and is influenced to a limited degree by environmental factors, including medications. In persons with this trait, however, increased risk of atherosclerosis occurs primarily in those who already have coexistent high levels of LDL cholesterol, so its role should be viewed as secondary and additive. Even if high levels of Lp(a) were eventually shown to be associated with CHD in blacks, its overall contribution would be small and conditioned by serum LDL cholesterol. As this field develops, it will become important to keep this issue in perspective and avoid the misperception that blacks are genetically susceptible to CHD because of high Lp(a). Caution must be exercised in interpreting differences between population subgroups and to avoid exaggerating the importance of single genes.

Hypertension

It has been recognized for most of this century that persons of African descent who live in the United States experience rates of hypertension twice those of whites. The underlying cause of the steeper rise of blood pressure with age in blacks is not known. Blood pressure aggregates in families and is likely to be under genetic control to some degree. By extension, it is widely held that blacks are genetically susceptible to this condition. It bears restating, however, that no direct evidence exists to support this hypothesis. Hypertension is uncommon in all of sub-Saharan Africa, except for urban areas in South Africa. Although genetic susceptibility could potentially provide a background of hypertension risk, it is exposure to causal risk factors that has driven blood pressures upward in the U.S. black population.

Evidence for population-specific genetic susceptibility requires identification of differential frequencies of genes which condition risk in similar ways in both populations, although simultaneously accounting for possible gene-gene and gene-environment interactions. Given that candidate genes with similar effects in black and white populations have not been identified, no hypotheses related to between-group differences can be tested at present. Without this evidence and given the obvious differences in risk factor exposures, it is, perhaps, surprising that the genetic hypothesis on the risk of hypertension in blacks is so well accepted. Again, this experience suggests the need for caution as research on the racial differences in CHD moves forward.

As noted above, CHD risk associated with increasing levels of blood pressure is similar in blacks and whites. Several studies show, however, that the risk of CHD is lower in black male hypertensives than in whites. This finding is supported by the NHEFS data, cited earlier, and the results concerning a large cohort of men screened for the MRFIT. The risks of stroke and total mortality associated with high blood pressure, however, are higher in blacks than in whites. Thus, the relative risk of death from all causes in the NHEFS, for hypertensives versus normotensives, was approximately 1.50 for whites and 1.75 for blacks.

These findings have led some observers to propose two specific racial contrasts; that is, level for level, high blood pressure is "more severe" in blacks than in whites, yet hypertension in blacks is associated with less risk of CHD than in whites. However, recent evidence does not support either conclusion. In the extended followup of the MRFIT cohort, the risks of stroke and CHD in black and white men have converged. Much of the confusion about whether hypertension is more severe in blacks than in whites results from the method of analysis used: When a defined cut point is used as the basis for defining hypertension, the result is two very unequal groups. Thus, in black hypertensives, average blood pressure is much higher than in white hypertensives. In the NHEFS, in which blood pressure is treated as a continuous variable, the risk of a unit increase in pressure, for all causes of death, is the same for black and white men and significantly higher for white women than black women (logistic coefficients 0.013 and 0.010 for white and black women, respectively, $p < 0.05$). At the same time, strata-specific adjustment for blood pressure, which takes into

account the higher rates of severe hypertension in blacks, demonstrates that the higher burden of hypertensive complications in blacks is because severe hypertension is more common and not because hypertension is more severe. Thus, level for level, high blood pressure confers the same risk in both black and white individuals.

Because of the crucial role of hypertension in determining CHD differentials between blacks and whites, this issue has been examined in some detail. Although additional data are clearly needed to verify these findings, an important conceptual issue emerges. First, the statistical approach to testing differences between blacks and whites is not very well developed. Second, there appears to be a strong tendency on the part of many investigators to conclude that observed differences are biological in nature, even before a thorough analysis has been completed. This problem recurs in many other areas of this field. The relatively abundant data available on hypertension risk should point to the hazards of premature conclusions.

Cigarette Smoking

In recent decades, a greater percentage of black men, compared with white men, have smoked, although black men tend to consume considerably fewer cigarettes per day. Black women, in general, use cigarettes at comparable rates as white women. Data on associated CHD risk from studies that include black participants are limited. The increased risk is virtually the same in black and white men. Published findings, however, do not demonstrate a comparable effect in women, and the role of cigarette smoking in the etiology of CHD has been difficult to define in women.

There is little reason to believe that cigarette smoking will have different health consequences in blacks than in whites. An important caveat applies, however. Although lifetime exposure to cigarette smoking, measured as "pack years," is considerably lower in black men than in white men, their rates of lung cancer approach twice those of whites. Does this phenomenon have a biological basis? Although it is more likely that other risk factors, such as occupational exposure or reduced dietary intake of antioxidants, account for these differentials, there are no data to support these suppositions. The causal relationship between smoking and lung cancer is among the best established in modern public health. It is, therefore, disquieting that such large racial differences emerge. This observation serves to underscore the dilemma referred to above: Should findings demonstrated in whites be accepted without confirmatory evidence? When is it reasonable to support research on potential biological or genetic factors?

Fortunately, for cigarette smoking, the research and public health agenda is clear, despite the uncertainty about biological mechanisms and the potential strength of the risk relationships. Smoking cessation continues to be the single most effective preventive measure available to improve the health of U.S. adults.

Hemostatic Variables

There have been few community-based studies of hemostatic factors in blacks. In ARIC, blacks were reported to have major differences in levels and distributions of hemostatic variables. The association of these hemostatic variables with personal and lifestyle characteristics, and their relationship to ultrasound-assessed carotid atherosclerosis and clinical CHD, are being investigated.

Data show that blacks have higher mean levels of fibrinogen. The differences between blacks and whites, in median values by gender and age, were 28 mg/dl for women and 11 mg/dl for men. No difference was noted in Factor VII by race. However, several hemostatic factors were higher in blacks than in whites: Factor VIII, 8 to 20 percent higher; von Willebrand Factor antigen, 25 percent higher; and antithrombin 3 activity, 3 percent higher. In addition, the level of protein C antigen was 0.09 μg/ml lower in blacks than in whites.

Left Ventricular Hypertrophy

In response to hemodynamic overload, particularly sustained hypertension, muscle mass of the LV chamber increases. The hypertrophic heart is characterized by accumulation of contractile proteins in individual cells and no increase in cell proliferation. Together with an increase in connective tissue, nutrient and oxygen supply may be reduced and the pattern of depolarization may be disrupted. Although hypertrophy may have adaptive value in some settings, such as physical training, prospective epidemiological studies demonstrate a strong association between LVH and risk of various cardiovascular events. If LVH is viewed as a time-integrated marker for hypertension, the association with risk of stroke and renal failure must be interpreted primarily as a result of confounding. That is, multiple end points are all the result of a common exposure. The question of whether LVH increases

susceptibility of the heart to morbid sequelae is more complicated. Clearly some individuals are more likely than others to develop LVH despite similar levels of high blood pressure. For cardiovascular epidemiologists, the crucial questions are whether LVH itself contributes to the risk of hypertension and, if so, what is the mechanism.

Our understanding of LVH in blacks and whites has developed in a confused way. Early studies, based on ECG evidence, demonstrate substantially higher rates of LVH in blacks than in whites. Most, but not all, of this excess could be attributed to hypertension. Recent data, in fact, confirm that among persons with normal ECGs at baseline, blacks had threefold higher rates of new LVH than whites during followup, after adjusting for blood pressure and other related variables. It appears well established, therefore, that blacks are more sensitive to the stimulus of pressure overload that leads to ECG voltage changes.

With introduction of the echocardiogram, however, it has been possible to obtain more direct and sensitive measures of LV muscle mass. Some, but not all, studies suggest that LV mass is greater in blacks than in whites, even after adjusting for blood pressure. Attempts to characterize the lifelong impact of blood pressure elevation is very difficult, particularly when the effect of intermittent treatment must be taken into account. The Coronary Artery Risk Development in Young Adults (CARDIA) study recently examined differences between blacks and whites in a large cohort of normotensives and confirmed the importance of blood pressure, even within the normal range. However, after adjusting for blood pressure, obesity, physical activity, and other factors known to influence LV mass, no race-specific effect remained. Although the possibility that blacks may be more sensitive to longstanding pressure overload cannot be excluded, current knowledge does not substantiate the hypothesis that there are major differences between blacks and whites in LV response to blood pressure elevation.

