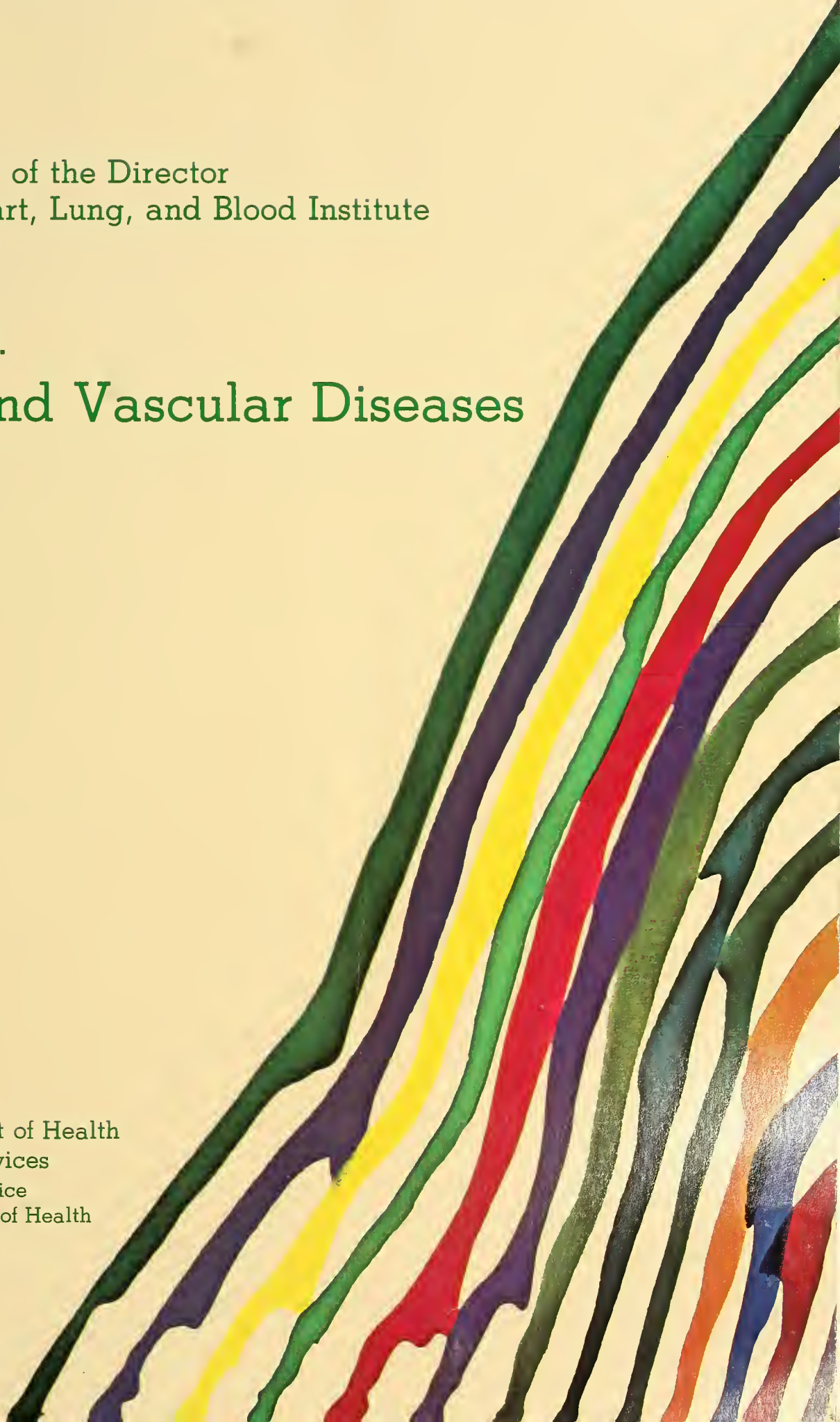
h Report of the Director
National Heart, Lung, and Blood Institute

Volume 2.
Heart and Vascular Diseases



U.S. Department of Health
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Public Health Service
National Institutes of Health

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Tenth Report of the Director
National Heart, Lung, and Blood Institute
Ten-Year Review and Five-Year Plan

Volume 2.

Heart and Vascular Diseases

U.S. Department of Health and Human Services
Public Health Service
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Preface

The National Heart, Lung, and Blood Institute is now in its fourth decade, following its original establishment in 1948 as the National Heart Institute (P.L. 80-655). With a growing awareness of national health problems over the years, such as those reflected in the President's Conference on Heart Disease and Cancer (April 21, 1961) and the President's Commission on Heart Disease, Cancer, and Stroke (December 9, 1964), it was redesignated by the Secretary of Health, Education, and Welfare (now Health and Human Services) as the National Heart and Lung Institute (NHLI) in 1969. The activities of the Institute were expanded in 1972 by the National Heart, Blood Vessel, Lung, and Blood Act (P.L. 92-423) to advance the national attack on diseases of the heart, blood vessels, lungs, and blood. With the passage of the Health Research and Health Services Amendment in 1976 (P.L. 94-278), in which the NHLI was redesignated as the National Heart, Lung, and Blood Institute (NHLBI), the authority was further enlarged to include research on the use of blood and blood products and on the management of blood resources.

The 1972 act was of special significance. The law mandated that the Director of the Institute, with the advice of its Advisory Council, develop a national plan for attacking heart, blood vessel, lung, and blood diseases. The need for the plan evolved from a recognition that isolated approaches were no longer appropriate to the growing magnitude of these public health problems. Twenty-eight task groups of approximately 250 medical and scientific advisors assessed these problems and identified new opportunities for initiatives. The effort culminated in the five-volume National Heart, Blood Vessel, Lung, and Blood Program (DHEW Pub. Nos. (NIH) 73-515, 73-516, 73-517, 73-518, 73-519, 73-520, 73-521, 73-522, and 73-524). The needs, goals, recommendations, and strategies presented in the document provided a National Program, which for the past decade has been updated annually and has guided the Institute. The process includes:

- Research on the epidemiology, etiology, and prevention of heart, blood vessel, lung, and blood diseases
- Research on basic cardiovascular biological processes
- Development and evaluation of techniques, drugs, and devices to aid diagnosis and treatment

- Programs to develop technological devices to assist, replace, or monitor vital organs
- Field studies and large-scale tests relating to those diseases
- Research on blood diseases and the use of blood resources in the United States, including such items as collection, preservation, fractionation, and distribution
- Education and training of scientists and clinicians
- Public and professional education programs in all aspects of those diseases
- Programs to research and study heart, lung, blood vessel, and blood diseases of children.

The 1972 act also requires the Director of the Institute to submit an annual report to the President, for transmittal to Congress, on the accomplishments of the National Program during the preceding year and on plans for the next 5 years.

This five-volume Tenth Report of the Director, NHLBI, which is a 10-year review and 5-year plan, commemorates the 10th anniversary of the National Program. This volume reports on program areas of the Division of Heart and Vascular Diseases, NHLBI. It begins with an executive summary and a description of the magnitude of the problem related to these diseases. Progress, achievements, and future goals are then reported in the following program areas:

- Arteriosclerosis
- Hypertension
- Cerebrovascular disease
- Coronary heart disease
- Peripheral vascular disease
- Arrhythmias
- Heart failure and shock
- Congenital and rheumatic heart disease
- Cardiomyopathies and infections of the heart
- Circulatory assistance.

The volume concludes with discussions of prevention research and of research training and development.

Volume 1 serves as an executive summary of the other four volumes. Volume 3 reports on the program areas of the Division of Lung Diseases, and Volume 4 reports on programs of the Division of Blood Diseases and Resources. The final volume contains a discussion of important companion issues, including international programs and program coordination and liaison.

The process by which these volumes were developed was modeled after the one used in 1972 for the National Program. Members of working and review groups were drawn from the NHLBI staff, the Advisory Council and advisory committees, the extramural scientific community, the community of health providers and health consumers, and the general public.

Foreword

The Division of Heart and Vascular Diseases plans and directs an integrated and coordinated research program in heart and vascular diseases with emphasis on the causes, diagnosis, treatment, and prevention of these diseases. The general mission of the Division is organized within 10 National Program areas that were identified in 1972 in accordance with the requirements of the National Heart, Blood Vessel, Lung, and Blood Act of 1972 (Public Law 92-423). The 10th anniversary of this mandate is an appropriate time to conduct a review of the key areas of accomplishments and progress toward those early goals and objectives, and to establish new goals and directions for future activities.

This volume is the 10-year review and 5-year plan of the Division of Heart and Vascular Diseases of the National Heart, Lung, and Blood Institute. It is based upon reports from 11 branch task groups, each of which was charged to determine key areas of progress and to identify accomplishments over the past 10 years in its respective area of research. Additionally, the groups were asked to develop for the Division an updated National Program plan for the coming 5 years. This effort was accomplished with the invaluable participation of members of the scientific community. Their very significant contributions and assistance are gratefully acknowledged by the Division. (A list of participants can be found on pages xiii-xxv.)

The reports generated by the branch task groups are presented by National Program areas. Each report includes discussions organized by: State of Knowledge 1972; Program Goals Through 1972; Accomplishments Through 1982; State of Knowledge 1982; Program Goals 1982 to 1987; and Research Activities 1982 to 1987.

In the preparation and review of this volume, the Division Director was assisted by the Division's Associate Directors, William Zukel, M.D., Gardner McMillan, M.D., Eugene Passamani, M.D., William Friedewald, M.D., and Manning Feinleib, M.D. Final editing and details of production were the responsibility of John A. Vaillancourt, M.D.

It is our hope that this report will prove of interest to the community and provide a framework to guide the Division's research directions and activities in the coming years. We welcome the interest of all those concerned with the research areas for which the Division is responsible, and we encourage a continued and

productive dialogue with our scientific community. We look forward with enthusiasm and anticipation to the next 5 years of progress and accomplishments.

Barbara Packard, M.D., Ph.D.

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1. Executive Summary

Contents

1. Executive Summary

The progress of the National Program, which was developed in response to the National Heart, Blood Vessel, Lung, and Blood Act of 1972 (P.L. 92-423) to expand and accelerate an attack against heart and blood vessel diseases, is reviewed in this report. In addition, an outline of major goals and opportunities for further advances is presented for the immediate period of 1982 to 1987.

MAGNITUDE OF THE PROBLEM

Dramatic reductions in mortality rates from all cardiovascular diseases have been continuing since 1968. Between 1968 and 1978, the age-adjusted death rate for all cardiovascular diseases declined 26 percent. The decline for coronary heart disease (CHD) was 25 percent, for stroke 37 percent, and for hypertensive disease 53 percent (figure 1). These gratifying advances have

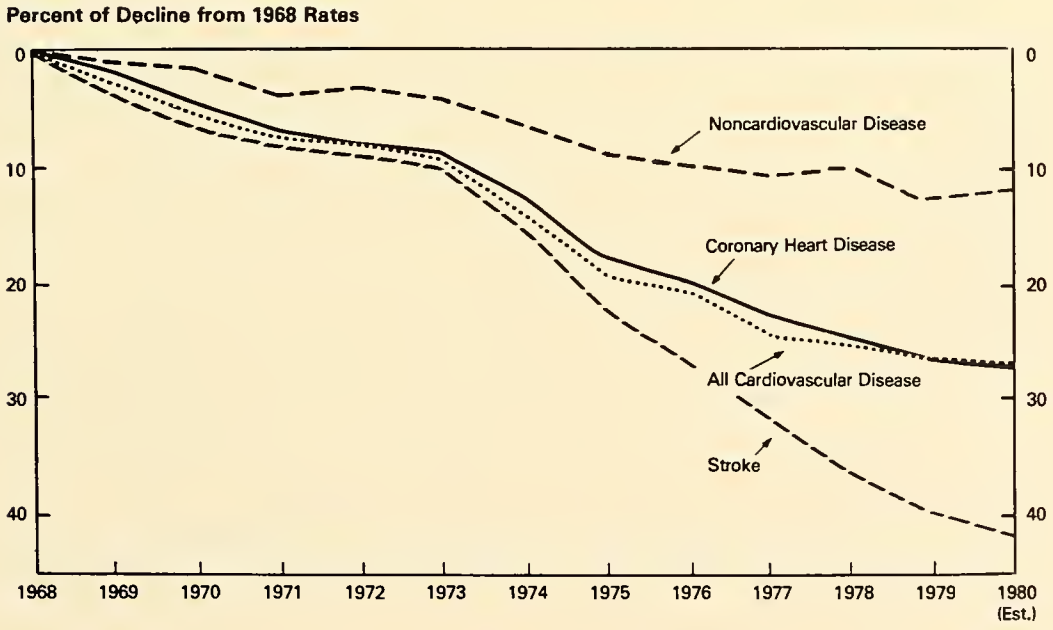


Figure 1. Trends in Cardiovascular Disease and Noncardiovascular Disease: Decline by Age-Adjusted Death Rates, 1968 to 1980

contributed 70 percent of the U.S. reduction in overall mortality rates for the same period. Preliminary data for 1981 to 1982 show a continuation of this favorable trend.

Despite this progress, heart and vascular diseases remained the cause of 51 percent of all deaths in the United States in 1980. Of a total of 1,977,000 deaths reported in 1980, cardiovascular diseases are estimated to have caused 1,005,000 deaths.

Based on National Health Interview Surveys, an estimated 35 million persons, or 16.5 percent of the U.S. population, have one or more of the heart or vascular diseases. The economic costs of these diseases are by far the largest for any diagnostic group of diseases and accounted for an estimated $80 billion in 1979. The continuing importance of these diseases is clearly evident.

MISSION OF THE DIVISION OF HEART AND VASCULAR DISEASES

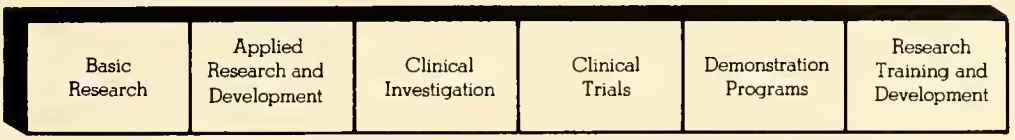
The Division of Heart and Vascular Diseases (DHVD) plans and directs an integrated and coordinated research program in heart and vascular diseases with emphasis on the causes, diagnosis, treatment, and prevention of the diseases. It carries out its mission through the support of research in the 10 National Program areas within the categories of the biomedical research spectrum illustrated in figure 2.

The National Heart Act of 1948 (P.L. 80-655), which created the National Heart Institute, mandated that the Institute "conduct, assist, and foster researches, investigations, experiments, and demonstrations relating to the cause, prevention, and methods of diagnosis and treatment of heart diseases." The provision was amended by the National Heart, Blood Vessel, Lung, and Blood Act of 1972 (P.L. 92-423) to include blood vessel, lung, and blood diseases. In addition, this act established the National Program, which requires:

- Investigation into the epidemiology, etiology, and prevention of all forms and aspects of heart and blood vessel diseases, including the social, environmental, behavioral, nutritional, biological, and genetic determinants and influences involved in the epidemiology, etiology, and prevention of such diseases;

- Studies of the basic biological processes and mechanisms involved in the underlying normal and abnormal heart and blood vessel phenomena;

- Research on the development, trial, and evaluation of techniques, drugs, and devices (including computers) used in, and on approaches to, the diagnosis, treatment



- Arteriosclerosis
- Hypertension
- Cerebrovascular Disease
- Coronary Heart Disease
- Peripheral Vascular Disease
- Arrhythmias
- Heart Failure and Shock
- Congenital and Rheumatic Heart Disease
- Cardiomyopathies and Infections of the Heart
- Circulatory Assistance

Figure 2. Division of Heart and Vascular Diseases
Biomedical Research Spectrum

(including emergency medical service), and prevention of heart and blood vessel diseases and the rehabilitation of patients suffering from such diseases;

- Establishment of programs that focus and apply scientific and technological efforts involving biological, physical, and engineering sciences to all facets of heart and blood vessel diseases with emphasis on refinement, development, and evaluation of technological devices that will assist, replace, or monitor vital organs and improve instrumentation for detection, diagnosis, and treatment of those diseases;

- Establishment of programs for the conduct and direction of field studies, large-scale testing and evaluation, and demonstration of preventive, diagnostic, therapeutic, and rehabilitative approaches to, and emergency medical services for, such diseases;

- Education and training of scientists, clinicians, and educators, in fields and specialties (including computer sciences) requisite to the conduct of clinical programs respecting heart and blood vessel diseases;

- Public and professional education relating to all aspects of such diseases.