Diabetes

Noninsulin-dependent diabetes mellitus (NIDDM) was less frequent in blacks than in whites through the 1960s. During the 1970s, a crossover occurred, as with CHD, and NIDDM rates are now almost twice as high for blacks as for whites. An explanation of these trends, from an epidemiological perspective, presents a classic dilemma: The distribution of known risk factors, namely obesity, physical inactivity, and low SES, explain most, but not all, of the differences between blacks and whites. Are there important factors that have not been measured? Are the measurements simply inaccurate? Has the analysis been performed improperly? Are there genetic differences between the races? These questions need to be answered.

Diabetes is a potent risk factor for CHD. Persons with diabetes are two to three times more likely to suffer a CHD event and, once CHD is present, survival is 50 percent lower in diabetics than in nondiabetics. These findings have now been replicated in black patients. As with other risk factors, comparisons across racial groups become more complicated. Although diabetes is more common in blacks, several reports suggest that CHD risk in blacks with diabetes is lower than in whites with this disease. This phenomenon may represent a cohort effect, whereby blacks, followed over this period, developed diabetes more recently than whites, or it could be an artifact related to a competing cause or to death certification.

Survey data from the 1990s indicate that the prevalence of NIDDM in blacks over the age of 40 is approximately 15 to 20 percent. Although this prevalence is only half that of hypertension, the relative risk associated with diabetes is considerably higher and current forms of treatment are less effective. The PAR for diabetes is 10 to 15 percent; for hypertension, it is 20 percent. Given the rapidly rising incidence of NIDDM, this condition may well account for a greater burden of disease than hypertension by the end of the 1990s.

Physical Activity

Regular physical activity has a strong protective effect against CHD, lowering the risk of CHD by as much as 50 percent. Limited data suggest the same or higher levels of activity at work in blacks as in whites and considerably lower levels during leisure time.

The cultural and social determinants of low levels of leisure-time physical activity in blacks are not known. It is important to remember that, in large urban centers, the options for exercise are often limited. Survey data suggest that participation in vigorous recreational activity is uncommon; such self-reported data, however, are of limited value in etiological research. Methods for directly measuring energy expenditure in field settings are needed. Examples include techniques that rely on more sophisticated motion sensors, portable instruments for measuring indirect calorimetry, and doubly-labeled water.

In the NHEFS, the protective benefit of increased activity was similar in black men and white men; relatively little effect was noted in women of either race. Given the threat posed by diabetes and obesity, there is an urgent need to encourage aerobic exercise in black women. Although community intervention studies have been undertaken, only modest effects have been demonstrated. The limited experience available suggests a strong interaction with the underlying social health of communities. Thus, well-organized communities can make good use of recreational facilities. Whether programs brought into communities from external sources will result in adequate change is an important question.

Alcohol

Although regular use of moderate amounts of alcohol reduces CHD risk, it has been shown to lead to a rise in blood pressure. The pattern of alcohol use in the black population has several unusual features. In men, average consumption is similar in blacks and whites, although the distribution of this consumption is substantially altered. The proportion of abstention, as well as heavy drinking, is higher in blacks than in whites; as a consequence, moderate drinking is less common in blacks. Multiple surveys repeatedly demonstrate that black women drink much less alcohol than white women. As many as 60 to 70 percent of black women over the age of 50 are lifelong abstainers. The consistent, positive relationship between income and alcohol consumption observed in whites is weaker in black men and reversed in black women. These findings are well established and have been documented over a period of 40 years.

The differential pattern of alcohol use in blacks compared with whites makes it inadvisable to transfer conclusions reached in whites. For example, despite lower drinking rates overall, death rates from cirrhosis of the liver are two to four times higher in blacks than in whites, raising questions about whether this represents bias in reporting; the presence of other, unidentified risk factors; differential patterns of alcohol use; or biological effects. There are limited data on the effect of alcohol use on CHD in blacks. In the NHEFS cohort, no relationship between alcohol use and CHD was observed for any gender or racial group, although the exposure measures were imprecise.

Socioeconomic Status

Social class gradients in risk occur for many diseases. During the early stages of the CHD epidemic, persons of higher SES were more likely to develop CHD. Since the 1960s, however, a consistent, negative correlation between various measures of SES and both incidence of CHD and survival with symptomatic disease have been reported. The NHEFS demonstrates very similar effects of income and education on the incidence of CHD in black men and women. Median income for black families in the United States has been only slightly more than half of that for whites over the past 50 years. This differential would be expected to contribute to an increased disease burden from CHD. The mechanisms by which social class influences CHD risk are currently controversial. Based on national surveys, the levels of all major CHD risk factors, with the possible exception of serum cholesterol, are negatively correlated with social class. In many studies, SES measures are no longer significant predictors of CHD in multivariate analyses. Other data, most notably from the United Kingdom, suggest that a large SES effect remains after controlling for CHD risk factors. A psychosocial mechanism has been postulated to explain this observation.

The relationship between individual CHD risk factors and SES in blacks is similar to that in whites. At least in the 1970s, when the last national surveys were completed, smoking, hypertension, diabetes, and obesity tended to be more common in blacks of lower SES, although elevated serum cholesterol was less common. It must be recognized, however, that relatively few blacks are included in the upper distribution of SES, so between-race comparisons are based on different absolute levels of income. The importance of SES lies in the large difference in the mean level between the races. Adjustment for income differences alone would reduce the current variation in the black and white all-cause mortality gap in men by 60 percent and in women by 30 percent.

Of particular concern has been the substantial increase in income disparity over the past two decades. A widening of income differentials began during the recession of the 1970s. Contrary to all econometric predictions, and for the first time in this century, the differential continued to increase during the economic expansion in the 1980s. Overall variation, as measured by the Gini coefficient for family income, increased 17 percent from 1968 to 1989. In 1989, real income for a family at the 20th percentile was 5 percent below the level in

1969; for a family at the 80th percentile, real income had increased 19 percent. This trend toward a widening gap in SES levels was even more pronounced within the black community. Thus, although actual income at each percentile was lower in blacks than in whites, the spread from the top to the bottom was larger in blacks and this trend increased relative to whites. Although annual earnings of blacks with a college education rose 6 percent relative to whites over the period 1969 to 1984, annual earnings fell 5 percent for black high school graduates.

Research Opportunities

Although research on the etiology of hypertension may not fall within initiatives on CHD, a better understanding of CHD risk associated with hypertension is of considerable interest. Current high levels of treatment have ended the era of "natural history" studies, and many of the questions remaining from earlier studies of risk comparisons between blacks and whites may forever go unanswered. The most productive research in the future will focus on randomized trials and primary prevention.

CHD risk is approximately doubled in patients with LVH, and half of black patients with CHD have LVH. It can, therefore, be estimated that as much as one-third of the mortality in black patients with established CHD can be attributed to LVH. The mechanisms underlying this relationship are not known. LVH is strongly associated with ventricular arrhythmias, but it is not known whether they confer risk directly. No data have yet been published that demonstrate an increase in sudden versus nonsudden death in patients with LVH. Hypertrophied ventricles contain a higher collagen content and become stiff. Pulmonary artery pressure, which reflects, in part, reduced LV compliance, is highly predictive of mortality independent of LVH even in patients with normal LV function. It is possible, therefore, that the impact of LVH on diastolic function may be more important than previously recognized. Heart failure from both systolic and diastolic dysfunction is an important sequela of LVH. The natural history of this process has not been well documented. Another issue is regression of LVH, which results in a ventricle with an excess of fibrous tissue. It is not known whether a smaller ventricle with a higher proportion of collagen is better than the original hypertrophied ventricle.

Precise and efficient techniques for measuring LVH are available. Both ECG and echocardiographically demonstrated LVH have been shown to predict risk of future morbid events in blacks. Although there are no echocardiographic data from community studies, large patient series have been followed prospectively. Hypertension causes both LVH and CHD, and CHD itself leads to modest increases in LV mass. This complex effect of hypertension on the heart can be examined in an angiographic registry. Even after severity of CHD is taken into account, LVH is an independent predictor of mortality. In patients with angiographically normal coronary arteries, LVH has also been shown to predict future fatal events. In addition to community-based epidemiological studies, this research setting could be used to investigate a series of new, more sophisticated questions.