In planning, the Division must meet the mandates of this legislation.

BUDGET 1972 to 1982

The Division has welcomed the legislative mandate that the 1972 act provided and has worked energetically with its advisory committees and with outside professional and research groups to identify priority areas of research that implement the recommendations in the 1972 National Program.

The majority of funds in the Division is allocated to the support of investigator-initiated research on the problems of heart and vascular diseases. Funds provided in annual appropriations have allowed a steady growth of support for such research.

The Division is strongly committed to the training and career development of scientists in heart and vascular research. Emphasis on the need for well-trained research investigators in atherosclerosis, cardiology, hypertension, epidemiology, behavioral medicine, and biostatistics has provided highly capable scientists who can conduct independent research on the problems of cardiovascular disease.

A modest level of funds has been invested in clinical trials, research and development contracts, National Research and Demonstration Centers, and Specialized Centers of Research in arteriosclerosis, hypertension, and ischemic heart disease.

THE PLANNING PROCESS

The planning process of the Division is the key to the orderly development and implementation of its research programs. Members of the three advisory committees of the DHVD--cardiology; atherosclerosis, hypertension, and lipid metabolism; and clinical applications and prevention--together with the staff continually review progress in ongoing Division programs and the state of knowledge within the mission of the Division and its 10 National Program areas to identify and prioritize research needs and opportunities. Recommendations from this intensive process are developed into program initiatives that become part of the DHVD Implementation Plan. If approved by the NHLBI and the National Heart, Lung, and Blood Advisory Council, these programs are initiated and supported by the Division.

TEN-YEAR REVIEW AND FIVE-YEAR PLAN

Over the past 10 years, support of research in heart and vascular diseases by the DHVD has led to numerous significant advances that have improved the understanding of these diseases and improved the health of the Nation. Review of these accomplishments has stimulated the development of new goals and research activities in each of the 10 DHVD National Program areas.

This report will serve as a framework for the planning process of the Division for the next 5 years. The effort required significant contribution by members of the scientific community as well as by Division staff. The report is based on 11 reports prepared by branch task groups composed of leading cardiovascular scientists. The reviews and recommendations of each task group were collated and edited according to each of the 10 DHVD National Program areas. An eleventh program area, prevention research, was added during the process to emphasize the importance of research on prevention to all of the other areas and to highlight research activities, goals, and directions in this important field. The report also reviews the progress and provides goals for the research training and career development effort of the Division.

The material that follows provides a summary of accomplishments and goals. Additional information is included in sections 2 through 14.

Arteriosclerosis

Arteriosclerosis is a complex pathologic condition characterized by focal lipid and fibrous tissue accumulation in the arterial wall that may lead over time to a reduction in blood flow to the organs and tissues supplied by the affected vessel. While the mechanism by which plaques occur is still not clear, three major factors--cigarette smoking, high blood pressure, and high concentrations of cholesterol in the blood--predispose individuals to the formation of plaques and accelerate the process. As a plaque increases in bulk and becomes a lesion occupying space, it may lead to such occlusive diseases of clinical importance as heart attack, sudden cardiac death, or brain stroke.

The overall mission in the arteriosclerosis program is to obtain a better understanding of the basic process of arteriosclerosis and to improve the diagnosis, treatment, and prevention of the process and its sequelae.

Accomplishments

Key areas of progress over the past decade include:

- The observation that cells from many tissues of the body, including those of the arterial wall, possess receptors that have high affinity to bind low density lipoprotein and play a key role in the regulation of cholesterol and lipoprotein homeostasis.

- Definition of specific details of receptor-mediated uptake of low density lipoprotein (LDL)-cholesterol by use of cell culture and of clinical studies of genetic disorders.

- Clarification of the structure and function of apoproteins and their relationship to clinical disorders, and demonstration of the dependence of cellular uptake of cholesterol on specific apoprotein components of the lipoprotein carriers.

- Demonstration of a growth factor derived from platelets that results in smooth muscle cell proliferation at a site of endothelial cell loss and in the development of muscle-cell-rich, plaque-like lesions.

- Discovery of increased quantity and altered composition of collagens and ground substance secreted by the endothelial and smooth muscle cell components under conditions that lead to plaque development.

- Elucidation of the roles of certain prostaglandins in causing platelet aggregation or disaggregation as well as in causing vascular constriction or dilatation.

- Recognition of the effects of dietary fats on the constituents of the prostaglandin system.

- General recognition of high density lipoprotein (HDL) as a potent, independent inverse CHD risk factor that is affected by physical activity, estrogen status, smoking, obesity, alcohol consumption, and race.

- The Lipid Research Clinic laboratory standardization process for serum lipid determinations.

- Application of noninvasive techniques for imaging of atherosclerotic plaques in peripheral arteries.

- Knowledge gained from extension of epidemiologic studies of risk factors to diverse populations in widely separated geographic and cultural settings.

Program Goals 1982 to 1987

- Advance the understanding of the basic pathogenetic mechanisms of atherosclerosis at the tissue, cellular, and molecular levels, using all suitable mechanisms and techniques, including those of cellular and molecular biology.

- Enhance the knowledge of the causal mechanisms and associated risk factors that play important roles in atherogenesis.

- Improve the understanding of the natural history of arteriosclerosis in all vascular regions in humans, utilizing modern methods of research and reassessing, with modern techniques, existing older studies.

- Improve the understanding of the epidemiology of arteriosclerotic disease, improve data-gathering capability and analytic methods, and improve predictive capability for all populations.

- Develop improved minimally invasive and noninvasive methods for detection of atherosclerosis in various regions of the vascular system.

- Expand investigations to ascertain the effectiveness of therapeutic interventions to reduce or prevent atherosclerosis.

- Elucidate the roles of behavior in relation to the etiology, pathogenesis, treatment, and prevention of arteriosclerosis and related diseases.

Hypertension

Hypertension, or high blood pressure, is defined as a chronically elevated blood pressure at or above the 140/90 mm Hg level. In the vast majority of cases of hypertension, the cause is unknown. Hypertension accelerates atherosclerosis and increases the risk of brain stroke, heart failure, heart attack, kidney failure, and eye damage.

The mission of the hypertension program is to investigate the etiology and pathogenesis of the disease and to improve treatment and prevention.

Accomplishments

In hypertension, highlights of progress are:

- Demonstration of genetic dysfunction of the electrogenic pump of vascular smooth muscle membranes in experimental animal hypertension and in some cases of human hypertension.

- Further accumulation of extensive data pointing to a necessary role of sodium in some cases of genetic susceptibility to hypertension.

- Increase in basic knowledge of the importance of neural control in maintenance of blood pressure, including evidence pointing to hyperreactivity of arterial smooth muscle in response to an altered sympathetic nervous system and demonstration of the critical role of the brain and of nervous system interactions in the regulation of blood pressure in normal and hypertensive states.

- Identification, through the use of cellular and molecular approaches, of a number of vasoregulatory and other peripheral hormones in the brain (for example, renin, angiotensin II, bradykinin, epinephrine, norepinephrine).

- Advances in the molecular characterization of alpha and beta receptors in the identification and functional characterization of pre- and postsynaptic receptors and of their agonists and antagonists.

- Introduction of chemical and pharmacologic probes that block the renin-angiotensin system at various points, facilitating analysis of the contributions of the system to individual cases of hypertension and leading to development of drugs that are used to control human hypertension.

- Discovery of prorenin and its convertibility to renin by kallikrein, and the integration of the kallikrein-kinin and prostaglandin systems in the schema of interacting neural, hormonal, electrogenic, and membrane phenomena concerned with regulation of blood pressure.

- Application of epidemiologic studies to confirm the role of genetic influences in human essential hypertension and in the renal responses to sodium loading.

- Demonstration of the "tracking phenomenon" in juvenile hypertension.

- Introduction of new antihypertensive agents having specific activity on the renin-angiotensin system or on central or peripheral alpha-adrenergic receptors.

- Conclusion of the Hypertension Detection and Followup Program (HDFP), which demonstrated significant reduction in mortality in hypertension of all degrees of severity treated by intensive antihypertensive therapy administered in the stepped care mode, and application of these methods and results to urban and rural community health centers.

- Improvement, on the national level, in the degree of detection, referral, treatment, and control of hypertension.

- Recognition of the role of behavioral factors, including caloric intake in relation to energy expenditure, and sodium intake that can be addressed in hypertension control programs.

Program Goals 1982 to 1987

- Expand further fundamental research on the etiology and pathogenesis of hypertension including investigations in neural, humoral, genetic and environmental factors, with emphasis on interdisciplinary approaches.

- Investigate in all age groups the influence of familial, genetic, and environmental factors in the determination of blood pressure levels in order to establish the relative importance of the multiple factors that contribute to the development of high blood pressure.

- Continue to develop and refine noninvasive technologies for measurement of blood pressure and other relevant parameters related to hypertension that can be used as needed for the evaluation of the health status of persons with high blood pressure.

- Continue to improve pharmacologic and nonpharmacologic methods for the long-term management of hypertension, and evaluate for each their relative roles in terms of benefits as well as risks. Continue the study of the benefits and risks of blood pressure reduction in elderly individuals with systolic hypertension.

- Continue the improvement of control of high blood pressure in the population, especially in segments of the population where the disease is prevalent, through demonstration and education activities.

- Continue research and development programs that attract and sustain high caliber hypertension research investigators to maintain progress against this disease.

Cerebrovascular Disease

The term cerebrovascular disease usually refers to atherosclerotic or hypertension-induced disease of cerebral arteries manifesting as transient episodes of cerebral dysfunction (transient ischemic attacks) or as permanent loss of function (stroke). Brain infarction due to atherosclerosis of cerebral arteries is the most common type of stroke, and brain hemorrhage is second in frequency. Hypertension is a very common, preventable antecedent of both types of injury. During the past decade, a substantial reduction in stroke mortality (37 percent) occurred against a backdrop of a somewhat less acute decline in mortality from all types of vascular diseases.

The mission of the Division is to decrease the incidence of stroke through studies of the pathology and pathogenesis of cerebrovascular disease and through its prevention.

Accomplishments

Key areas of progress in cerebrovascular disease are:

- Successful application of minimally invasive imaging techniques in the recognition and the assessment of the clinical significance of atherosclerotic lesions in the extracranial arteries nourishing the brain.

- Validation of hypertension as a strong risk factor for stroke.

- Dramatic decline (37 percent) in death rate due to stroke, and concurrent prospective demonstration of the efficacy of systematic antihypertensive therapy in reducing stroke morbidity and mortality.

- Clarification of the generally nonvascular etiology of senile dementia of Alzheimer's type.

Program Goals 1982 to 1987

- Improve the fundamental understanding of the nature of lesions of the vessels of the head and neck that lead to

stroke with a view toward improving the diagnosis, prediction, treatment, and prevention of cerebrovascular disease.

- Continue to conduct epidemiological studies of risk factors of cerebrovascular disease.

Coronary Heart Disease

Coronary heart disease (CHD) is the term most commonly used to refer to disease or dysfunction that occurs when critical narrowing of the coronary arteries--most often due to atherosclerosis--compromises the blood supply of the heart muscle (myocardium). The most common clinical expressions of CHD are sudden death, angina pectoris, or myocardial infarction (also known as heart attack). Despite a 25 percent decline in CHD mortality during the past decade, it is still the leading cause of death in the United States.

The mission of the Division is to develop improved understanding of the mechanisms, diagnosis, therapy, rehabilitation, and prevention of symptomatic coronary heart disease.

Accomplishments

The major accomplishments of the Division in coronary heart disease are listed below:

- Application of the methodologies and new technologies of cellular and molecular biology to characterize the events that occur in ischemic myocardium and to provide a rationale for development of drugs that may be useful in protecting ischemic myocardium.

- Demonstration of the occurrence of thrombus formation in coronary arteries in the early stages of myocardial infarction.

- Discovery of the contributions of arachidonic acid metabolites and of platelet aggregation to the development of symptomatic ischemic heart disease.

- Continuation of steady decline of CHD mortality, amounting to a 25 percent decrease between 1968 and 1978, with an accentuation of the decline in the past 5 years.

- Development of more precise means of detecting myocardial infarction.

- Demonstration of the feasibility of medical management of patients in the acute phases of unstable angina.

- Establishment of a registry of 24,959 patients studied with coronary arteriography to provide longitudinal study of the natural history of this large group of patients with the disease.

- Refinement of techniques used in coronary artery bypass surgery with resultant decline in operative mortality and perioperative myocardial infarction.

- Identification of suitable candidates for percutaneous transluminal coronary angioplasty (PTCA) by analysis of patients enrolled in the NHLBI International PTCA Registry.

- Demonstration, in the Beta-blocker Heart Attack Trial (BHAT), of a significant reduction in mortality in post-myocardial infarction patients treated chronically with propranolol.

- Further delineation of normal and abnormal cardiac anatomy and function by the use of noninvasive assessment techniques, including real-time ultrasonic scanning and nuclear imaging.

- The commitment of academic medical centers to prevention by establishing preventive cardiology academic programs, and the increased awareness by large segments of the population of the importance of prevention as a result of demonstration and education projects and communitywide prevention programs.

Program Goals 1982 to 1987

- Improve the understanding of the fundamental pathogenetic mechanisms involved in coronary heart disease and its various manifestations, including sudden death.

- Develop and refine methods for use in diagnosis and in estimating prognosis in patients with asymptomatic and symptomatic coronary heart disease.

- Develop and refine improved medical and surgical interventions for the treatment of acute coronary events and chronic ischemic heart disease.

- Identify factors that are involved in the pathophysiology of coronary heart disease and the transition from latent to overt CHD.

- Continue to support research on the mechanisms underlying arrhythmias in myocardial ischemia.

- Continue development of reliable methods of studying the coronary collateral circulation in humans and the factors influencing its development.

- Elucidate profiles of individuals at enhanced risk of first myocardial infarction and of postmyocardial infarction sequelae in order to develop means of risk reduction in these groups.

- Enhance methods to reduce or prevent new and recurrent myocardial infarction.

- Improve the rehabilitation of patients with CHD.

- Study the phenomenon of silent myocardial ischemia, its prevalence, and its significance.

Peripheral Vascular Disease

The term peripheral vascular disease refers to congenital and acquired disease of all of the arteries, veins, and lymphatics in the body, excluding those in the heart, the thoracic aorta, and the intracranial circulation. Arteriosclerotic occlusive disease is the most common affliction of peripheral vessels. When occlusion at any of these sites becomes critical, severe leg pain on walking occurs (intermittent claudication). Progression of the disease may lead to gangrene and loss of limbs. A similar, progressive occlusion can involve the arteries that supply the kidneys and various segments of the intestinal tract.

The mission of the Division is to improve the diagnosis, therapy, and understanding of the mechanisms causing peripheral arterial and venous diseases.

Accomplishments

Achievements of the past 10 years are highlighted below:

- Enhanced understanding of the dynamics, flow, ionic gradients, regulation, rheology, and pathology of capillaries and other components of the microcirculation through

multidisciplinary application of a diversity of innovative and sophisticated techniques.

- Recognition of the contribution of the endothelial cell, interacting with platelets, to the genesis of occlusive pathology in small and medium-sized vessels.

- Completion of a prospective study that delineated the natural history of intermittent claudication in a free-living population.

- Application of duplex ultrasonic scanning, subtraction radiography, and nuclear magnetic resonance to the minimally invasive study of clinical problems and of experimentally induced lesions in animal models.

- Improvement in the physical characteristics of synthetic vascular grafts that permits their use when autogenous grafts are not available or suitable.

Program Goals 1982 to 1987

- Promote fundamental research on the nature, etiology, and pathogenesis of disorders of the peripheral arteries, veins, and lymphatics in order to enhance diagnosis, treatment, and prevention.

- Continue to develop and refine methods to diagnose peripheral vascular disease.

Arrhythmias

Arrhythmia refers to an irregularity or abnormality in the rhythm of the heartbeat. Some arrhythmias are life-threatening because of excessively rapid or chaotic heart action. Multiple lines of evidence indicate that such arrhythmias are the immediate precursors of a substantial majority of cases of sudden death in adults and that myocardial ischemia is most often the underlying pathologic process responsible for the arrhythmias. In this context, arrhythmias are the cause of the majority (350,000) of coronary heart disease deaths each year.

The mission of the Division is to develop and improve methods for prevention, diagnosis, and management of arrhythmias and other electrical disturbances of the heart.

Accomplishments

In response to its mandate, the Division has attained several milestones during the past decade including:

- Development of fundamental knowledge of ionic currents through ion-specific channels of the membranes of cardiac myocytes, and recognition of the linkage of these currents to changes in membrane permeability and other events underlying excitation.

- Discovery of the slow inward, or calcium, channel in myocardial cells and of its role in the genesis of serious reentrant arrhythmias.

- Recognition, in electrophysiologic studies, of oscillatory after-potentials and of their importance, in certain situations, in triggering paroxysmal tachycardia.

- Utilization of ECG averaging techniques to permit surface recording of His bundle electrograms, enabling rational analysis of cardiac conduction disturbances.

- Use of the electrophysiology laboratory to apply programmed electrical stimulation in identifying patients at high risk for lethal arrhythmias and in planning the most appropriate, individualized therapy.

- Development of analytic techniques permitting rapid, more accessible, and definitive studies of the pharmacodynamics and interactions of antiarrhythmic drugs.

- Introduction of calcium-channel blocking agents for the treatment of cardiac arrhythmias, and extension of the use of sodium-blocking local anesthetics to the effective prevention of lethal arrhythmias in persons suffering acute myocardial infarction.

- Demonstration of a significant reduction in mortality in postmyocardial infarction patients treated chronically with propranolol.

- Multiple advances in design, performance, and reliability of monitors, defibrillators, long-term ECG recorders, and implantable pacemakers and defibrillators.

Program Goals 1982 to 1987

- Continue to identify the fundamental electrophysiologic mechanisms of normal and ischemic myocardium and their relationship to sudden death.

- Develop and refine methods useful in identifying individuals in all age groups at risk of sudden death.

- Improve the understanding of the nervous system and its role in the pathogenesis of cardiac rhythm abnormalities.

- Develop and refine medical and surgical interventions to reduce or prevent sudden death in high-risk populations.

Heart Failure and Shock

Heart failure is a pathophysiologic state in which an abnormality of cardiac function leads to failure of the heart to pump blood at a rate commensurate with the metabolic requirements of the tissues. At the same time, there is a high filling pressure in the cardiac chambers, leading to accumulation of excessive quantities of fluid in the lungs, liver, and dependent parts of the body. This failure of the pump can be due to any of several causes, the most common ones being coronary heart disease, hypertension, and congenital or acquired malformation of the heart valves. When pump failure complicates acute myocardial infarction (heart attack), it is called cardiogenic shock--a condition responsible for the majority of deaths of those heart attack patients who die in coronary care units.

The mission of the program is to minimize heart failure associated with and following heart attack by enhancing the survival of damaged heart muscle as well as that associated with hypertension or with valvular disease by improved treatment and prevention.

Accomplishments

Highlights of program accomplishments over the past decade are itemized below:

- Refinements in understanding the time course of myocardial ischemia and in the ability to estimate the interval beyond which ischemia becomes irreversible.

- Development of the capability to localize and measure areas of infarction or ischemia by use of radioisotope

tracers that have preferential avidity for necrotic or normal myocardium.

- Refinement of minimally invasive techniques utilizing radioisotopes that permit sequential measurement of function of the failing heart.

- Utilization of vasodilator drugs as an effective means of afterload and preload reduction of the failing heart.

- Introduction of new inotropic agents that act via the adenylcyclase system or by enhancing calcium transport across the myocardial cell membrane.

- Development and refinement of short-term left ventricular assist devices that can support the circulation during the period needed for recovery from myocardial dysfunction sometimes occurring with open heart surgery.

- Improvement in techniques of cardiac transplantation and immunotherapy, which offers another therapeutic approach in certain patients whose heart failure is refractory to all other measures.

Program Goals 1982 to 1987

- Improve the understanding of the basic mechanisms and the natural history of heart failure and shock.

- Improve techniques for the clinical detection, treatment, and prevention of heart failure and shock.

Congenital and Rheumatic Heart Disease

Congenital cardiovascular disease results from failure of normal development of the heart and great vessels during gestation. Examples include defects in the partitions separating the cardiac chambers, malformed heart valves, persistence of fetal short-circuit vessels between major arteries, and combinations of these defects. The causes are multiple, and a few of them have been identified. Rheumatic heart disease is the term applied to the scarring and deformity of heart valves that follow one or more attacks of acute rheumatic fever. Congenital and rheumatic heart diseases are serious illnesses that impair the quality of life from childhood through adolescence to adulthood, and are often the cause of premature death.

The mission of the program is to understand better the causes of congenital and rheumatic heart diseases, to improve diagnosis and therapy, and to prevent these diseases.

Accomplishments

Key accomplishments of the past decade include:

- Recognition of the causal role of certain drugs and toxins in congenital heart disease.
- Refinements of noninvasive imaging techniques permitting their application to the study of complex malformations of cardiac valves and chambers in infants and small children.
- Reduction in surgical mortality associated with primary repair of complex congenital cardiac defects in infants--a reduction attributable to refinements of surgical methods and improvements in prosthetic valves.
- Pharmacologic induction of closure of ductus arteriosus by use of indomethacin in premature infants, obviating the need for surgery in at least 40 percent of infants with this condition.
- Discovery of structural similarities between group A streptococcal M proteins and alpha fibrous proteins, such as tropomyosin, of mammalian muscle.

Program Goals 1982 to 1987

- Improve the understanding of the genetic and environmental factors involved in the pathogenesis of various congenital cardiac malformations.
- Develop and refine methods for accurate diagnosis and curative or palliative therapy for patients with congenital heart disease.
- Explore the fundamental etiology and pathophysiology of valvular heart disease.
- Develop and refine medical and surgical interventions for valvular heart disease.

Cardiomyopathies and Infections of the Heart

Cardiomyopathy refers to a group of generally fatal cardiac diseases in which there is primary involvement of the heart muscle and in which there is enlargement of the heart accompanied by severe heart failure. This diagnosis requires that known causes of cardiac enlargement and failure, such as coronary heart disease, valvular abnormalities, and hypertension, be excluded. When the cause of the primary heart muscle involvement is known, the term specific heart muscle disease is used. It appears that cardiomyopathy is increasing in frequency and is contributing to a larger number of patients suffering from intractable heart failure. Alcohol and certain other chemical agents are suspected of playing a role in some cases. Diabetes may be a factor in a considerable proportion of cases, and viral infections will probably be shown to be important in the etiology of many others.

Bacterial infections of the heart most commonly involve the heart valves, particularly valves previously damaged by rheumatic fever or otherwise predisposed to bacterial colonization by congenital malformation. Infection further damages the valves, and this results in severe heart failure or embolic complications.

The mission of the Division is to prevent, diagnose, and treat the various cardiomyopathies and infections of the heart, with particular emphasis on improved understanding of their causes.

Accomplishments

Program highlights of the past decade include:

- Advances in knowledge of cardiac muscle membrane biology, including the relation between ion transport and electrical and mechanical events in the muscle fibers.
- Refinements in knowledge of the ultrastructure of individual myocytes and of the linkage of mechanical and chemical events associated with muscle contraction.
- Augmentation of basic understanding of the heart failure of cardiomyopathy by study of a variety of animal models that simulate this condition.
- Identification of an increasing number of specific infectious, toxic, nutritional, metabolic, and physical causes of cardiomyopathies.

- Improved knowledge of the biochemical, histological, and pathophysiologic features of diabetic cardiomyopathy and also of adriamycin-induced and alcohol-induced cardiomyopathies.

- Utilization of echocardiography and endomyocardial biopsy in the serial study of certain cardiomyopathies.

- Early recognition of serious valvular damage by use of B-mode ultrasound in patients with bacterial endocarditis.

- Improved surgical techniques, intraoperative myocardial preservation techniques, and improvement in valve prostheses.

Program Goal 1982 to 1987

- Develop and refine methods for diagnosis, treatment, and prevention of cardiomyopathies and infections of the heart.

Circulatory Assistance

Circulatory assistance is the use of mechanical systems to augment or replace the pumping function of the heart. Such mechanical assistance can take the form of blood pumps to replace the natural heart (total cardiac replacement device) or to bypass a diseased ventricle (the left ventricular assist device or LVAD). Lesser degrees of circulatory assistance can be achieved by providing a pump-like action through the synchronous expansion and contraction of a balloon in the aorta. This technique is designed to diminish the arterial pressure when the heart is ejecting blood and to raise the arterial pressure after ejection to augment perfusion throughout the body.

The mission of the circulatory assist program is to develop and assess therapeutically effective, safe, and reliable cardiac assist and total replacement devices for supporting or taking over the workload of the heart.

Accomplishments

Key accomplishments of the program during the past decade include:

- Development of a number of biocompatible materials that can be incorporated into the bladder, valves, and other

surfaces of assist devices in contact with physiologic systems.

- Successful application of the intra-aortic balloon as a means of supporting the circulation in patients suffering cardiogenic shock.

- Demonstration of the safety and effectiveness of the pneumatically powered axisymmetric short-term ventricular assist device in patients suffering postoperative heart failure.

- Refinements in size, efficiency, and reliability of electrical and thermal engines and power converters to be used to power ventricular assist or replacement devices.

- Improvements in size, design, and efficiency of the pump to be used in implantable ventricular assist devices.

- Advances in understanding of blood-material interactions and in techniques that facilitate recognizing and minimizing these events.

- Development of a number of techniques of modifying polymer chemistry to render the blood-contacting surface monolayers of polymers compatible with body fluids and to prolong the flex life of these polymers.

Program Goal 1982 to 1987

- Continue to develop effective, safe, and reliable cardiac assist and total cardiac replacement devices for partial or total assumption of heart function.

Prevention Research

The ultimate goal of the Division of Heart and Vascular Diseases is prevention of heart and blood vessel diseases. Preventive measures can focus on reducing risk factors, on preventing the appearance of the earliest symptoms in high-risk individuals, on retarding the development of major clinical events, and on delaying recurrences of clinical events. In the National Program areas of arteriosclerosis, hypertension, cerebrovascular disease, and coronary heart disease, the multiplicity of variables to be controlled requires a high degree of knowledge about human behavior and motivation, and skills in research on demonstration and education measures.

The mission of the Division is to plan, conduct, and direct a program of applied clinical research for the prevention of morbidity and mortality from heart and vascular diseases, including research on prevention that has potential for application in the general population.

Accomplishments

Highlights of accomplishments in the area of prevention research during the past decade include:

- On a national level, a widespread increase of knowledge of high blood pressure, increased acceptance of the need for treatment, and increased numbers of individuals whose blood pressure is effectively controlled.

- Utilization of clinical trials and communitywide intervention trials to validate the efficacy of a number of interventions in controlling diseases in large populations.

- Preventive cardiology research fellowship training programs that enhance the commitment of academic medical centers and individual clinicians to carry out research relevant to effective modes of cardiovascular disease prevention.

- Investigation of a variety of techniques that may be used in diverse population subgroups to modify food intake habits.

- Recognition and elucidation of the contributions of multiple biobehavioral factors that must be addressed in attempts to modify risk factors and prevent early stages of disease.

- Implementation of a national program of centers of demonstration and education research that serve as vehicles for testing and implementing preventive measures.

- Institution of worksite, regional, and statewide models for study of the feasibility and impact of a variety of methods of applying hypertension control services.

Program Goals 1982 to 1987

- Continue to conduct population studies and demonstration and education strategies for the prevention of the development and of the progression of heart and vascular disease.

- Improve the diagnosis, treatment, and cure of existing heart and vascular disease in order to prevent its recurrence and progression.

- Improve the characterization of risk factor distributions and their changes over time, the understanding of health behaviors especially in youth, and the approaches to foster healthy habits.

- Continuation of research on the most effective means, consistent with achieving the goals of health promotion, of translating and disseminating research findings to health professionals and the public.

- In subpopulations identified as being at especially high risk for heart and vascular diseases, improve the detection of individuals at such risk, the understanding of the host-environmental interactions responsible for the increased risk, and the efforts to modify health behaviors.

Research Training and Development

The magnitude of the challenges facing the DHVD and the broad scope of the research programs through which the Division strives to meet those challenges depend upon the availability of well-trained research scientists and clinicians in a wide array of fundamental and clinical research areas. The Division is committed to the policy that research training and development are essential to the implementation of a responsive, high quality U.S. program directed to the prevention of heart and vascular diseases and the control and relief of their complications.

The mission of the program is to provide a sufficient number of investigators trained in fundamental and clinical research related to the etiology, pathogenesis, diagnosis, treatment, and prevention of diseases of the heart and blood vessels, and continuous surveillance of national needs for cardiovascular research specialists.

Accomplishments

Accomplishments in the research training and development program of the Division during the past decade include:

- Introduction of national research service awards to support individual postdoctoral fellows in specific areas of need in biomedical and behavioral research and to allow

eligible institutions to enhance research training opportunities through selection of trainees best suited to the institutions' fellowship programs.

- Reintroduction of the research career development award to provide additional research training and experience in a productive scientific environment for scientists having a demonstrable capacity for independent research.

- Introduction of the young investigator research grant program in 1976, later incorporated into the new investigator research awards program. The purpose of this track is to encourage new investigators in basic and clinical science disciplines to develop their research interests and capabilities in biomedical and behavioral research.

- Support of over 200 minority school faculty members and graduate students in the Minority Hypertension Research Development Program, initiated in 1977. The goals of the program are to foster the recruitment and development of these individuals in hypertension research, prevention, control, and education.

- Participation in the Minority Biomedical Research Support Program to encourage research efforts of minority school students by supporting cardiovascular research projects and to foster presentation of research results in scientific forums.

- Participation in the Minority Access to Research Careers Program, the goal of which is to stimulate and encourage research development of minority persons by supporting cardiovascular fellowships in a program operated by the National Institute of General Medical Sciences.