The fundamental problem confronting all of diabetes research is the urgency of prevention. In collaboration with other government agencies and NIH components, additional support for research on the methodology and conduct of prevention trials is greatly needed.

A large increase in the SES mortality gradient for both blacks and whites has recently been documented by researchers. This widening health gap is most likely related to growing differentials in economic well-being. For the black community, average wages have fallen and income disparity within it has increased over the past 1.5 decades. The relationship between SES and mortality often appears to be nonlinear: The risk increases sharply at the lowest end of the distribution, but tends to become flat above the median. It is of concern that the major socioeconomic change that has occurred has been an increase in the proportion of black families with very low income. Given the pervasive and potent effect of SES on health risk, these trends are likely to have played a major role in the deterioration of health status in blacks over the past decade. Although the broad aspects of this problem are well known, its significance is not well recognized in the biomedical research community and its mechanisms are poorly understood.

Relatively little attention has been given to studying socioeconomic factors in blacks. Although current data sets that could be used for this task are limited, it may be possible to identify culture-specific patterns within this community that would enhance

analytical capability. This information would be particularly useful to investigators who attempt to compare racial differences in the effects of risk factors.

Recommendations

Specific recommendations for research on the distribution and effects of CHD risk factors in blacks are:

1. Establish culturally specific, reliable, and valid dietary assessment tools that allow determination of the nutrient composition of the diets of black populations.

2. Define, in family and cross-cultural studies, whether there are racial and gender patterns of genetic differences in lipids and lipoproteins, particularly in HDL cholesterol, triglycerides, and Lp(a).

3. Collect additional data on CHD risk associated with lipid and lipoprotein abnormalities in blacks.

4. Develop mechanisms to encourage the biomedical community to take greater responsibility for the ways in which genetic research comparing ethnic groups is communicated.

5. Include measures of LVH in existing and future population-based studies.

6. Develop innovative, new methods for assessing energy expenditure related to physical activity, particularly in community-based studies.

7. Improve understanding of the culture of exercise in black communities as a basis for CHD interventions.

8. Support community-based interventions to increase leisure-time physical activity as a means of reducing CHD risk in blacks.

9. Define the mechanisms by which SES contributes to CHD risk within the black community and to differences between blacks and whites.

Behavior and Prevention Research

V. Behavior and Prevention Research

Prevalence rates of CHD risk factors, such as hypertension, diabetes, high levels of Lp(a), increased LV mass, cigarette smoking, and obesity, have been documented as higher in blacks than in whites, although cholesterol abnormalities appear to be less common in blacks. Differences in risk factor profiles may potentially contribute to at least a portion of the differences in racial epidemiological patterns of CHD. Racial differences in physiological mechanisms of clinically manifest CHD have also been posited. Several studies found that the degree of atherosclerosis associated with CHD events is less in blacks than in whites. These studies suggest a potentially greater role for other causal mechanisms, including thrombogenicity, enhanced vasomotor tone, and the substrate for lethal ventricular arrhythmias.

The emphasis on prevention in the general population has been on identification and treatment of physiological factors primarily associated with atherogenesis. Although the greater prevalence rates of some physiological risk factors in blacks has similarly focused efforts on identification and treatment, it is important to recognize the need for behavioral research, education, and prevention efforts. These activities need to address ethnic-specific factors that may result in increased risk for blacks. Topic areas are: behavioral risk factors that operate differentially in the black population to increase risk, and health care seeking factors related to CHD risk and events that may lead to better methods of promoting the seeking of early treatment for CHD risk factors and acute and chronic symptoms. Although limited ethnic-specific data are available, several recommendations can be made, based on available data, to support effective strategies for reducing CHD risk in blacks, and areas can be identified for future research efforts.

The working group focused on three main topics:

- Behavioral risk factors
- Health care behavior
- Education and prevention strategies.

Advances, opportunities, and recommendations for each topic are presented below.

Behavioral Risk Factors

State of the Science

Behavioral risk factors are those that are influenced by a person's choice and, as such, should be amenable to intervention. It is important to note that changes in habitual and addictive behaviors are not a simple matter of just choosing to change the behavior but may require systematic application of behavior-change principles and methods. Cigarette smoking, high fat diets, physical inactivity, and obesity are lifestyle factors that influence CHD risk in the American culture. Although more controversial, exposure to stress and methods of coping with stress, including social support systems, also appear to affect CHD risk. However, the extent to which each behavioral risk factor plays a role in CHD risk and the extent to which each appears to be amenable to intervention may differ markedly by ethnicity.

Cigarette Smoking

Since the prevalence of smoking remains higher in both black men and women, smoking may be more important in the genesis of clinically manifest CHD in blacks than whites. From 1987 to 1991, the National Health Interview Survey (NHIS) found that smoking rates declined among persons 18 years and older in the general population to approximately 25.7 percent, although blacks had an overall smoking prevalence of 35 percent. Black women appeared to smoke only slightly more than white women, 24.4 percent and 23.8 percent, respectively. The rate of smoking decline in blacks has not been as great as in the general population. Although most studies found that blacks smoke significantly fewer cigarettes per day, the assumption that this translates to a lower exposure to tobacco smoke may not be true; blacks smoke stronger cigarettes and may have different inhalation patterns compared with whites. In the CARDIA study, the average nicotine and tar content of cigarettes smoked by blacks was three times higher than whites. Blacks and whites have similar levels of cotinine, the major metabolite of nicotine, which suggests that, in spite of smoking fewer cigarettes, blacks may experience nicotine exposures similar to whites. There is little

information on differences in true exposure and on smoking topography (e.g., inhalation patterns, how much of the cigarette is smoked, number of puffs) that would allow a true comparison of black and white differences in smoking-attributable CHD risk. In addition to direct smoking exposure, passive exposure from inhaling the smoke of others may also be greater among blacks than whites due to the greater prevalence of smoking in the black community. This may possibly lead to increased risk for CHD and other smoking-related diseases in nonsmokers.

Smoking rates in both blacks and whites are highest in persons with incomes below the poverty level. Data from NHIS (1985) and CARDIA also show higher rates of smoking persisting in persons with lower levels of education. Analysis of these studies indicates that black and white differences in smoking rates disappear when levels of education are taken into account.

Smoking appears to have a risk-enhancing effect on factors that favor sudden death as a CHD manifestation, including increased platelet adhesiveness and attendant thrombogenicity, increased vasomotor reactivity, and a lower threshold for lethal arrhythmias. Although not well studied, it is possible that the higher case fatality and sudden death rates observed in blacks may be attributable in part to higher rates of smoking.

Smoking cessation and smoking prevention interventions targeted specifically to black populations have been studied. A number of potentially modifiable reasons may explain why there may be a persistently higher smoking prevalence and lower quit rates in blacks. They include advertisements targeted to blacks, different sociocultural norms that support continued smoking in the black community, and lack of access to resources to assist in cessation efforts. There is evidence that selective targeting of the black community has occurred with advertising, media drives, and promotional campaigns, including free distribution of cigarettes and single cigarette sales which appeal to youth and persons with limited incomes. Certain social factors play a strong role in maintaining high smoking rates in black communities and, although individual smoking cessation efforts may be useful in high-risk groups, community-wide policy level interventions are probably the most effective route for reducing the overall prevalence of smoking in blacks, although this remains to be demonstrated.

Smoking habits among blacks are not well understood. Many more blacks than whites smoke sporadically, smoke less than half a pack per day, and change brands frequently. It is not clear whether this is a reflection of economics or choice, and it is not clear to what extent this influences nicotine addiction and its treatment. Since measures of addiction have been largely defined in white populations, very little is known about the extent to which nicotine addiction plays a role in the lower quit rates seen in blacks. Because many blacks do not smoke daily and, when they do, smoke fewer cigarettes with longer periods between cigarettes, theoretically, physiological addiction should not be a problem for some. In addition, little is known about the response of blacks to the use of the nicotine patch or other nicotine replacement methods as adjuncts to behavioral treatment. It has been reported that blacks are more reluctant than whites to use prescribed nicotine as a drug to aid in smoking cessation.

Blacks also start smoking at an older age than whites, which may reflect economics or a social environment for youth that is not supportive of smoking initiation. In either case, once discovered, these factors could be mobilized to improve prevention strategies. Smoking, specifically in black youth, is not well studied or understood.