- Announcement of the national research service awards for short-term training: students in health professional schools program. Its goal is to attract highly qualified professional students into biomedical and behavioral research careers.

- Introduction of the clinical investigator award to encourage newly trained clinicians to develop clinical and basic research interests and skills in cardiovascular diseases.

- Collaboration with another Institute in the sponsorship of the special emphasis research career award in diabetes mellitus. The goal of this program is to encourage individuals in the early stages of their postgraduate medical and scientific careers to develop multidisciplinary

research interests and skills in the metabolic, endocrinologic, and cardiovascular aspects of diabetes mellitus.

- Implementation of the preventive cardiology academic award. Its goal is to encourage development of high quality preventive cardiology curricula in schools of medicine and osteopathy that will attract outstanding students to research and practice in the field of preventive cardiology.

Program Goals 1982 to 1987

Research training and research career development programs of the Division have been instrumental in attracting outstanding scientists and fostering the high level of scientific accomplishments in heart and vascular disease research. Continuation of such productive programs is considered essential for continued progress of heart and vascular disease research in the future. Program goals in research training and development are:

- Continue those research training and career development programs that have a demonstrated need and have been productive in providing the training of research scientists for advancement of heart and vascular diseases research.

- Continue to develop fellowship or training programs that attract outstanding young potential scientists into cardiovascular research careers to provide the leaders needed to maintain scientific progress in the future.

- Undertake programs at predoctoral years that attract the most gifted and motivated young individuals into biomedical research, and undertake additional programs in postdoctoral years directed to attracting creative young physician scientists into research in cardiovascular disease.

- Improve the research training capabilities, including multidisciplinary opportunities, in research training programs in order to provide the highest quality of training with the best qualified scientists and the finest research environment.

- Investigate the needs for research training in special discipline areas that may provide particular contribution in emerging areas of research so that new techniques in other fields are rapidly incorporated into research training in cardiovascular disease research.

2. Magnitude of the Problem

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2. Magnitude of the Problem

From the standpoint of an individual, the problem of cardiovascular disease is measured by the probability of developing a heart attack, stroke, or other vascular condition, and the prognosis and survivability if afflicted. From the standpoint of the Nation at large, the magnitude of the problem of heart and vascular diseases in the United States is measured by their morbidity, mortality, and economic impact.* Progress made toward reducing the Nation's problem is measured by time trends of morbidity and mortality. The question is simply: To what extent do heart and vascular diseases impact on the quality of American life, and has that impact lessened in recent years?

An estimated 35 million persons,** or 16.5 percent of the U.S. population, have one or more of the heart or vascular (cardiovascular) diseases listed in table 1, of whom 8.5 million are limited in activity because of it (figure 3).[1,2] Two-thirds of the 35 million persons are under 65 years of age. The most common cardiovascular diseases are hypertension and the arteriosclerotic-related diseases: coronary heart disease, cerebrovascular disease, and peripheral vascular disease. Heart conditions and hypertension rank third and fourth respectively among the leading chronic diseases causing disability (table 2). In 1978, cardiovascular diseases accounted for an estimated 595 million days of restricted activity, 172 million bed days, and 44 million work-loss days.[1] Most of these disability days were due to heart disease and hypertension. In 1979, there were 49 million days in short-stay hospitals and 50 million visits to physicians' offices for these diseases (table 3).[3,4] In 1975, over 177,000 workers with a cardiovascular disease were allowed Social Security disability benefits. This number is 30 percent of all such benefits (table 4).[5]

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*For definitions of these and other terms, see the glossary on pages 59-62.

**This estimate, which is based on household health interviews, does not include institutionalized persons or persons unaware they have a cardiovascular disease. If all persons who have elevated blood pressure or who are on antihypertensive medication were included, the number of persons with a cardiovascular disease would exceed 60 million.

Table 1. Prevalence and Disability Days for Cardiovascular Diseases United States, 1979

Cardiovascular Diseases	No. of Persons (in thousands)		Number of Days (in thousands)		
	Total Prevalence	Limited in Activity	Restricted Activity Days	Bed Days	Work-Loss Days
Heart conditions	16,428	5,305	377,146	141,780	17,063
Active rheumatic fever and chronic rheumatic heart disease	1,672	338	24,907	9,647	267
Hypertensive heart disease*	140	47	7,238	5,745	**
Coronary heart disease	5,265	2,637	138,266	40,196	8,890
Other specified heart disease	1,021	382	29,515	12,071	**
Unspecified disorders of heart rhythm	5,710	561	42,331	11,108	2,713
Heart trouble, NOS†	2,620	1,340	134,888	62,213	5,194
Hypertensive disease*, NEC§	23,745	3,203	318,650	112,073	12,761
Cerebrovascular disease	1,740	614	88,457	50,457	7,315
Arteriosclerosis, NEC§	3,894	615	76,683	23,735	**
Phlebitis and thrombophlebitis, NEC§	745	155	12,347	5,291	1,138
Poor circulation, NOS†	1,002	259	28,427	1,120	291
Congenital anomalies of the circulatory system	697	222	11,284	6,079	874

*This estimate understates prevalence primarily by not including persons unaware of their condition. See the discussion of hypertension in this section.

**Too few in sample for a reliable estimate.

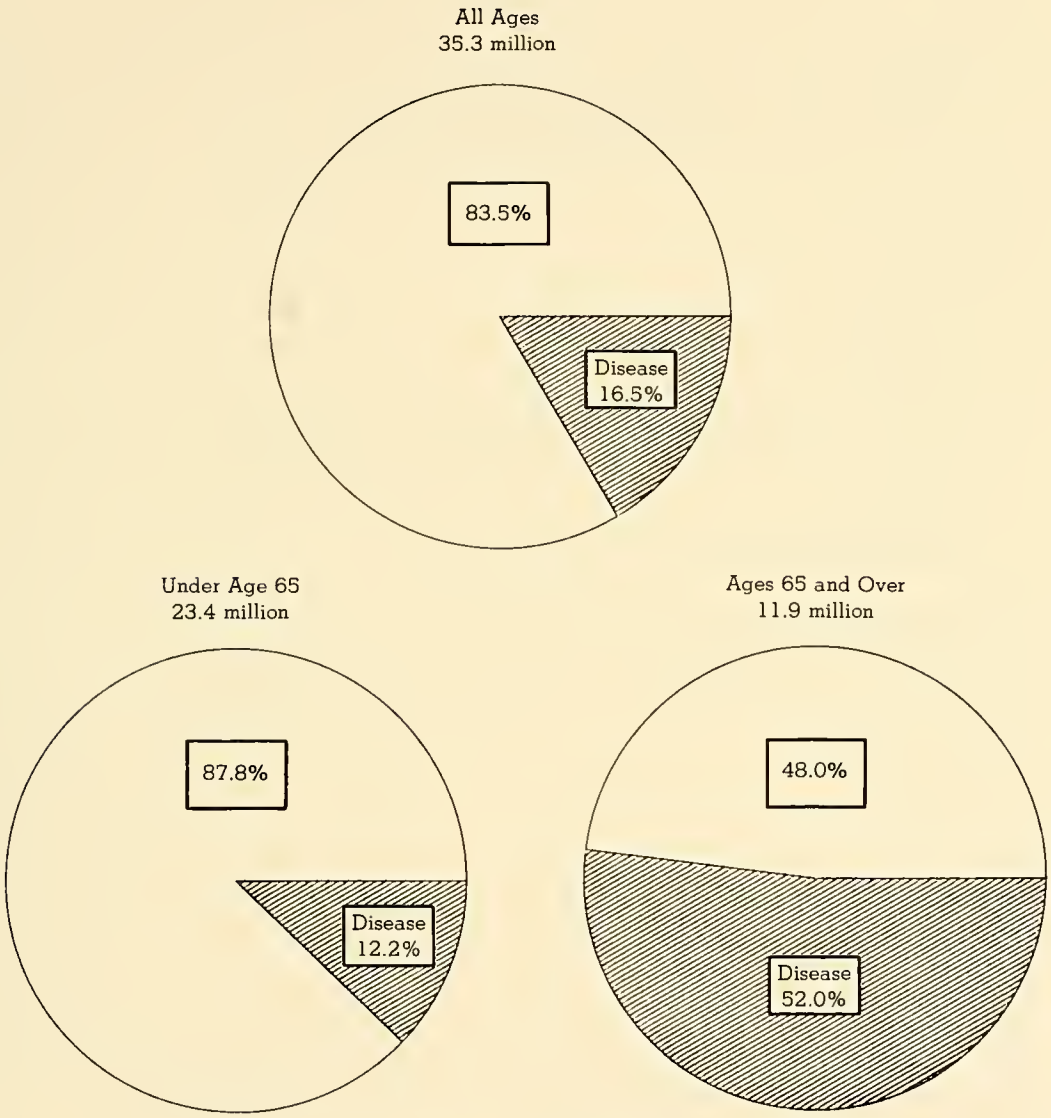
†NOS: Not otherwise specified.

§NEC: Not elsewhere classified

Note on standard errors: An estimate below 215,000 is statistically unreliable, i.e., a relative standard error in excess of 30%. An estimate of restricted activity days or of bed days below 34 million and of work-loss days below 22 million is statistically unreliable.

General caution: These estimates are based on reporting in household interviews among the noninstitutionalized population, and they also exclude persons unaware of an existing cardiovascular condition. Estimates add to more than the number of persons with a cardiovascular disease shown in figure 1 because some persons have more than one of these conditions.

Source: Health Interview Survey, National Center for Health Statistics (Ref. No. 2).



Source: National Health Interview Survey,
National Center for Health Statistics (Ref. No. 1).

* Includes only persons who were told by a physician they have a cardiovascular disease. Excludes persons with varicose veins or hemorrhoids who have no other cardiovascular disease.

Figure 3. Estimated Number and Percent of Persons With One or More of the Major Cardiovascular Diseases*; United States, 1978

Table 2. Prevalence of the Leading Chronic Conditions Causing Limitation of Activity, United States, 1979

1.	Deformities or orthopedic impairments	5,620,000
2.	Arthritis, NEC	5,372,000
3.	Heart conditions	5,305,000
4.	Hypertension, NEC	3,203,000
5.	Diabetes	1,593,000
6.	Visual impairments	1,486,000
7.	Asthma	1,274,000
8.	Displacement of intervertebral disc	1,207,000
9.	Emphysema	1,118,000
10.	Hearing impairments	776,000
11.	Paralysis	753,000
12.	Hernia of abdominal cavity	703,000
13.	Diseases of urinary system	640,000
14.	Arteriosclerosis, NEC	615,000
15.	Cerebrovascular disease	614,000

NEC: not elsewhere classified
Source: Health Interview Survey; National Center for Health Statistics (Ref. No. 2).

Table 3. Estimated Number of Hospital Discharges, Hospital Days, and Physician Office Visits for Cardiovascular Diseases, United States, 1979

Cardiovascular Diseases*	Hospital Discharges** (000)	Hospital Days (000)	Physician Office Visits (000)
TOTAL	4,964	48,922	49,880
Arteriosclerotic-related	2,761	29,463	13,241
Coronary heart disease	1,739	16,695	9,133
Cerebrovascular disease	747	9,225	1,817
Peripheral vascular disease	275	3,543	2,291
Peripheral vascular disease (nonarteriosclerotic)	492	4,054	4,699
Hypertensive disease	454	3,506	25,573
Arrhythmias	371	2,877	1,986
Cardiac failure and cardiomyopathies	445	4,685	1,951
Rheumatic fever and rheumatic heart disease	66	600	508
Congenital heart disease	57	437	271
Infections of the heart	9	215	21
Other cardiovascular diseases	309	3,085	1,630

*First-listed diagnosis on the face sheet of the hospital record; principal diagnosis at office visit.
**Discharged alive or dead.
Note on standard errors: Estimates of 50,000 discharges, and of 1,000,000 hospital days have a relative standard error of 10 percent. Estimates of 350 million visits or less have a relative standard error of 30 percent or more.
Source: Hospital Discharge Survey (non-Federal, short-stay hospitals) and the Ambulatory Medical Care Survey; National Center for Health Statistics. (Ref. Nos. 3 and 4).

Table 4. Number and Percent of Disabled-Worker Social Security Allowances Total and for Cardiovascular Diseases, United States, 1975

Primary Diagnosis	Allowances	Percent of Total
All Diagnoses	592,049	100
Total Cardiovascular Diseases*	177,276	29.9
Arteriosclerotic-related	144,155	24.3
Coronary heart disease	114,206	19.3
Cerebrovascular disease	20,226	3.4
Peripheral vascular disease (arteriosclerotic)	9,723	1.6
Peripheral vascular disease (nonarteriosclerotic)	7,452	1.3
Hypertensive disease	12,816	2.2
Chronic rheumatic heart disease	5,575	0.9
Other forms of heart disease	7,278	1.2

*Excludes congenital heart disease.

Note on standard errors: An estimate of 5,000 or more allowances has a relative standard error of less than 1.3 percent.

Source: Social Security Administration, (Ref. No. 5).

As a cause of death, cardiovascular diseases accounted for an estimated 1,005,000 deaths in 1980, or 51 percent of all deaths (table 5 and figure 4).[6,7] Over 20 percent of these deaths (215,000) occurred before age 65. This number is one-third of all deaths that occurred before that age. Even among persons 35 to 74 years of age, 46 percent of the deaths are due to these diseases. Compared to other major diagnostic groups, the cardiovascular diseases are the leading cause of deaths, of hospital days (short-stay), and of worker disability allowances, and they are the second leading cause of bed days.

Because cardiovascular diseases account for one-half of the Nation's mortality and much of the Nation's morbidity, their cost to the Nation's economy is by far the largest for any diagnostic group, an estimated $81.3 billion in 1979 (table 6).[3,4,8-14] For cardiovascular disease patients in that year, the Nation spent $30 billion for hospital care, physician and other professional care, drugs, and nursing home care, or 1 percent of the gross national product. The economy lost $50 billion in productivity due to illness and premature deaths attributed to these diseases.

Underlying most of the cardiovascular diseases are hypertension and the arteriosclerotic process. The latter manifests itself clinically in coronary heart disease (heart attack), cerebrovascular disease (stroke), and peripheral vascular disease. Estimates of morbidity, mortality, and economic costs of these and other cardiovascular diseases are given below.

ARTERIOSCLEROSIS

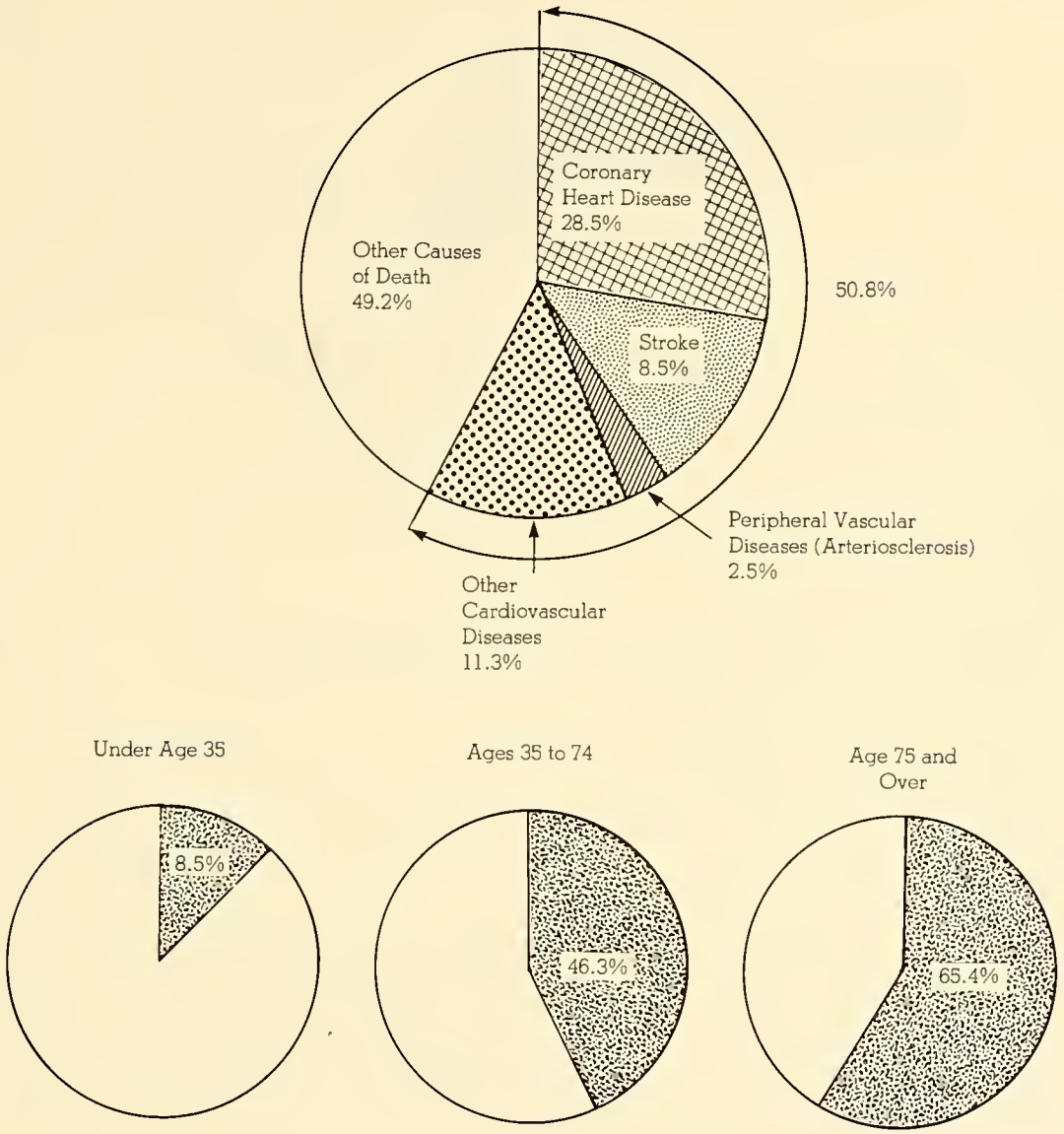
The process of arteriosclerosis underlies the disease in most of the estimated 11 million persons with coronary, cerebrovascular, or peripheral arteriosclerotic disease and about 780,000 of the deaths that occur each year.[1,6] Together, these clinical manifestations of arteriosclerosis account for an estimated 236 million restricted activity days, 82 million bed days, 21 million work-loss days, 29 million short-stay hospital days, 13 million physician office visits, and 145,000 Social Security disability allowances each year.[1-5] Starting in youth, the arteriosclerotic process builds so that after age 75, it is the underlying cause of 60 percent of all deaths and 90 percent of the cardiovascular disease deaths. The estimated cost to the Nation of the arteriosclerotic-related diseases was $57 billion in 1979.

Table 5. Total Mortality and Mortality from Heart and Vascular Diseases in Two Age Groups, United States, 1980

Cause of Death	Estimated Number of Deaths	Percent of All Deaths	Estimated Number of Deaths	
			Under Age 65	Age 65 and Over and Not Specified
All Causes	1,977,000	100	646,000	1,331,000
Total Cardiovascular Diseases	1,005,000	50.8	215,000	790,000
Arteriosclerotic-related	781,000	39.5	157,000	624,000
Coronary heart disease (heart attack)	563,000	28.5	126,000	437,000
Cerebrovascular disease (stroke)	169,000	8.5	25,000	144,000
Peripheral vascular disease (arteriosclerotic)	49,000	2.5	6,000	43,000
Hypertensive disease	32,000	1.6	8,000	24,000
Congenital heart disease	6,000	0.3	6,000	--
Rheumatic fever and rheumatic heart disease	8,000	0.4	3,000	5,000
All other heart and vascular diseases*	178,000	9.0	41,000	137,000
All other causes of death (noncardiovascular)	972,000	49.2	150,000	822,000

*Some of these deaths would have been classified to a specific rather than generalized cause of death if appropriate information had been available at the time of death certification. The unavailability of that information also means that the numbers of deaths nominally assigned to arrhythmias, heart failure, shock, cardiomyopathy, and infections of the heart do not reflect their proper magnitude and are, therefore, not separately identified in this table.

Source: Estimated from vital statistics reported by the National Center for Health Statistics. (Ref. Nos. 6 and 7)



*Data by age are for 1978.

Source: Mortality data from the National Center for Health Statistics (Ref. Nos. 6 and 7).

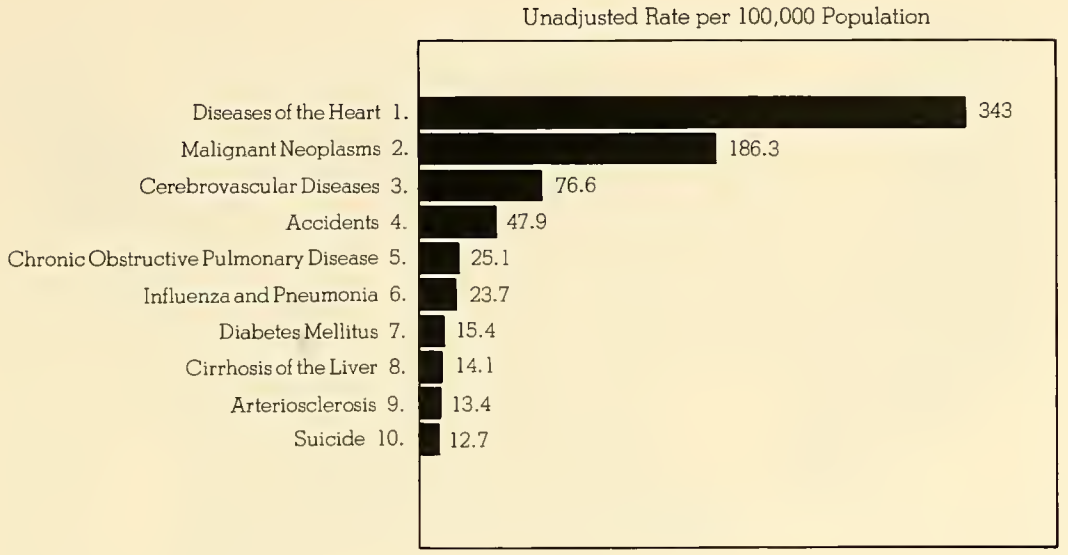
Figure 4. Percent of Deaths Attributed to Cardiovascular Diseases: Total and for Major Components by Broad Age Groups*; United States, 1980

Table 6. Estimated Economic Costs of Cardiovascular Diseases United States, 1979

(dollars in millions)

Cardiovascular Disease	Total	Direct Health Expenditures					Morbidity	Mortality
		Total	Hospital Care	Physicians and other Professional Care	Drugs	Nursing Home Care		
TOTAL	$81,339	$29,688	$14,260	$5,216	$2,884	$7,328	$9,690	$41,961
Arteriosclerotic-related	56,950	16,556	8,655	1,393	873	5,635	3,399	36,995
Coronary heart disease	37,819	6,857	4,905	960	706	286	1,880	29,082
Cerebrovascular disease	12,107	4,282	2,709	193	98	1,282	1,022	6,803
Peripheral vascular disease	7,024	5,417	1,041	240	69	4,067	497	1,110
Hypertensive disease	8,892	5,915	1,027	2,691	1,479	718	2,230	747
Arrhythmias	NA	1,148	841	209	98	NA	NA	NA
Cardiac failure and cardiomyopathies	NA	2,368	1,383	203	130	652	NA	NA
Rheumatic fever, rheumatic heart disease	751	246	171	52	23	NA	122	383
Infections of the heart	NA	57	57	NA	NA	NA	NA	NA
Other cardiovascular diseases	14,746	3,397	2,126	668	280	323	3,939	3,836

NA: Not available
Source: Ref. Nos. 3, 4, and 8-13.

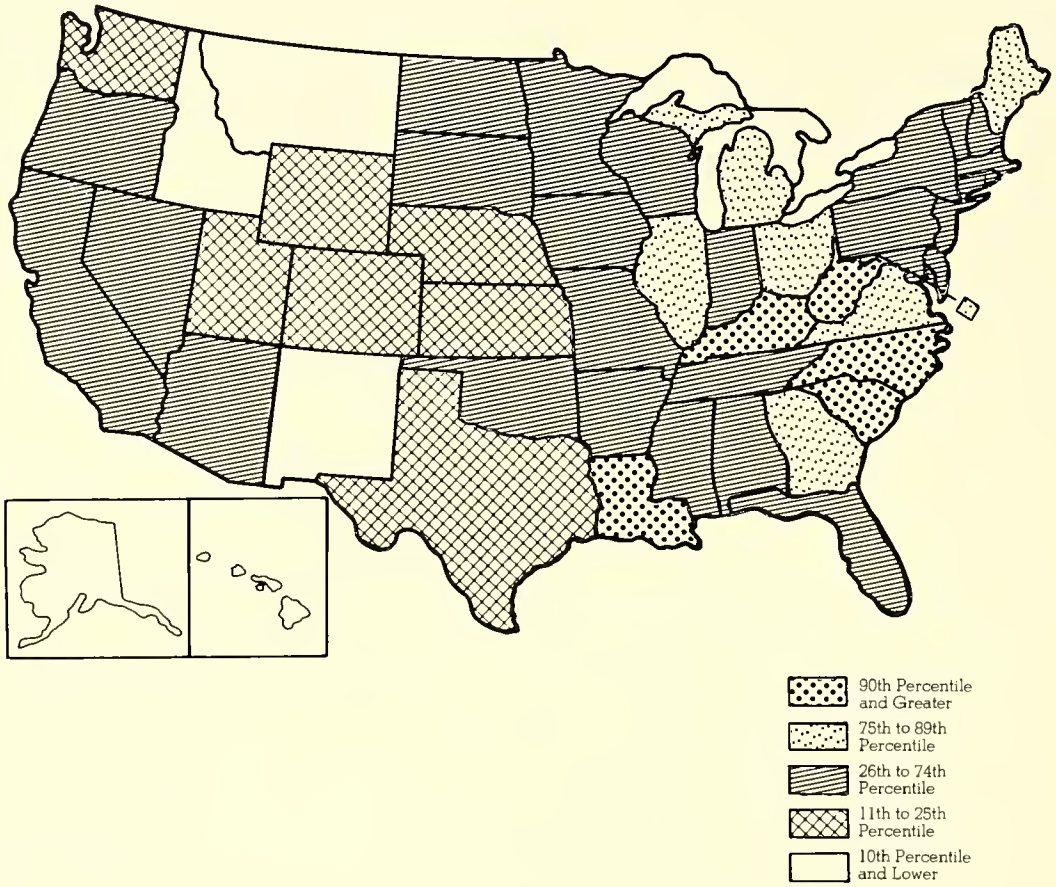


Source: Mortality data from the National Center for Health Statistics (Ref. No. 6).
Provisional Statistics, *Monthly Vital Statistics Reports* 29(13) 1981, NCHS.

Figure 5. Death Rates for the Ten Leading Causes of Death; United States, 1980

CORONARY HEART DISEASE

In the official list of causes of death, heart disease is the leading cause (figure 5). Since 75 percent of these deaths are due to coronary heart disease (563,000 in 1980), it is said that "heart attack" is the Nation's number one cause of death. Unlike deaths from other diseases, two-thirds of heart attack deaths occur suddenly or before hospitalization. Geographic variation in CHD death rates for middle-aged persons ranges from a low in Hawaii to a rate 1.5 times higher in West Virginia (figure 6). Southeastern states show the highest rates, and the Rocky Mountain states have the lowest rates. International comparisons show that CHD mortality in the United States ranks seventh from the highest for men and eighth from the highest for women in industrialized countries (figure 7).[14] Coronary heart disease is the leading diagnosis in Social Security worker-disability allowances, and among men, it is the second leading diagnosis in hospital admissions. An estimated 1.4 million heart attacks occur each year, of which 800,000 are first attacks.[6,15,16] That datum amounts to nearly 3 heart attacks per minute in the United States, or 4,000 per day. The economic cost of coronary heart disease in 1979 was $38 billion, or 46 percent of the combined costs for all cardiovascular diseases.

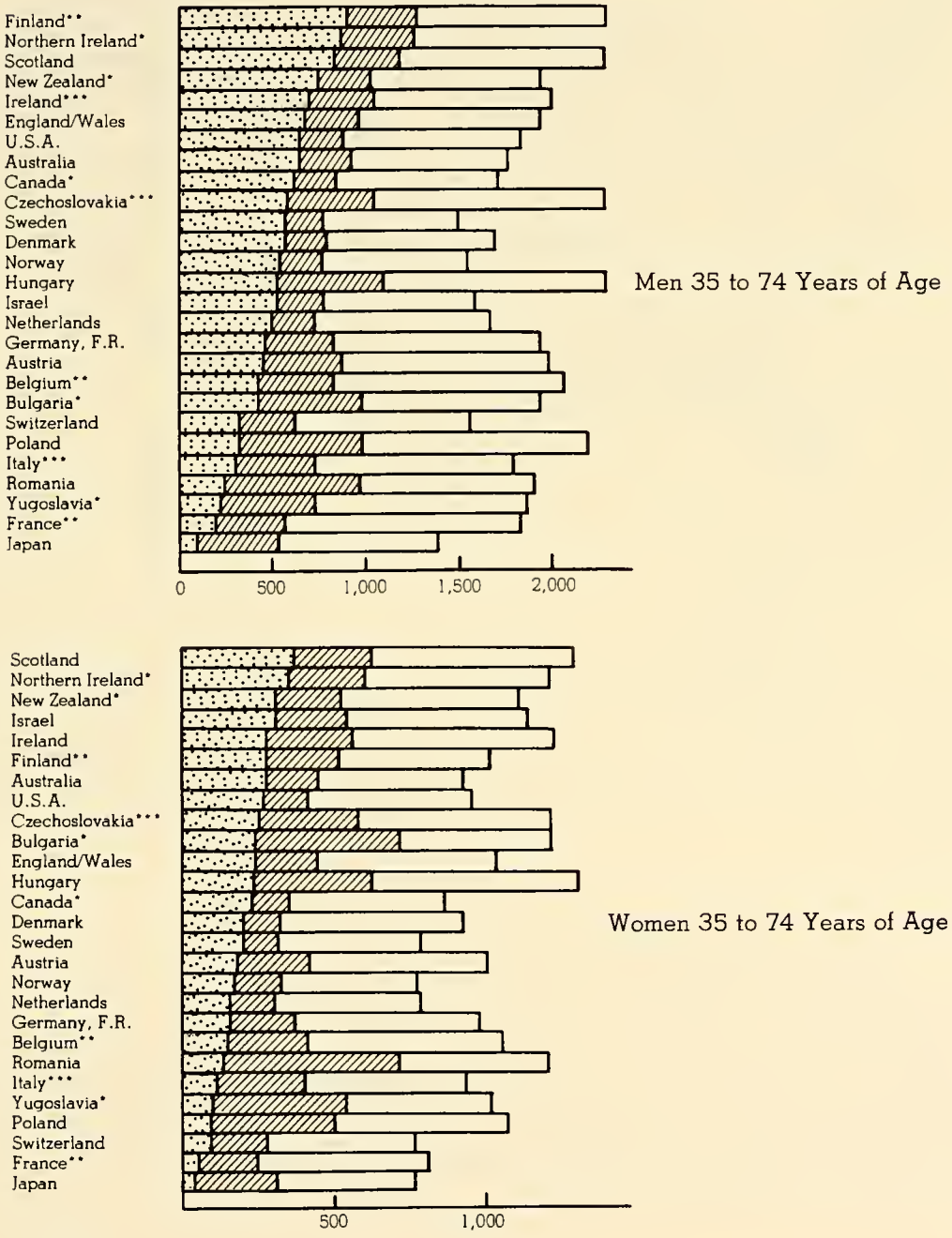


Source: Mortality data from the National Center for Health Statistics (Ref. No. 7).