Most black smokers, 66 percent, indicate the desire to quit smoking and many (64 percent of men and 53 percent of women) have made serious attempts to quit on their own. Up to 70 percent indicate a desire for formal help in quitting. Trends in current smoking rates indicate that black smokers, both men and women, are not quitting at the same rates as their white counterparts. In the MRFIT study, among a group comprised of blacks and whites of relatively high SES with a strong volunteer ethic, quit rates were slightly less for black smokers compared with whites among those receiving intensive interventions (43 percent and 46.2 percent, respectively). Quit rates in the group not receiving an intensive intervention were 22.5 percent in blacks and 29 percent in whites at 6-year followup. This finding suggests that, within homogeneous SES groups, differences by race in quit rates are not great. Lower spontaneous quit rates observed among blacks in population studies may reflect racial differences in education or other SES variables. Nonetheless, given the high smoking-attributable CHD rates in blacks and the high numbers of those who continue to smoke, it would be important to develop strategies to markedly lower the use of cigarettes in the black population and to determine the impact of smoking cessation on presumed associated health

risks. Social interventions that attempt to shift the sociocultural environment relative to tobacco are likely to be more effective than approaches that target individuals.

Diet

Diet and eating behaviors are associated with an array of CVD risk factors, including hypertension, diabetes, and hyperlipidemia. Although major differences between black and white populations in eating patterns have been posited, there are few empirical data to support this assumption. Since obesity is more prevalent in blacks, it has been assumed that blacks consume more fat and calories. However, the daily proportion of total calories from fat in the NHIS (1987) appears to differ only a few percentage points between blacks and whites. The NHANES II showed that blacks consumed 35 to 38 percent of their calories from fat, a level that is substantially higher than national recommendations of 30 percent, but very comparable to the level of whites.

Although fat consumption may not differ much between whites and blacks, preferences for certain food groups appear to differ. NHANES II found that soluble fiber, fruits, and vegetables were consumed less by blacks compared with whites. Meta-analyses of several large nutritional data bases suggest that more blacks than whites consumed a diet rich in meat, used whole rather than skim milk, and consumed more eggs, sweets, and salty snacks. Bacon and lunch meats were also more commonly consumed by blacks. Black populations appear to use more table salt, but precise measures of sodium intake have not been accurately assessed in most studies. The INTERSALT study suggested a lower potassium intake for blacks than whites in both urban and rural Mississippi, but found no differences in sodium consumption.

Although the limited race and ethnicity-specific data available suggest some dietary-pattern differences between whites and blacks, the nutritional composition of foods selected by blacks does not appear to differ dramatically from that of whites. Nevertheless, differences in dietary patterns (i.e., higher sodium, fewer vegetables and fruits, lower soluble fiber, and lower potassium consumption) may be associated with a higher risk for CHD. This distribution of risky eating patterns is probably more defined by SES than by ethnicity.

Physical Inactivity

Limited data are available on racial and ethnic differences in levels of physical activity and prevalence of sedentary lifestyle. Most studies have been conducted primarily in white populations. The Minnesota Heart Survey examined leisure-time physical activity levels in both blacks and whites between the ages of 35 and 74 years. In both black men and women, the energy expenditure for leisure-time physical activity was significantly lower than in their gender-specific white counterparts. The percentage of individuals expending 2,000 calories or more per week in leisure-time physical activity was markedly lower in black men, but not in black women, compared with whites. In both men and women, work-related levels of energy expenditure related to physical activity were greater in blacks but were not related to the amount of leisure-time physical activity. The greatest gap between blacks and whites in leisure-time physical activity occurred in persons with less than a high school education, among whom blacks had notably less leisure-time physical activity. Racial differences in physical activity levels in the Minnesota Heart Survey were independent of age, gender, and educational level. These findings were supportive of earlier studies, including the NHIS and Statewide Behavioral Risk Factor Surveys (BRFS). Analysis of the NHIS showed that 52.7 percent of black men and 48.9 percent of white men could be classified as sedentary, and that 66.8 percent of black women and 60.9 percent of white women were sedentary. In the BRFS, 35.5 percent of whites and 40.8 percent of blacks reported no energy expenditure in active sports.

In general, adult blacks may be more sedentary and less fit than whites. For example, in a study of teachers, blacks had significantly lower treadmill times than whites. Some investigators have concluded that, generally, low income and less education are associated with low physical activity. However, blacks are more sedentary than whites independent of income and education. Thus, although there appear to be statistically significant racial differences in levels of both leisure-time and work-related physical activity, absolute differences may be modest. Most of the U.S. population is relatively physically inactive.

Few studies are available of interventions to increase physical activity specifically in blacks compared with whites. Thus, little is known about the potential of any remediation for sedentary lifestyle, although there is some preliminary

evidence that church-based exercise programs and programs linked to a social network may engage persons from the community in activity. However, measures of physical fitness and information about participation rates are lacking.

Obesity

Obesity represents a complex interaction of biological host factors, individual behavior, and culture. In concert with genetic factors, diet and physical activity are major determinants of body weight. The prevalence of overweight, defined by gender-specific thresholds for body mass index (BMI), is approximately double in black women compared with white women. Racial differences in the prevalence of obesity do not emerge until after adolescence. Prospectively, in the 10-year followup of NHANES I, the increases of BMI over time were of sufficient magnitude to make black women 60 percent more likely to become obese than their white counterparts, although this appeared to be accounted for largely by SES levels.

Obesity appears to play a role in CHD rates through its association with other risk factors or independently. Estimates from the NHANES I 10-year followup suggest that up to 35 percent of all CHD in black women and 21 percent in white women were attributed to obesity. This finding has been supported in other longer-term studies. There is also potent evidence that obesity plays a major role in hypertension, hyperlipidemia, and diabetes, all factors strongly associated with CHD.

The Evans County Study and the CARDIA study have shown that obesity, usually expressed as BMI, is associated with blood pressure levels and with the presence of hypertension. Overweight individuals are up to twice as likely to be hypertensive as those whose weights are normal. Although a link between obesity and blood pressure has been reported in most studies, the magnitude of the relationship has been relatively modest. Lack of a highly correlated relationship between weight and blood pressure does not necessarily indicate that obesity or body weight is not an important factor in the development of hypertension in blacks. This finding may be a function of the high prevalence of hypertension in blacks, even in those of normal weight. In support of the relationship of body weight to hypertension in blacks, weight gain over time has been shown to be significantly associated with development of hypertension, independent of baseline body weight. Excess body fat also remains significantly associated with development of hypertension in adults, although this association appears to be less consistent and weaker than the association of blood pressure with weight.

In some age groups, blood cholesterol levels are associated with body weight. Overweight persons have up to a 20-percent greater probability of having a high-risk total cholesterol level. Blacks with the greatest excess in body weight have an average total cholesterol level that is 30 mg/dl higher than normal-weight persons. In some studies, blacks who are overweight also have lower levels of the protective HDL-cholesterol subfraction when compared with those whose body weights are normal. Obesity is also associated with a higher prevalence of LVH and with other ECG abnormalities, although it is not known to what extent blood pressure or other attendant risk factor variables mediate this relationship in blacks.

Obesity is more prevalent in black women compared with white women or with black men. It is not definitively known whether this translates into an independent risk factor for CHD or whether obesity imparts an excess CHD risk through its influence on blood pressure, diabetes, lipid abnormalities, or any other risk factors. It should be noted, however, that obesity is a prevalent health problem in Americans, blacks and whites, and that CHD is only one of many diseases that may be causally linked to obesity.

Adoption of a healthy diet may have a major impact on the expression of CHD by lowering the risk of overweight, hypertension, diabetes, and hyperlipidemias. Yet, the American public, both blacks and whites, continues to lag behind national dietary recommendations. There is, nonetheless, a propensity of the American public to be concerned about body weight, perhaps because of the negative social image associated with being overweight. Because the prevalence of obesity is so high in black women, some investigators have hypothesized that this represents a cultural norm whereby heavier weights are considered more socially desirable. All of the evidence to date suggests that this is not the case and that both black women and men do not favor heavier body images. A large percentage of black women in the United States are “on a diet” at any given time, although they are significantly less likely to be successful in losing weight than white women. In formal weight-loss programs and in controlled trials, black women fail to lose weight more often than do white women, although sustained weight loss is extremely difficult to accomplish in any group. The 10-year followup of NHANES I participants supports the findings of smaller studies that show

the failure of black women to lose weight as frequently as white women. In the Hypertension Prevention Trial and the Trials of Hypertension Prevention (TOHP) studies, differences between black and white men in weight-loss interventions were apparent in the early months but were not evident at 1 year. White women lost weight more frequently than black women, although differences at 36 months of followup were minimal. Thus, sustained weight loss and identification of its predictors remain elusive in both blacks and whites. However, it should be noted that there may be sociocultural, behavioral (including differences in exercise patterns), biological, or hereditary influences that favor maintenance of a lower body weight in whites in comparison with blacks. This matter is poorly understood. In regard to adoption of heart-healthy eating patterns, so little is known about the basic food patterns in blacks that it is impossible to trace secular trends in consumption of fat, sodium, fiber, and other nutrients associated with CHD risk.