Figure 6. Coronary Heart Disease Mortality in the United States: Total Population Ages 35 to 74, Age-Adjusted Rates per 100,000, 1978

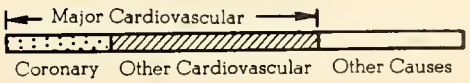
From the National Heart, Lung, and Blood Institute prospective community study in Framingham, Massachusetts, it has been estimated that for men, the chance of developing a first heart attack (overt or silent myocardial infarction, coronary insufficiency, or CHD death) by age 60 is 1 in 5.[16] The probability increases with age to 41 percent by age 75 and is several times greater for men than for women. Incidence rates for women "lag" behind men some 20 years for first myocardial infarction.[17] Although recovery from an acute myocardial infarction is frequently incomplete, 88 percent of myocardial infarction patients under age 65 are able to return to their usual occupations.[16]

Age-Averaged Death Rate per 100,000 Population, 1978



*1977
**1976
***1975

Source: Mortality data from the World Health Organization (Ref. No. 14).



Within 5 years after an initial infarction, 13 percent of the men and almost 40 percent of the women develop a second infarction.[18] The case-fatality rate is 30 percent for initial infarctions and 50 percent for recurrences.[16] Even the unrecognized (silent) infarctions carry these high fatality rates.[16] Ten-year survival following an infarction is 50 percent for men and 30 percent for women.[16]

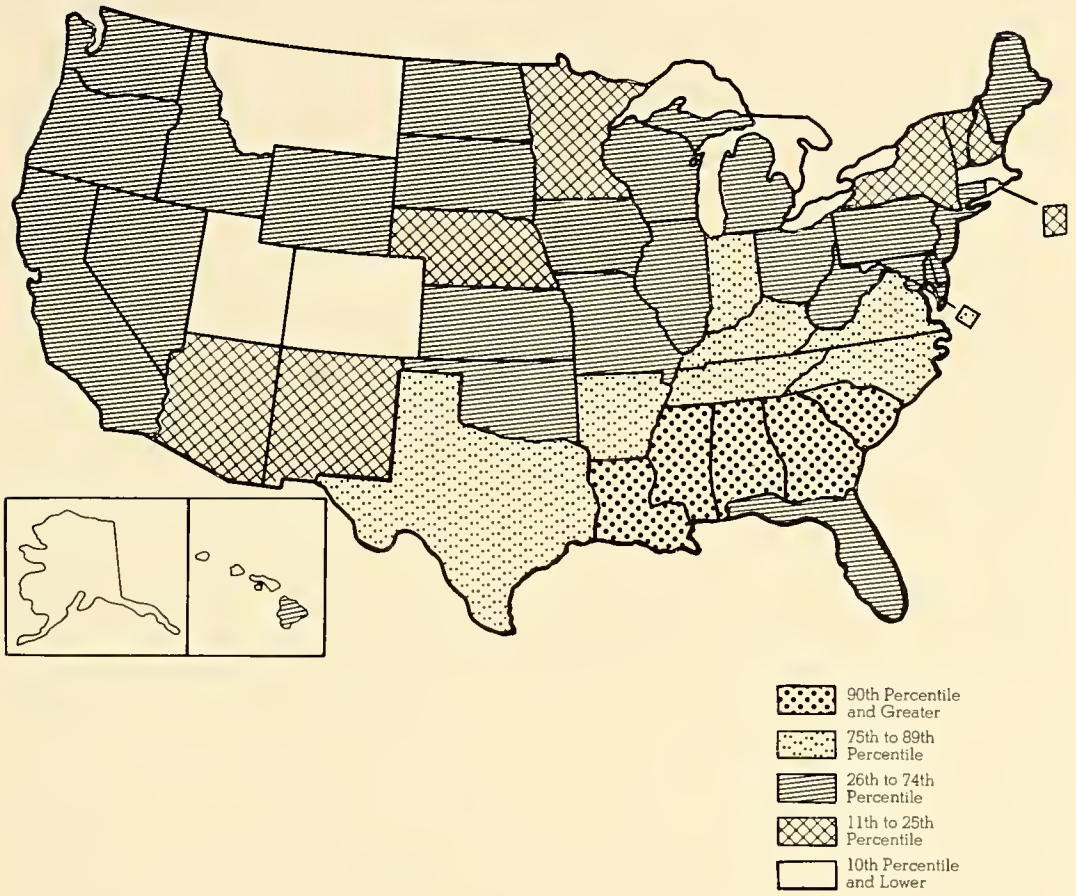
CEREBROVASCULAR DISEASE

Stroke is the third leading cause of death, accounting for 169,000 deaths in 1980. Whereas death rates for stroke are about the same for men as they are for women, among adults under age 65 the rate is 3 times higher for blacks than for whites. For all ages combined that ratio is 2.5 to 2. Other U.S. ethnic groups have much lower rates. There is considerable geographic variation in stroke death rates, with South Carolina having a rate twice as high as that for Alaska (figure 8). Rates are highest in the Southeast and lowest in the Rocky Mountain states. There are an estimated 1.7 million persons who have cerebrovascular disease, and each year there are 400,000 new strokes and 100,000 recurrences.[2,19]

Before age 70, the chance of an atherothrombotic brain infarction, which comprises 59 percent of all first strokes, is 1 in 20.[20] The chance in 8 years for a person age 60 is 16 out of 1,000, with little difference between men and women.[21] The case-fatality rate is about 20 percent, but the disease is disabling in a greater proportion of cases.[20] Only about 40 to 50 percent of persons having an atherothrombotic brain infarction survive 5 or more years.[22]

PERIPHERAL VASCULAR DISEASE

It is estimated that perhaps as many as 4 million persons have peripheral vascular disease. More than 750,000 persons were discharged from short-stay hospitals in 1979 with peripheral vascular disease, which amounted to an estimated 7.5 million days of care. In 1980, approximately 65,000 deaths were attributed to peripheral vascular disease, making it one of the 10 leading causes of death. Morbidity and mortality from these diseases cost the Nation an estimated $7 million in 1979.



Source: Mortality data from the National Center for Health Statistics (Ref. No. 7).

Figure 8. Stroke Mortality in the United States:
Total Population Ages 35 to 74, Age-Adjusted Rates per 100,000, 1978

HYPERTENSION

Almost 26 percent of the U.S. population, or approximately 60 million persons, have hypertension.*[23,24] The percent prevalence

*Hypertension is defined as either a systolic blood pressure of at least 140 mm Hg or a diastolic pressure of at least 90 mm Hg or on antihypertensive medication. Prevalence (that is, the percent of persons with the condition) is for 1976-1980 and is applied by age to the 1980 population.

increases with age and is two times higher among blacks than among whites. This condition limits the activity of almost 3 million persons (table 2). Besides this high prevalence, the problem is compounded because 30 percent of those with hypertension do not know that they have it. One-half of the persons who suffer a heart attack and two-thirds who suffer a stroke have hypertension.[24,26] As a contributor to mortality, hypertension accounts for an estimated 250,000 deaths each year, many of which are nominally classified as stroke, coronary heart disease, congestive heart failure, or kidney disease.[27,28] Hypertensive disease mortality rates are two to eight times higher among blacks than among whites, depending on the age group. Because hypertension predisposes to arteriosclerosis, is a risk factor for coronary heart disease and for cardiac failure, and is the major predisposing factor for stroke, the statistics of economic impact shown in table 6 understate the magnitude of the problem associated with this pervasive condition.

CARDIAC FAILURE, CARDIOMYOPATHY, AND INFECTIONS OF THE HEART

An estimated 2 million persons suffer from cardiac failure, and each year, about 250,000 more persons develop the condition.[29] In 1979, cardiac failure and cardiomyopathies were the first-listed diagnosis for an estimated 450,000 hospital discharges, accounting for 4.7 million hospital days. There were an estimated 1.6 million such discharges in 1979. Cardiac failure and shock are the most common causes of in-hospital deaths from heart attack and most other types of heart disease. In 1979, there were 2 million physician office visits for cardiac failure and cardiomyopathy. Cardiac failure is listed as either the underlying or contributory cause on about 130,000 death certificates annually. The contribution of these diseases and of infections of the heart to disability cannot be estimated, but their role in complicating recovery from a stroke or heart attack is a substantial one.

CONGENITAL AND RHEUMATIC HEART DISEASE

Each year an estimated 25,000 babies are born with heart or vascular defects that result in about 3,700 deaths prior to 1 year of age.[7,29] Thus, cardiovascular disease is the cause of 44 percent of the deaths under age 1 that are classified as resulting from congenital anomalies. Those who survived with their congenital heart defect amount to 700,000 in the U.S. population, of whom almost one-third are limited in activity because of the disease.

The incidence of rheumatic fever and rheumatic heart disease is not known. In estimates for 1979, it could be as low as the 2,000 hospital discharges under age 15 or as high as the 63,000 physician office visits under age 15. The disease is present in about 1.7 million persons and accounts for about 8,000 deaths each year.

ARRHYTHMIAS

Although the frequency of arrhythmias is not known, they are a common manifestation of various types of heart disease and are frequently the immediate cause of heart failure and death. More than one-half of the victims of coronary heart disease die of arrhythmias. In 1979, of an estimated 1.5 million hospital discharges that had arrhythmia listed as one of the diagnoses, 371,000 had arrhythmia as the first-listed diagnosis, the primary reason for admission. In 1979, there were an estimated 2 million physician office visits for arrhythmias. This estimate is larger than that for visits for cerebrovascular diseases. It is not known how many deaths can be attributed to arrhythmias because deaths are classified according to the underlying, not the immediate, cause of death.

In summary, cardiovascular diseases account for 1 out of every 2 deaths, they are a leading cause of illness and disability, and they contribute to a large share of U.S. health care costs and lost economic productivity. These diseases, particularly arteriosclerosis, hypertension, and heart attacks, affect a vast segment of the population of working age as well as the elderly. In terms of serious disease, cardiovascular diseases are the Nation's leading health problem.

Economic Impact

The estimated economic cost of cardiovascular diseases in 1979 (table 6) represents the impact of these diseases on the Nation's economy. It is measured in terms of direct costs, which are health expenditures for these diseases, and indirect costs, such as lost productivity due to illness (morbidity costs) and death (mortality costs) from these diseases. Lost productivity is measured in terms of lost earnings and the value of lost housekeeping services. Mortality costs include not only lost earnings in 1979 but all lost future earnings that persons who died of these diseases in 1979 would have received during their expected remaining lifetime. Although estimates of morbidity and mortality

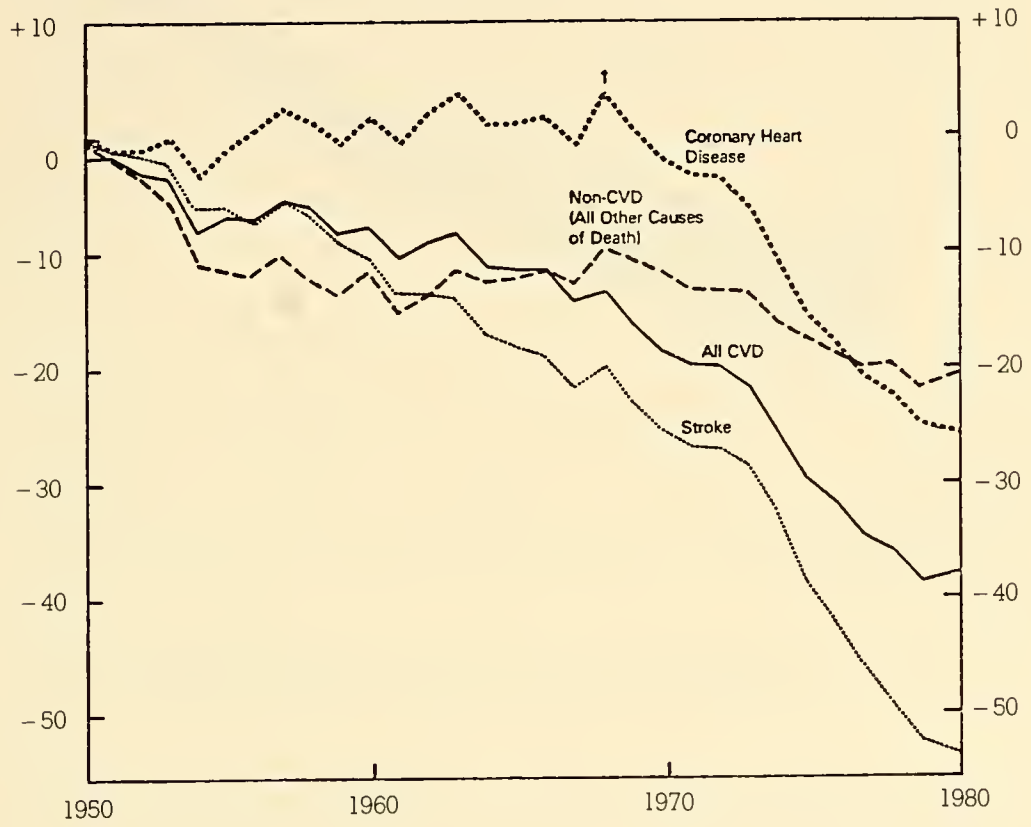
costs are reasonably complete, some direct costs cannot be allocated to cardiovascular diseases--namely, expenditures for research, construction of medical facilities, government public health activities, and other health administration and services.

Direct Costs. The Health Care Financing Administration (HCFA) estimated that about $85.3 billion was spent for patient care in all hospitals during 1979.[9] A Georgetown University study in 1975 estimated that 16.7 percent of hospital care expenditures were for cardiovascular (CV) diseases.[10] This percent applied to $85.3 billion gives about $14.3 billion for these diseases. This figure is then allocated by the proportion of hospital days in short-stay hospitals for each component of CV disease.[3] A similar method is used for allocating expenditures for physicians and other health professional services, for nursing home care, and for drugs and medical sundries. The main assumption in each table is that the basis for percentage allocation is appropriate.

Indirect Costs. Estimates of morbidity and mortality costs of the cardiovascular diseases in 1977 were made by the National Center for Health Statistics.[3,4,8-13] These costs are increased by an inflation factor and shown in table 6 for 1979.