Social Support

There are a number of reasons to believe that blacks experience more stress and less tangible and perceived social support, often conceptualized as a moderator of stress, than their white counterparts. Less tangible social support may decrease the ability of blacks to cope with stress. The presence of social support from family, friends, and social networks, particularly the church, have been linked to a lower risk of hypertension and stroke in blacks and to better health outcomes across a broad array of illnesses. In one study, lack of social support was a better predictor of mortality than cigarette smoking. In blacks, the level of perceived emotional support and actual support provided for activities related to health care and life activities is a stronger predictor of health outcomes than it is in whites. A study of stroke mortality found that those measures that reflected a lack of social support were consistently among the strongest predictors of stroke rates for blacks but not for whites. Regular church attendance, a possible reflection of access to a large and supportive network, both emotionally and operationally, has been shown to be related to lower levels of hypertension, better control of hypertension, lower rates of cigarette smoking, and a better response to smoking cessation interventions, independent of SES measures. Most studies show that the ameliorating effects of social support are strongest in blacks in the lowest SES levels, which suggests that, in the absence of resources, social support is particularly important.

In blacks, the increase in households headed by women, lower rates of marriage, and disruption of cohesive extended-family structures are factors that have been posited to be related to the failure of CHD rates and attendant risk factor prevalences to decline at the rates occurring in whites. Unfortunately, most studies are cross-sectional or ecological, and important interrelationships between economic hardship and social factors remain poorly defined. Thus, although social support, defined in a number of ways qualitatively and quantitatively, appears to be particularly important in blacks, specifically relative to hypertension and stroke, it is poorly studied in relation to CHD and is a concept that warrants further study.

It is noteworthy that, among blacks, social networks may facilitate implementation of preventive health care programs. Group empowerment strategies in minority communities may be particularly important for lowering aggregate CHD risk.

Stress and the Social Environment

Continued exposure to racial prejudice and inequality probably leads to a number of secondary sources of stress, including a greater proportion of blacks with lower wages than their white counterparts, although the income gap between comparably trained and skilled workers has narrowed. Higher prevalences of poverty exist among blacks. Efforts to overcome a longer history of poverty and educational disadvantage and to assist family members to overcome financial and educational disparities may predispose to a more stressful environment.

The effects of racial discrimination are poorly understood as they relate to the stress and CHD paradigm in blacks. Racial discrimination may be a strong environmental stressor that is differentially influential depending on coping style. Studies show that black women who quietly acquiesce to discriminatory practices are four times as likely to be hypertensive than their counterparts who actively report fighting discrimination. Black women who perceived that they had been discriminated against are less likely to experience hypertension than those who indicate that this had not occurred, which suggests that the experience of internalizing racial injustice places black women at higher risk of hypertension, a major CHD risk factor. Racism and discrimination as obstacles to success in blacks are concepts that have been hypothetically linked to CHD, but about which little is known.

If the assumption that the environments of blacks hold more potential stressors is correct, as supported by the consistent finding that blacks list more negative daily life events than whites, then it is possible that continued stressful exposure may result in adaptation or coping styles that either ameliorate the response to stress or deny it. In either case, such differences in cultural experiences and definitions of stress continue to make cross-cultural comparisons difficult, and there are no data yet to shed light on how continued exposure to frequent negative life events affects CHD risk in blacks. Further, coping mechanisms and the influence of social support as possible mediators of stress are not well understood in blacks, particularly in the context of CHD.

Hostility, Anger, and Type A Behavior Pattern

In several studies examining blood pressure, suppressed anger or hostility has been associated with higher blood pressure in blacks, particularly in men and in persons living in areas that could be identified as having high exposure to social problems. In one study, blacks with elevated levels of expressed anger had a high likelihood of having hypertension. Unfortunately, the lack of culturally validated tools for measuring these factors in blacks and the difficulty in assessing the degree of sociocultural stress may account for inconsistent findings of related studies. When blacks are asked to list CHD risk factors, environmental stress is often noted among the first three perceived causes of CHD, which suggests that valid issues related to stress have not been well defined or examined in prior studies in blacks.

Type A behavior pattern, characterized by time urgency, competitiveness, a hard-driving workstyle, impatience, and high levels of hostility, has been related to CHD outcomes in some studies, but not in others. Several recent investigations found that the hostility component of the Type A pattern may be the dominant feature in relation to CHD. This has not been well studied in blacks and data remain sparse relative to Type A, hostility, and CHD in blacks. Nonetheless, several small studies show that blacks have higher levels of internalized hostility on standardized questionnaires than do whites, but that expressed hostility and anxiety rates are lower in blacks. It has been frequently posited that suppressed hostility may provide a background for development of hypertension or risk behaviors associated with CHD. At this time, however, most investigations lack sufficient sample sizes from which to draw definitive conclusions.

Strong achievement motivation has been proposed to explain behavior in individuals who have an overwhelming drive to succeed and few resources and who are exposed to major barriers. Such persons are at increased risk of developing hypertension and other adverse sequelae. Several small studies confirm that this active coping strategy increases the risk of hypertension, particularly in persons with low SES and other barriers to success, perceived or real.

Cardiovascular Reactivity

Although blacks may fail to perceive chronic social stress related to their environments, epidemiological studies consistently identify many such social stressors as predictors of the presence of hypertension. Studies have shown that the presence of chronic stress also increases cardiovascular reactivity to acute psychological stressors in blacks. Several studies suggest that the expression of stress response may differ by culture or ethnicity. Thus, it is possible that, despite the lack of differences in perceptions of stress and coping, there may be biological expressions of stress response. Blacks have often shown a greater elevation in blood pressure and heart rate than whites in response to both mental stressors and cold pressor testing, particularly if they have borderline or elevated blood pressure levels at baseline. Studies in normotensive individuals suggest inconsistent racial differences in cardiovascular reactivity. Nonetheless, it is possible that heightened vasomotor reactivity occurs in some subsets of the black population, possibly those with a personal or family history of elevated blood pressure. If there are racial differences in cardiovascular reactivity in any subset, the effects of acute or chronic stressors, and the relationship of reactive responses to the genesis of CHD or attendant risk factors, are not known at this time.

Research Opportunities

Recent evidence suggests that blacks have the same rates of CHD mortality as whites or even greater mortality in younger age groups, but there may be differences in the relative importance of specific mechanisms, some of which are linked to sociobehavioral factors. Further, it is likely that there are complex interactions of social, behavioral, and physiological CHD risk factors that require an understanding of black heritage and culture and the current social milieu. In order to develop effective preventive strategies, the unique contribution of

sociocultural context to racial differences in CHD risk factors, mechanisms of CHD, and attendant lifestyles needs to be understood. Available data on these issues are sparse. Thus, research opportunities abound relative to behavioral, social, and environmental factors; the seeking of health care for prevention; and care of chronic and acute symptoms of CHD to lower overall risk for CHD morbidity and mortality. Because so little is known, it is important to recognize that the research agenda may need to be evolutionary and may have to be built from successive approximations toward increasing knowledge. The early initiative in promoting reduction of CHD risk in blacks may need to be relatively broad and focus on models that are generic and test hypotheses. It is critical for all studies of CHD in blacks that deal with clinical or free-living populations to address social, cultural, and behavioral factors in an integrative manner to develop a complete, nonfocal portrait of the problem.