Progress in Reducing Morbidity and Mortality

The long-term trend in the overall death rate for the cardiovascular diseases has been downwards, with the steepest decreases occurring in the most recent years (figure 9).[6,7,30] Between 1968 and 1978, the age-adjusted death rate for all cardiovascular diseases declined 26 percent. The decline for coronary heart disease was 25 percent, for stroke 37 percent, for hypertensive disease 53 percent, and for rheumatic heart disease 38 percent. The effect of this decline has been to delay death--that is, to add to life expectancy (figure 10). The gain has been substantial in just 10 years. A person of age 45 in 1978 could expect to live 31.9 more years, 2.3 years longer than what could be expected in 1968. The portion of that gain in life expectancy to which the decline in cardiovascular disease mortality contributed is 70 percent, or 1.6 additional years of life. The recent rate of decline for these diseases greatly outpaced the decline for all other causes of death combined, averaging 2.3 percent per year. Since 1972, the cardiovascular disease mortality decline accounted for 70 percent of the general decline in U.S. mortality (see figure 11).



Year	CVD‡	Coronary Heart Disease	Stroke	All Other Causes	Total All Causes
1950	425.6	232.2	88.8	415.9	841.5
1980	264.9	173.5	41.5	329.2	594.1
Change	−160.7	−58.7	−47.3	−86.7	−247.4
% Change	−37.8	−25.3	−53.3	−20.8	−29.4

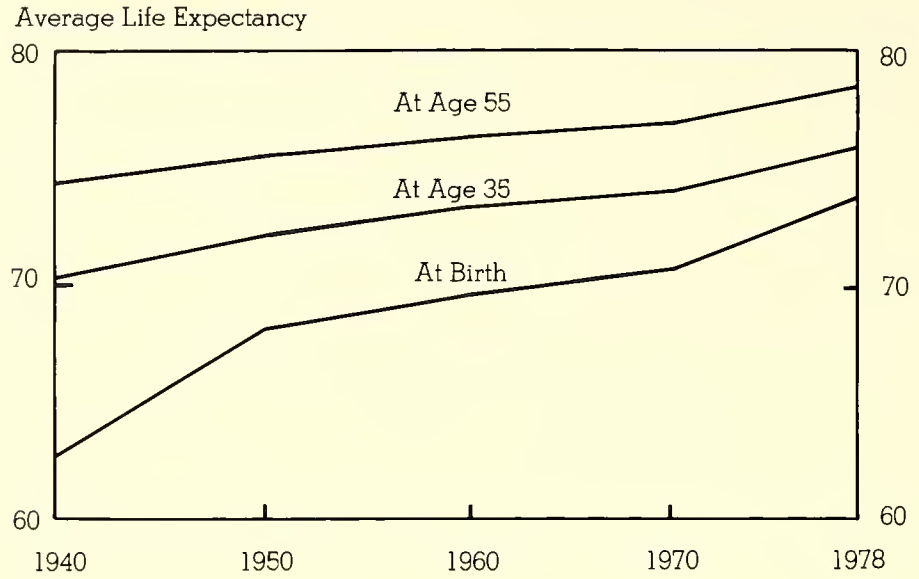
*Age-adjusted to 1940 U.S. population.

†Increase caused by the shift to the Eighth Revision of the International Classification of Diseases in 1968, a year in which an epidemic of influenza/pneumonia also occurred.

‡Excluding congenital heart disease.

Source: Mortality data from the National Center for Health Statistics (Ref. No. 23).

Figure 9. Percent Change in Death Rates Since 1950 for All Cardiovascular Diseases (CVD), Coronary Heart Disease, Stroke, and All Other Causes of Death (Non-CVD) for All Ages in the United States

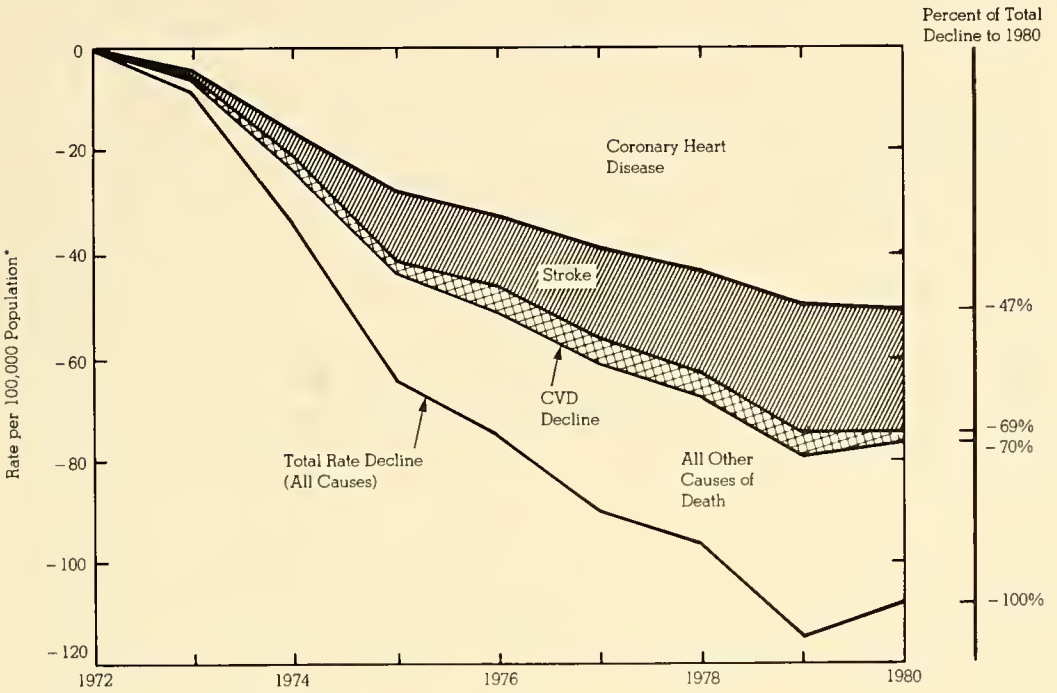


Source: Mortality data from the National Center for Health Statistics (Ref. Nos. 7, 31).

Figure 10. Increase in Life Expectancy at Birth, at Age 35, and at Age 55 for Total Population, United States, 1940 to 1978

As shown in figure 11, there was an upturn in mortality in 1980. That upturn from 1979 amounted to 2.7 percent for the cardiovascular diseases whereas the unadjusted death rate for all other causes of death combined increased 3.3 percent. This increase for the cardiovascular diseases in 1980 is only temporary and reflects two severe influenza epidemics and extreme summer and winter temperatures, all of which increase the number of deaths from these diseases. Although there was also a severe influenza epidemic in the early months of 1981, the provisional unadjusted death rate for major cardiovascular diseases is down in 1981 by 2.2 percent compared to a 0.3 percent increase for all other causes of death combined. Clearly, relative to other diseases, the mortality trend for the cardiovascular diseases continues to be favorable.

Whether trends in cardiovascular morbidity are favorable is not as clear. Between 1972 and 1978, prevalence rates for most of the cardiovascular diseases increased (table 7).[2,31] Although none of the changes is statistically significant because of high standard errors, the pattern of change is consistent with other information. The smallest increases occurred for coronary heart disease and stroke, two diseases for which death rates fell dramatically during that 6-year period and for which incidence



*Age-adjusted to U.S. 1940 population.

Source: Mortality data from the National Center for Health Statistics

Figure 11. Change in Death Rates Since 1972 for Coronary, Stroke, and Other Cardiovascular Diseases and for Other Causes of Death; United States

rates may have declined. For ages 65 and over, there was a decrease in the prevalence rate for stroke. Although prevalence rates for hypertension in this table increased substantially, the change probably reflects the expected increase in persons aware of their condition.[25] The prevalence rate for hypertension as measured in health examinations appears to be declining, as shown later in this report. National trends in hospital discharges in the 1970's are upwards for the cardiovascular diseases but only modestly so for acute myocardial infarction or cerebrovascular disease (figure 12).[32]

TRENDS IN CORONARY HEART DISEASE

Although heart disease is by far the Nation's leading cause of death, a significant improvement has been made in the mortality trend for the major component, coronary heart disease. Coronary mortality rose at an epidemic rate to a peak in the mid-1960's

Table 7. Prevalence Rates Per 1,000 Persons for Cardiovascular Conditions for Selected Age Groups, United States, 1972 and 1978

Cardiovascular Diseases	Ages 45-64		Ages 65 and Over	
	1972	1978	1972	1978
Heart Conditions	88.8	112.4	198.7	214.6
Active rheumatic fever and chronic rheumatic heart disease	6.3	9.7	5.1	7.3
Hypertensive heart disease*	19.9	31.4	52.8	45.3
Coronary heart disease	34.7	41.6	84.0	84.8
Other specified heart disease	4.0	4.6	6.8	8.0
Unspecified disorders of heart rhythm	12.8	12.3	22.0	23.8
Heart trouble, NOS†	11.1	12.8	28.1	45.5
Hypertensive disease*, NEC§	126.7	184.8	199.4	251.6
Cerebrovascular diseases	11.5	12.3	48.2	44.9
Arteriosclerosis, NEC§	1.0**	3.3	25.7	25.1
Phlebitis and thrombophlebitis, NEC§	3.8	7.2	3.2	6.8
Poor circulation, NOS†	8.1	11.7	24.1	25.1
Congenital anomalies of the circulatory system	2.9	5.6	3.2	1.5

* These estimates understate prevalence primarily by not including persons unaware of their condition.

** Under age 65.

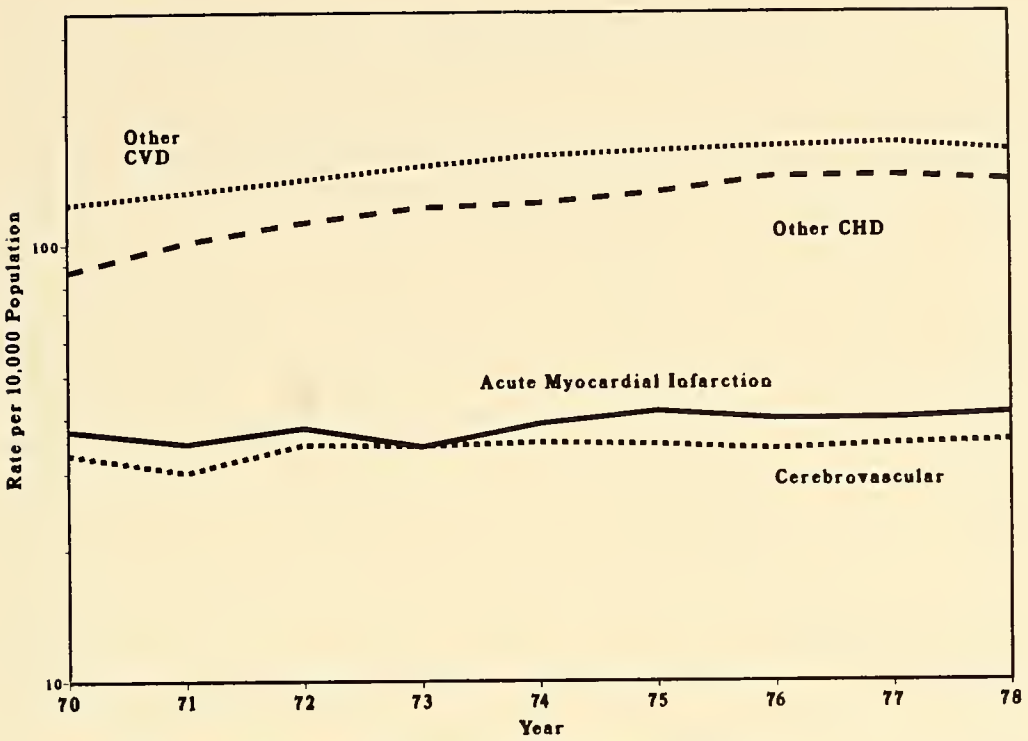
† NOS: Not otherwise specified

§ NEC: Not elsewhere classified

Note on standard errors: The relative standard error exceeds 10% for all cells except those for hypertensive disease.

General caution: These estimates are based on reporting in household interviews among the noninstitutionalized population.

Source: Health Interview Survey; National Center for Health Statistics (Ref. Nos. 2 and 31).



Source: Hospital Discharge Survey; National Center for Health Statistics.

Figure 12. Rate of Hospital Discharges for Major Components of Cardiovascular Diseases; Ages 45-64; United States, 1970 to 1978

then declined a remarkable 31 percent between 1963 and 1980.* The decline began slowly, averaging 1.5 percent per year between 1963 and 1972, but between 1972 and 1980, the decline accelerated and averaged 2.7 percent per year. Compared to a 1.1 percent per year increase in the 1940's, there was a 2.3 percent per year decline in the 1970's. For middle-aged men, the reversal in the trend is even more striking: from a 2 percent per year increase in the 1940's to almost a 3 percent per year decline since 1970. Because of the CHD mortality decline, heart disease is no longer the leading cause of death among persons 25 to 44 years of age and soon

*The coronary mortality trend is measured by the age-adjusted death rate, using the 1940 U.S. population as the standard, with comparability ratios used to convert rates to make them as comparable as possible over time.

will probably rank second for persons 45 to 54 years of age. Declines are seen in all age, race, and sex groups and in nearly all geographic entities within the United States. Most European countries, however, are not experiencing such a decline for men (figure 13). Among middle-aged men, the U.S. now ranks seventh from the highest in coronary mortality among the industrialized countries compared with first rank in 1960.

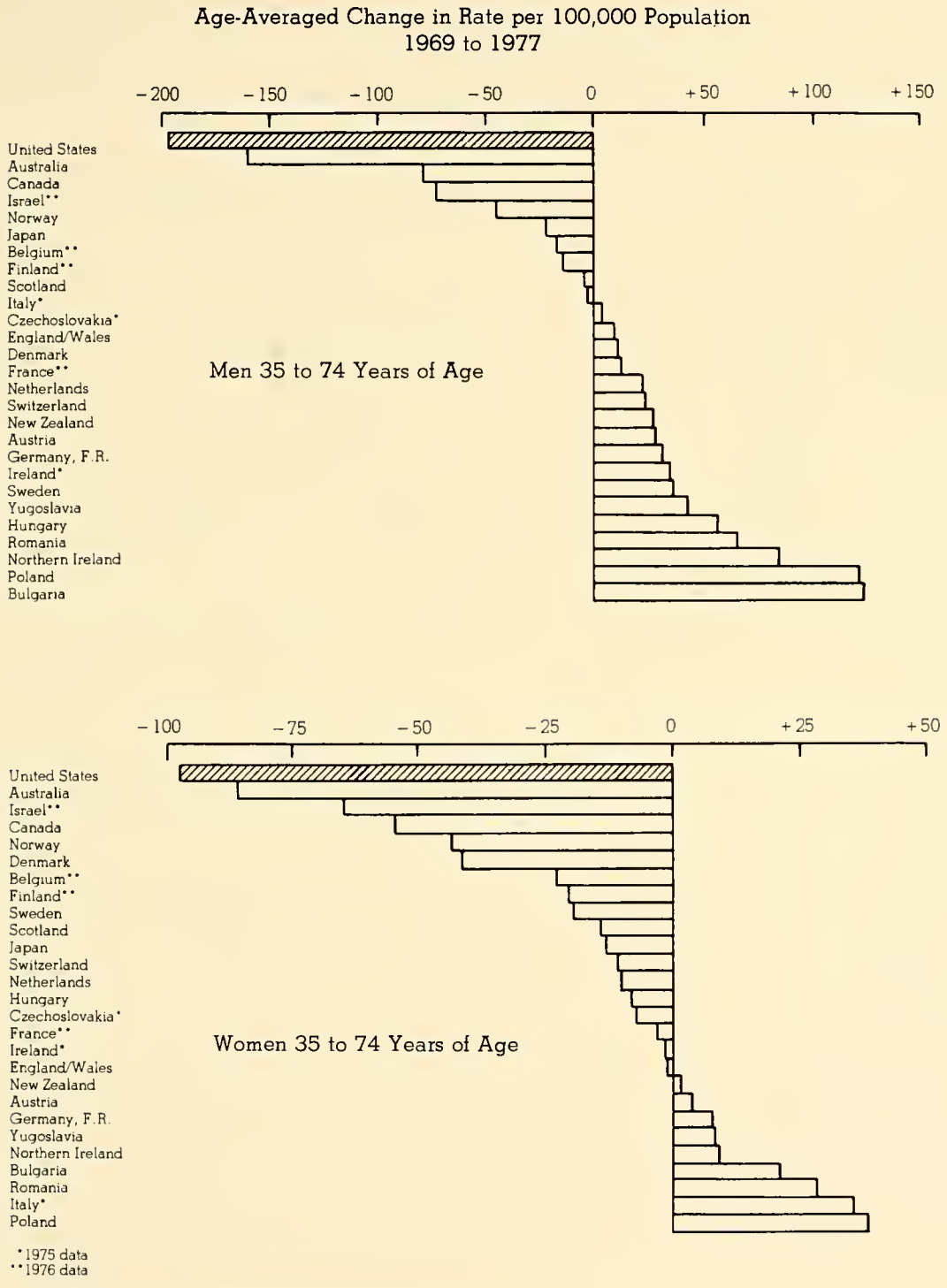
Clearly, the Nation's mortality trend for this disease has changed dramatically. One way to measure the impact of this change is with the following calculation: If the CHD death rate among adults under age 75 (premature mortality) had not declined in the 10 years after 1968, 114,000 additional premature deaths would have occurred in 1978 alone. Measured against the 302,000 premature deaths from CHD that did occur in 1978, the addition would have amounted to 38 percent more coronary deaths among adults under 75 years of age.