Smoking

Smoking is a major concern in black Americans because of its high prevalence, its association with sudden death, and a higher CHD case-fatality rate. A number of current NHLBI initiatives address smoking cessation on an individual level. State-of-the-art cessation programs, even using pharmacological adjuncts, rarely achieve cessation rates above 25 to 30 percent in participants who are usually volunteers with strong intentions to quit. Among persons who do not volunteer for cessation programs, the probability that any intervention, including nicotine replacement, will be effective is even lower. The most promising strategies appear to alter personal behavior through environmental interventions, namely macrolevel tobacco control. However, many of these are not in the purview of the NHLBI.

Diet and Obesity

Blacks and whites continue to consume diets that influence CHD risks by being high in total fat, cholesterol, and salt, and low in fiber, fruits, and vegetables. Eating patterns are not well understood, and there are few sources of prospective data on eating patterns in black communities to allow determination of population shifts in diet. Because of the major contributions of diet to overall CVD risk and other risk factors, dietary factors and dietary interventions related to obesity, hypertension, and other diet-associated risk factors need to be addressed specifically in black populations. Although not meant to replace individual approaches for diet change that may be necessary in persons with diagnosed disease or existing morbidity, when dealing with prevention it is likely that approaches that target entire families and communities will have a higher probability of achieving success and reaching a larger number of people to lower CHD risk on a population basis. Thus, with diet, as with smoking, opportunities for research to reduce CHD risk should focus on a sociocultural research paradigm that is complementary to traditional individual behavior-change approaches. Again, these issues include but are not specific to CHD risk.

Social and Psychological Factors

Although there are longstanding assumptions about the impact of the sociocultural environment on perceived and physiologically manifested stress levels in blacks, little is known about how or whether this impact translates into increased CHD risk. Studies that examine these issues in black populations are critical to the selection of preventive strategies since the social milieu may act not only on lifestyle choices and adoption of risky habits, but also may induce the biological substrate for elevated blood pressure, heightened reactivity, and altered immune response.

Physical Inactivity

Leisure time, work-related physical activity, and social and cultural factors that influence sedentary lifestyle are poorly understood in black populations. The effects of interventions on adoption of active lifestyles and their impact on CHD risk factors and CHD risk are simply not known in blacks. There are opportunities for addressing the entire spectrum of physical-activity issues in blacks. With the shift among blacks to jobs with less physical-labor intensity, the relative importance of work versus leisure physical activity is increasingly important.

Recommendations

Specific recommendations for research on behavioral risk factors are:

CHD Risk Factors: General

1. Design and develop culturally validated tools and methods to characterize CHD risk factors (e.g., smoking, unhealthy dietary habits, physical inactivity, stress) that have already been established in the general population.

2. Develop prospective data bases to enable assessment of known and potential CHD risk factors that may differentially affect blacks, including smoking and smoking topography, social support, and stress and its influence on coronary vasomotor activity.

3. Examine psychosocial predictors of mortality and morbidity outcomes for acute CHD events.

4. Determine individual psychosocial and biological factors that influence compliance with prescribed pharmacological and nonpharmacological risk factor control regimens.

5. Develop and evaluate effective programs for promoting adherence to CHD risk-reduction programs.

Smoking

1. Develop valid and reliable instruments and community sampling methods to assess smoking prevalence adequately in blacks, including identification of smoking topography and its effects on direct and passive exposure to cigarette smoking.

2. Define unique social, cultural, and environmental needs of black communities and develop approaches that specifically will increase the smoking-cessation rates in men and persons of low educational attainment and will prevent the adoption of cigarette smoking in black youth.

3. Test the effectiveness of community-wide multimodal approaches to tobacco control and smoking cessation that take into account cultural institutions such as churches.

4. Determine the relevance and applicability of state-of-the-art psychosocial models of smoking cessation in blacks.

Diet and Obesity

1. Establish a prospective nutritional data base with sufficient sample size and socioeconomic and geographic heterogeneity to allow tracking of dietary information over time and comparisons by SES within the black population.

2. Determine the social and cultural factors and norms related to body weight in black men and black women and test innovative, culturally based strategies to lower the population prevalence of obesity through sustained weight loss.

Social and Psychological Factors

1. Design and test culturally validated tools to ascertain the nature and impact of environmental stressors such as employment, low income, poor housing, high crime rates, substance abuse, racial discrimination, and factors that are defined by the culture itself. Determine the association and interaction of these stressors with CHD risk factors and with overall CHD risk.

2. Determine the impact of acculturation (adoption of mainstream cultural values and lifestyles) on CHD risk factors and risk.

3. Determine whether some high-risk subsets of blacks manifest heightened vasomotor reactivity in response to psychological stress and the degree to which this is associated with the substrate for potentially lethal arrhythmias or vasomotor spasm.

Physical Inactivity

1. Determine the role played by the cultural and social environment in physical activity in blacks.

2. Evaluate intervention models to increase levels of physical activity and physical fitness, especially in black youth, young adults, and women.

3. Include measures of physical activity in blacks in national data bases.

HEALTH CARE BEHAVIOR

State of the Science

Utilization of Health Care Services

Differences in dimensions of the seeking of health care for CHD events and attendant risk factors between blacks and whites may contribute to racial differences in CHD morbidity and mortality pat-

terns. For example, blacks delay longer than whites in seeking care for general medical problems as well as for acute CHD symptoms, including acute MI. Blacks are also less likely to see a physician within the year prior to a cardiac event, despite higher rates of chronic and acute health problems. When health status is taken into account, both blacks in good health and those in poor health remain less likely than whites to see a physician for acute care or preventive services. Ethnic differences are independent of other potentially influential variables, including income level, health status, age, and gender. Importantly, among persons aware of being hypertensive, 30 percent of blacks and 19 percent of whites reported that they had not had their blood pressure checked within the past year. Blacks are also more likely to use public clinics and emergency departments of acute care hospitals for their primary source of care—systems that, by their nature, are not oriented to prevention or care of health concerns that are asymptomatic, such as hypertension and hyperlipidemia.

Access to care is undoubtedly the source of some of this delay. Patients without a usual care provider and those with low-income levels, low SES, and poor insurance coverage delay longer in seeking health care for acute events. Access to care is, thus, most commonly associated with the seeking of health care. Although there are a broad range of variables that constitute access to care, the seeking of health care is determined by many other factors, including knowledge and beliefs concerning CHD, symptom perception, symptom attributions, adherence with treatment recommendations, and physiological differences.

Access to Care

Access to medical care is a major influence in health care seeking behavior, whether for preventive or acute care services. Financial factors clearly play a major role in access to care. In one recent study, 1 in 11 blacks reported not receiving health care for economic reasons, compared with 1 in 20 whites. Racial differences in care for hypertension are partially accounted for by differences in health insurance. Blacks are less likely to have any health insurance at all, in comparison with whites, and less likely to have insurance by a private insurer (85 percent in whites, 72.5 percent in blacks). Reimbursement for services for management of hypertension and high cholesterol levels is likely to be better among private insurers than with Medicare and Medical Assistance Programs, and many blacks have been shown to live in states that have the least generous state-assistance health programs. Thus, accessibility to preventive services is, at least in part, a function of the differential representation of blacks in lower income groups.

Access to care is often conceived as unidimensional, reflecting primarily financial constraints. However, careful examination of access issues has resulted in the genesis of multidimensional models that incorporate several structural and perceptual elements. Structural issues that influence access to care involve affordability or the actual ability to pay for services, accessibility reflecting transportation issues, and accommodation reflecting factors such as how long one is kept waiting and the adequacy of time spent with health care providers. Black patients have reported greater barriers to accessibility and less structural accommodation within their health care settings than white patients. There is also evidence that blacks perceive traditional, acute care-oriented systems as unresponsive to their needs, particularly their preventive needs. Perceptual or physiological variables may be equally important.

Satisfaction with care and psychological acceptability reflecting perceptions of how well persons feel they were treated within the health care setting are important factors that influence access to care and health care seeking behavior. Because there are few black physicians, primary providers who serve most black patients rarely come from the same communities or represent the same cultures, perhaps adversely affecting psychological accommodation and acceptability. Blacks are less likely than whites to report satisfaction with their interactions with physicians and are more likely to believe they have received inadequate care. Although structural barriers are prominent impediments to care, psychological barriers also undoubtedly persist in affecting access.

For both black and white Americans, access to convenient, reimbursable, acceptable, and effective preventive services has been elusive. Unfortunately, the lack of fiscal or health care alternatives for the many blacks who fall into low-income groups in U.S. society may be a crucial factor in maintaining the wide racial gap in access to preventive and acute care that may decrease CHD risk. For blacks above low-income levels, perceptual or physiological barriers may also persist that continue to affect preventive and acute medical care.

Knowledge and Beliefs About CHD

In community surveys, black respondents are often less knowledgeable about CHD symptoms, risk factors, and methods of prevention than whites even when controlling for other factors such as demographic, risk factor, and medical care variables. Although only limited data are available, differences have also been reported between black and white community respondents in actions they would take if they thought that they were having a heart attack: Black women would less commonly call a doctor than white women, and black men would less commonly call emergency numbers than white men. Even with CHD outpatients and inpatients, preliminary reports suggest that blacks are less knowledgeable about prevention and CHD symptoms than whites. Black patients in the medical care system may, thus, not be educated sufficiently to overcome racial disparities in awareness of prevention and symptoms also seen among community respondents.

Racial comparisons of prevention and treatment beliefs that may influence the seeking of health care are limited and may constitute an important area for future research. Believing that CHD is preventable has been associated with reduced delay in seeking treatment for acute cardiac events. Conversely, believing that symptoms would subside or were not serious has been related to increased delays. Lowered expectations concerning treatment benefits and elevated expectations concerning treatment risks have been posited to account for some of the differences between blacks and whites in utilization of medical care and adherence with prevention measures.

Perception of Symptoms

Perception of symptoms clearly influences the seeking of health care and may be influenced through both physiological factors and perceptual mechanisms. Although preliminary results suggest that black and white CHD patients may not differ in prevalence of Rose-questionnaire angina, such comparisons do not consider possible differences in those individuals with undiagnosed CHD or not receiving care. In addition to the need for additional data to address the appropriateness of using the Rose questionnaire with minority patients, racial differences in symptom patterns need to be examined beyond those surveyed by the Rose questionnaire. Initial data suggest that black patients are less likely to report painful symptoms and more likely to report gastrointestinal symptoms than white patients, even when controlled for other factors. However, racial differences in symptom reports appear to differ regionally.

Attribution of Symptoms

Symptoms are attributed to some cause by persons who experience them. Attributions reflect an individual's belief about the source of the problem and, thereby, influence the care that will be sought for the problem. For example, patients who attribute acute MI symptoms to noncardiac origin have been shown to delay seeking treatment to a significant extent. Anxiety and denial increase attribution of symptoms to the wrong cause and may result in not seeking appropriate care. The perception of symptoms for an array of health problems appears to differ between blacks and whites. Since knowledge about CHD is known to be low among black populations, this factor may also contribute to failure to seek appropriate preventive services or treatment for acute symptoms. Black patients in the hospital who sought treatment and were admitted for their acute symptoms attributed their symptoms less often to cardiac origins. Even when only those patients who had painful cardiac symptoms were examined, black patients still attributed their CHD-related symptoms less often to cardiac origins.

Treatment Adherence

Although medical care adherence rates for all race and gender groups are usually lower than estimates by physicians, adherence to recommended treatments or medical tests may account for some of the excess of risk factors found in some populations. For example, CABG surgery is used less often in blacks than in whites, even in settings such as Veterans Administration hospitals that would be expected to ameliorate any differential effect of financial access. Adherence to treatment guidelines by health care practitioners has also been shown to be lower in blacks, with biases in the referral of black patients for interventions as well as diagnostic tests. Adherence to antihypertensive regimens may be poorer by blacks than their white counterparts. Adherence to medical regimens is affected by communication between patients and health care providers. Among patient variables, health care seeking factors such as beliefs in treatment efficacy and social support from significant others constitute one class of variables that affect adherence. Another class of patient variables results from low education, low income, and low SES and includes such factors as poor access to followup sources; difficulties in meeting the financial costs of treatment; difficulties in taking time off from work and other activities to

comply with recommendations; problems with understanding treatment recommendations; and less knowledge about risks, methods of preventing risks, and benefits of preventing or controlling risks. Although these barriers are undoubtedly disproportionately encountered by minority groups, they do not appear to result from ethnic or cultural background but are more likely the result of educational and financial disparities.

Poor adherence is influenced by inadequate access to acceptable and affordable health care and by the priority of psychosocial issues over the treatment of asymptomatic health problems. Although inadequate blood pressure control has been cited as evidence of widespread nonadherence in black hypertensives, it also may reflect an element of biological intransigence or an interaction of biology and nonsupportive sociocultural environment. Most studies consistently identify a problem of therapy adherence among lower-income blacks, although assessment and intervention methods to improve adherence have not yet been well delineated.

Physicians tend to believe that minority and low-income individuals are less adherent to prescriptive regimens and primary prevention methods, and data suggest that fewer efforts are made to promote primary prevention methods by physicians who primarily serve low-income people. Rates of control of hypertension are unacceptably low for individuals who are aware that they are hypertensive in all race groups. Although it has long been claimed that this is a result of poor patient adherence, data suggest that health providers may not provide adequate monitoring of blood pressure or may not adhere to national guidelines for blood pressure treatment and control. Physicians may also be remiss in ensuring that patients understand their medication regimens and have access to pharmacies and other means to be adherent. Patient characteristics, including lower socioeconomic class, have been implicated in medical practitioners' behavior and negative stereotyping of patients. These factors may result in differences between blacks and whites in therapeutic management, referral patterns, and use of diagnostic options. Although low-income and poorly educated people may have special barriers to adherence, this does not mean that they will not be adherent if approached with appropriate methods of addressing these barriers.

Physiological Factors

The high prevalence of certain types of physiological problems in minority groups may affect their perception of symptoms for other problems, such as CHD, in several ways. Afferent sympathetic nerve fibers, involved in pain perception from the heart, may be impaired or damaged in patients with diabetes, resulting in higher asymptomatic ischemia rates in these patients. Persons who are at risk for hypertension show evidence of abnormal adrenergic control of systolic blood pressure. Data also suggest that hypertensives are more likely to experience silent ischemia than nonhypertensives. A recent report found that asymptomatic ST-segment depression occurs more commonly during normal activity and during induced stress in patients with systemic hypertension. In addition to the greater risk imposed through physiological mechanisms that results from higher rates of diabetes and hypertension in blacks, the higher prevalence of these risk factors in blacks may influence to a greater extent than in whites their perception of symptoms and, hence, their symptom attributions and treatment seeking. Interactions among physiological, psychological, and perceptual factors that influence the ultimate perception of symptoms and the seeking of health care are an important area for future research.

Research Opportunities

Because of the number of variables involved in making decisions about seeking health care, factors that differentially influence the seeking of health care for CHD risk factors and events in blacks compared with whites need to be studied. Lay referral patterns, for instance, have been posited as a more prominent factor affecting the seeking of health care in blacks than whites due to the cultural prominence and importance of networks in the black community. Since consultation with family members and friends has been significantly associated with increased delay in seeking care for acute CHD events, networks within the black community may adversely affect the seeking of treatment. Folk beliefs and remedies may also be factors that affect the seeking of treatment.

Efforts to implement and evaluate education and prevention strategies in the area of health care seeking behaviors have been extremely limited and need to expanded. There are limited data that address access, knowledge and beliefs, perception and attribution of symptoms, and adherence with both

pharmacological and nonpharmacological approaches. However, research is needed to delineate further these factors and their interactions and to develop approaches that facilitate appropriate symptom attributions as well as other factors that influence the seeking of acute and preventive health care.

Model research programs to increase access to care, health care seeking for acute and preventive care, and adherence with treatment recommendations need to be developed. Generally, approaches have involved community-based clinics that receive financial support to address financial and other structural aspects of access and to provide a culturally sensitive staff that favorably influence psychological access dimensions. However, additional efforts at the individual and community levels are necessary to improve early seeking of health care for CHD.

Recommendations

Specific recommendations for research on health care behavior are:

1. Determine and assess factors, including regional variations, that influence blacks to seek health care for the evaluation and management of chronic CHD, treatment of acute CHD events, prevention of CHD, and adherence with treatment recommendations.

2. Develop and evaluate the effectiveness of educational and behavioral programs targeted to individuals and communities to enhance early seeking of health care for evaluation and management of chronic CHD, treatment of acute CHD events, prevention of CHD, and adherence with treatment recommendations.

3. Determine individual, cultural, and system barriers to seeking of health care, such as those for access to primary and preventive care, and to the use of existing health care services for identification and control of CHD risk factors.

4. Explore health care practices and patient demographic and psychosocial predictors of access to and acceptance of invasive treatments for CHD (i.e., CABG surgery and angioplasty) to identify areas for future efforts to ameliorate racial disparities in treatment.

Education and Prevention Strategies

State of the Science

Approaches to prevention have been directed either at individuals, accessing them through various means such as churches or schools, or more broadly at the community, involving such means as social marketing and community education methods. Both approaches have been effective in lowering CHD risk factors in black and white individuals.

Strategies for Individuals

Individual strategies for amelioration of CHD risk factors are those that traditionally have been used in health education and behavior modification. Such approaches involve individual counseling, small-group interventions, or self-help and minimal contact materials that are designed to help people change lifestyles. Social psychology often provides the basic theoretical underpinning for such strategies. The problem with individual approaches is that they often isolate individuals from their social environment or require individuals to make decisions that involve marked deviations from the cultural norm. In the case of black Americans, whose culture is very social and behaviors are often determined as much by social interaction as by individual decision making, such approaches may be even less effective than they are in the general population. Dietary intervention trials for CVD risk reduction offer a case in point. For example, the TOHP reports less weight loss and lower sodium reduction among black participants than among white participants. This finding clearly argues for improved individual approaches for CVD risk reduction in blacks, alternative nonindividual approaches, or a combination of approaches. Due to the emphasis and prominence within the black community on formal and informal social networks, attention to this cultural and social context appears to be an important prerequisite for effective programs.

Strategies for Communities

Several different approaches to community-based prevention have been adopted. Some emphasize a particular mode of entry, such as churches; others emphasize a particular method, such as social marketing. Still others adopt a more broad-based approach of developing community partnerships to implement programs. Informal networks are also

prominent in black communities; they may be barriers to health services, if not involved, or facilitators, if involved actively. Approaches to community organization for health promotion emphasize the distinction between internal support and external support of program goals. Using this approach, promotion of activities is accomplished through members of internal groups. It capitalizes on the existing strong role of informal social networks and reliance on social support from these extended social networks and is consistent with empowerment strategies advocated for and by minority communities.

One approach to extending this partnership further is the use of trained community residents. This places the emphases on empowerment and on encouraging community capacity-building; community identification of goals, problems, and issues; and creation of an increased awareness of the problem and methods to accomplish CHD risk reduction. These efforts, thereby, utilize cultural traditions of many minority communities and benefit from the internal promotion of program goals. Critically important is the transfer or institutionalization of ownership to the communities through partnerships. Approaches that emphasize the community's central role in defining needs, identifying strategies, implementing methods, and encouraging and supporting local ownership and empowerment provide a basis for common organizational methods.

Church-based programs, building on the central role of the church in black culture and lifestyle, have proved to be particularly capable of overcoming many barriers related to effective health care. Church programs have been demonstrated to be effective in control of hypertension and smoking. Churches have been excellent sites for screening programs for CHD risk factors. Although persons who attend church regularly do not necessarily represent the population at highest CHD risk, more than 60 percent of persons in urban black communities attend church on some regular basis and more than 65 percent cite prayer as their major coping mechanism. Churches also espouse an ethic that is generally favorable to adoption of healthier lifestyles. Social support, natural helping networks, relative ease of forming groups, and ability to access and track families are additional benefits of church-based programs. The National High Blood Pressure Education Program has a two-decade history of successfully implementing church-based programs in black communities. This effort has resulted in improved blood pressure control in participating communities. The most effective risk-reduction programs have incorporated spiritual and cultural aspects of the church. Implementation of interventions in this setting has been most successful when the indigenous population becomes the purveyor and owner of the program. Attempts have been made by "outside" groups to use churches solely as sites of access or as venues for programs, but these approaches have not been sustainable. Other social structures in the black community could be mobilized to empower the community to make CHD risk reduction a valued sociocultural norm.

Specific methods for CHD risk reduction have been particularly amenable and appropriate for development within black communities. Prominent among these is a social marketing approach. For example, national education programs for blood pressure control and cholesterol control have developed components specifically for ethnic minorities. Although these programs appear to have, in part, contributed to the decline in rates of hypertension and a lowering of total cholesterol levels in the population, major racial gaps continue to exist. More whites than blacks are aware of their high blood pressure level, are on treatment, and are under control, although whites and blacks appear to be similarly aware of the risk associated with hypertension in contrast to knowledge disparities in most other risk factors.

Research Opportunities

Studies consistently identify problems associated with access to and appropriate utilization of preventive health services among blacks. Further, the effectiveness of such services may be reduced owing to problems in being able to support adequate adherence in blacks for primary prevention, treatment, and management of hypertension and diabetes. Although there is some knowledge about the profile of persons who fail to comply with regimens and utilize preventive care, little is known about the sources of nonadherence in blacks and ways to ameliorate this through systematic changes that address the unique needs of black communities. If realized, increased adherence could lower cost and possibly result in more accessible, community-based, alternative models of detection, prevention, and modification of CHD risk factors. Major research opportunities involve factors that would improve identification and utilization of services to detect and lower risk. Models that provide effective alternatives to existing systems or that alter existing systems sufficiently to increase utilization by residents of black

communities are important in the face of major national health care reform.

Recommendations

Specific recommendations for research on education and prevention strategies are:

1. Develop and evaluate effective programs for alternative models of preventive health service delivery, including community health care workers and health screening programs, that improve the likelihood of risk factor control in black communities.

2. Develop and evaluate individual and population-based approaches to enhance overall CHD risk reduction, including comparison of sequencing versus combining risk-reduction efforts, and assess interactions among program sequencing, influence on CHD risk factors, and overall CHD risk reduction.

3. Determine the relative effectiveness of community-based institutions (e.g., church and schools) as sites for community-wide CHD risk factor identification and intervention in black communities.

4. Develop and evaluate innovative primary prevention interventions in blacks which emphasize stepwise progression to change, such as individualized programs that involve interventions at worksites, churches, schools; community-based programs that utilize social marketing and community health workers; and physician-based programs that address changes in patient behaviors and in physician promotion of and confidence in primary risk reduction.

5. Develop and evaluate innovative treatment approaches for secondary prevention of hypertension and diabetes that address such issues as patient adherence to pharmacological and nonpharmacological control, community acceptance of wide-scale dissemination of information by physicians and their staffs, and physician expectations regarding their effectiveness in secondary risk reduction, as well as their use of adherence-promoting methods.

APPENDIXES

Bibliography

The following references are provided as a guide for individuals interested in obtaining additional information on the research areas mentioned in this report. The list provided is not intended to be comprehensive or to reflect all of the important and wide-ranging studies in research on CHD in blacks. The references are listed alphabetically for each of the four main sections of the report.

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Abbreviations

ACE	Angiotensin-converting enzyme
AIDS	Acquired Immunodeficiency Syndrome
AMI	Acute myocardial infarction
ARIC	Atherosclerosis Risk in Communities
BMI	Body mass index
BRFS	Behavioral Risk Factor Surveys
CABG	Coronary artery bypass graft
CARDIA	Coronary Artery Risk Development in Young Adults
CASS	Coronary Artery Surgery Study
CHD	Coronary heart disease
CVD	Cardiovascular disease
ECG	Electrocardiography, electrocardiographic, electrocardiogram
EDRF	Endothelial-derived relaxing factor
FRS	Family Risk Score
HDL	High density lipoprotein
HIV	Human immunodeficiency virus
HLA	Human Leukocyte Antigen
LDL	Low density lipoprotein
Lp(a)	Lipoprotein (a)
LV	Left ventricle, left ventricular
LVH	Left ventricular hypertrophy
MI	Myocardial infarction
MRFIT	Multiple Risk Factor Intervention Trial
NHANES	National Health and Nutrition Examination Survey
NHEFS	National Health Epidemiologic Follow-Up Study
NHIS	National Health Interview Survey
NHLBI	National Heart, Lung, and Blood Institute
NIDDM	Noninsulin-dependent diabetes mellitus
NIH	National Institutes of Health
NMR	Nuclear magnetic resonance
PAR	Population attributable risk
PCR	Polymerase chain reaction
PET	Positron-emission tomography
PTCA	Percutaneous transluminal coronary angioplasty
SES	Socioeconomic status
TOHP	Trials of Hypertension Prevention

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