The sizable CHD mortality declines may or may not be accompanied by parallel declines in the number of new or recurrent heart attacks or in improvements in case-fatality rates and survivorship. National statistics on prevalence and hospitalizations have quite limited usefulness as measures of these trends, and community studies show conflicting results. Rates of hospitalization for CHD increased in the early 1970's but then began to level off (figure 12). With increased numbers of catheterizations, insertions of pacemakers, and coronary bypass operations, that leveling off suggests that the rate of admissions for acute events may actually be declining.[33] Concurrently, the percent that are discharged dead (the hospital case-fatality rate for CHD) declined markedly (table 8).

In the study of male employees of the DuPont Company, the incidence rate of acute myocardial infarction was 18 percent lower in the period of 1973 to 1979 compared with that of 1957 to 1964.[34] Although 30-day case-fatality rates and the proportion of sudden deaths did not change significantly, the 30-day mortality among persons who survived 24 hours after the attack declined significantly beginning about 1969.

In the Kaiser-Permanente Medical Care Program in the San Francisco area, the proportion of persons hospitalized each year for acute myocardial infarction declined 27 percent between 1971 and 1977.[35] The proportion hospitalized for any manifestation of coronary heart disease declined 18 percent. The decline was seen in both first and recurrent events. There was no clear trend in the proportion of persons who died from acute myocardial infarction of all persons hospitalized for this disease each year.

In the population of Rochester, Minnesota, there was no change in the incidence of initial manifestations of coronary



Source: Mortality data from the World Health Organization (Ref. No. 1).

Figure 13. Death Rate Trend for Coronary Heart Disease by Country

Table 8. Hospital Case-Fatality Rate for Acute Myocardial Infarction and Chronic Coronary Heart Disease, United States, 1970 to 1978

Year	Acute Myocardial Infarction			Chronic Coronary Heart Disease		
	Discharges*	Deaths	Percent Dead	Discharges*	Deaths	Percent Dead
			Ages 45-64			
1970	156	25	16.0	292	12	4.2
1971	147	20	14.0	343	13	3.9
1972	160	19	11.9	386	13	3.5
1973	147	19	12.7	419	12	3.0
1974	166	17	10.3	425	10	2.4
1975	178	21	11.9	444	10	2.2
1976	172	21	12.1	492	14	2.9
1977	172	18	10.2	491	11	2.2
1978	177	17	9.7	484	11	2.3
			Ages 65 and Over			
1970	162	61	37.8	557	62	11.1
1971	162	53	33.0	583	59	10.1
1972	186	61	32.6	630	62	9.8
1973	177	56	31.5	661	62	9.5
1974	191	56	29.6	692	62	9.0
1975	185	53	28.4	687	58	8.5
1976	202	52	25.7	711	56	7.8
1977	208	54	25.9	722	55	7.6
1978	221	62	28.2	717	58	8.2

*First-listed diagnosis on discharge.
Source: Hospital Discharge Survey, National Center for Health Statistics (Ref. No. 3).

heart disease between 1950 and 1969,[36] but the case-fatality rate, based on sudden, unexpected deaths and myocardial infarction deaths under 30 days, was 34 percent in the period of 1970 to 1975 compared with 47 percent in that of 1950 to 1955.

TRENDS IN CEREBROVASCULAR DISEASE

The long-term decline in the death rate for cerebrovascular diseases (stroke) has accelerated remarkably in recent years (figures 9 and 11). The percent decline averaged 5 percent per year between 1972 and 1980 compared to more modest declines prior to that period. Instead of ranking as the third cause of death among persons as young as 45 to 54 years of age, as was the case prior to 1960, the disease now ranks fifth from the highest in that age group. While stroke accounted for 8.5 percent of all deaths in 1980, the decline in stroke mortality has been so steep since 1972 that it accounts for 22 percent of the general death rate decline since that year (figure 11). The stroke decline is observable in nearly all age, race, and sex groups and geographic entities. Although the downward trend is seen in most industrialized countries, the United States has one of the steepest declines in mortality from stroke (figure 14). If stroke mortality had not declined in the 10 years after 1968, 97,000 instead of 60,500 "premature" (before age 75) stroke deaths would have occurred in 1978.

As shown in figure 12, the rate of hospitalization for stroke is no longer increasing. Also, the hospital case-fatality rate declined from 19.4 percent to 14.3 percent between 1971 and 1978.[3 33] In a related but diagnostically more accurate study, the age-adjusted incidence rate for initial stroke declined about 15 percent between 1971 and 1976, primarily for persons 65 years of age and older.[37] In the Kaiser-Permanente study, the proportion of persons hospitalized for cerebral thrombosis declined 64 percent between 1971 and 1977, with most of the decline occurring after 1973. The decline for all cerebrovascular diseases combined was 15 percent. In the Rochester, Minnesota, population, there was a 45 percent decline in the incidence of stroke between 1945 and 1974, with reductions more pronounced in the elderly.[38] The Framingham study observed a lower incidence rate for stroke among women (but not among men) followed since 1962 than among women followed since 1950.[39]

TRENDS IN OTHER CARDIOVASCULAR DISEASES

Mortality trends are decreasing for hypertensive disease, rheumatic and congenital heart disease, and for peripheral vascular disease. Trends for cardiac failure, shock, arrhythmias, cardiomyopathies, and infections of the heart cannot be calculated

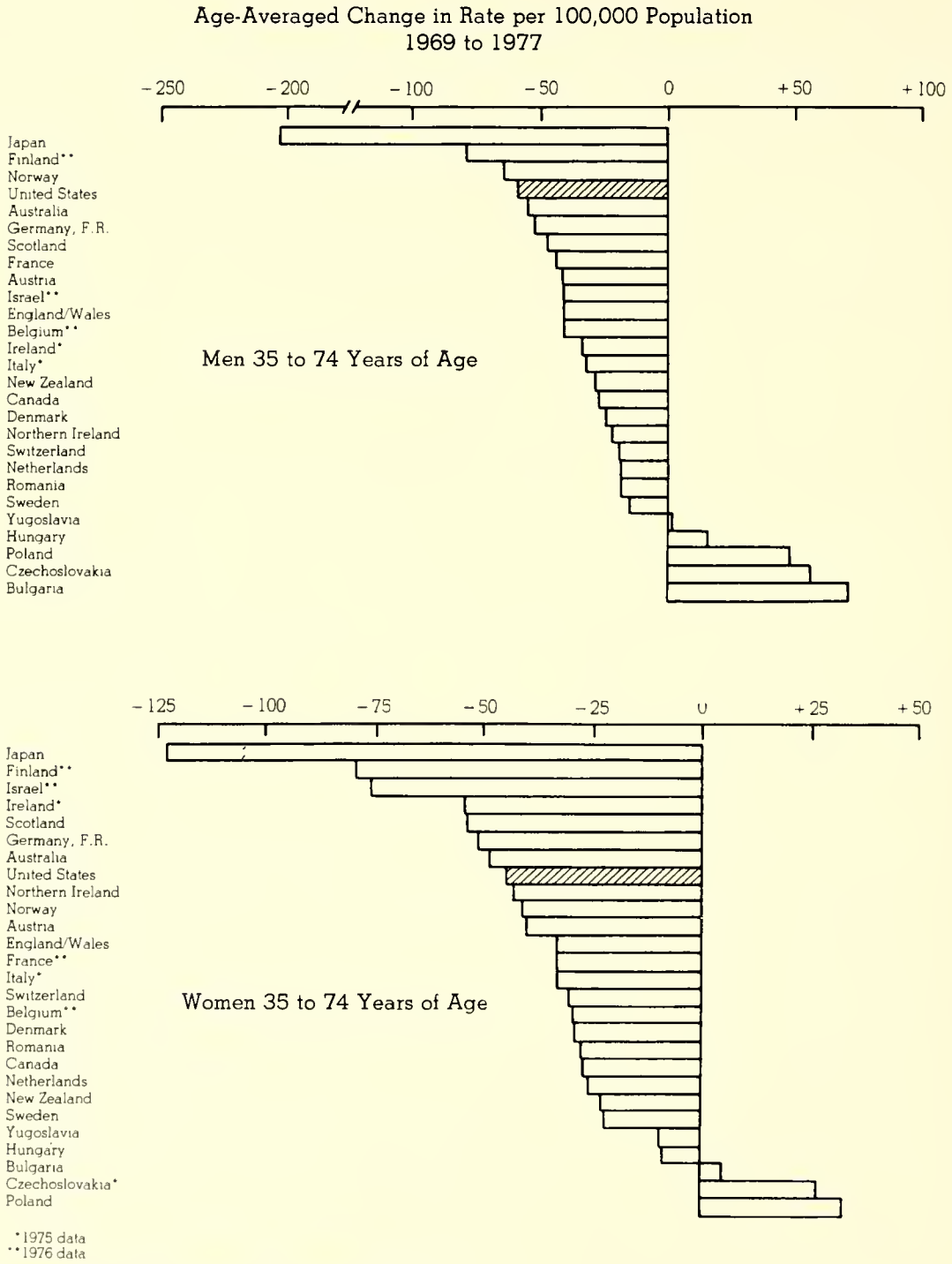


Figure 14. Death Rates for Cerebrovascular Diseases by Country

because death certifications and cause-of-death classifications do not accurately distinguish between them.

Not only has hypertensive disease mortality* declined steadily since 1940: The decline steepened each decade from 2 percent per year in the 1940's to 7 percent per year in the 1970's. Mortality from rheumatic fever and rheumatic heart disease declined steadily throughout the last 40 years so that by 1980, about 7,900 persons died from this disease compared to twice that many in 1968 and almost three times that many in 1950. Between 1940 and 1960, the infant mortality rate for congenital anomalies of the circulatory system ("congenital heart disease") declined 12.5 percent, and between 1960 and 1978, the rate declined 38 percent.

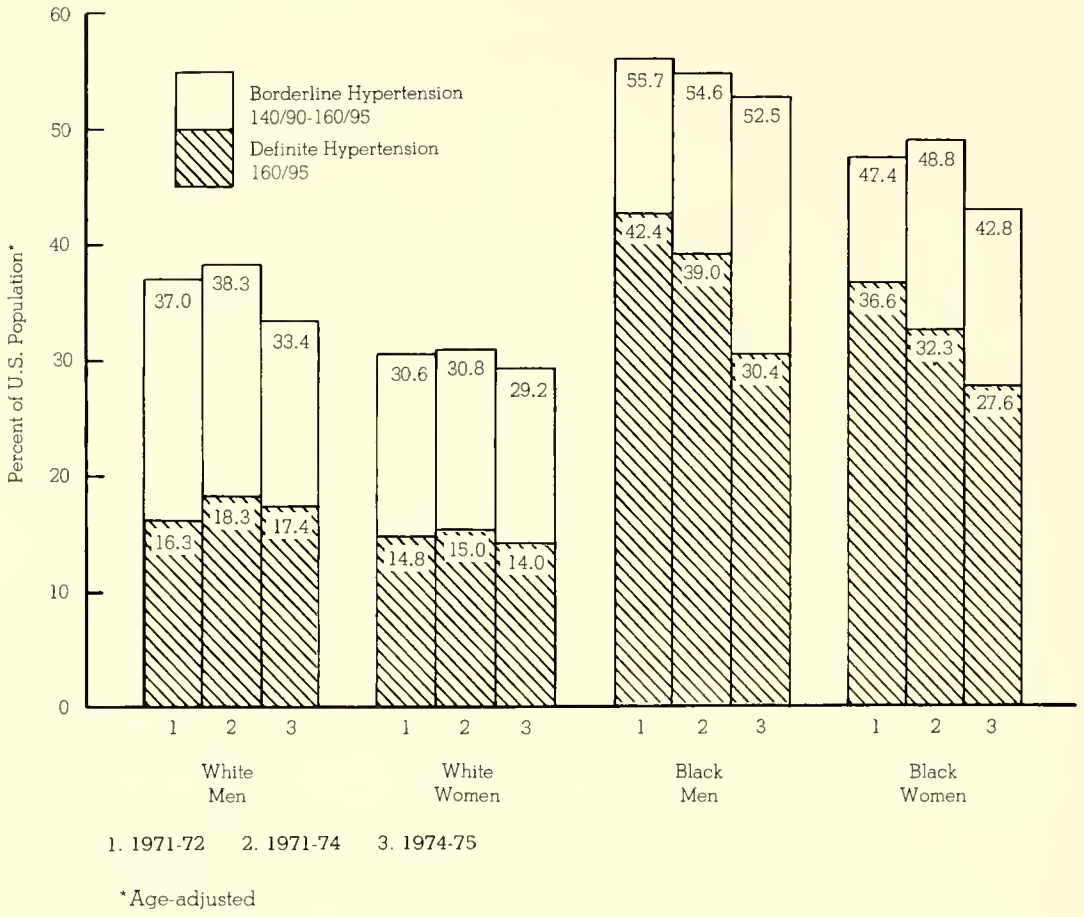
By actual blood pressure measurement, the estimated national prevalence rate of hypertension declined in the 1970's for each sex-color group (figure 15).[23] The percent of hypertensives not aware of their disease also declined while the percent under control increased (table 9). A number of surveys have shown that more persons with hypertension see their physicians for it more frequently, more are on treatment for it, and more have it controlled than in the past.[40]

In contrast with the declining mortality from congenital heart disease, the incidence rates for ventricular septal defects (VSD), for patent ductus arteriosus, and for transposition of the great vessels are all upwards in the 1970's.[41] The incidence of VSD nearly tripled between 1970 and 1980, with rates going from 0.4 to 1.18 per 1,000 total births.[42]

IMPLICATIONS

Because there have been fewer deaths each year from the cardiovascular diseases and a postponement of death to older ages, the quality of American life has improved in recent years for those families who otherwise would have suffered the loss of a member, particularly a member who is still of working age. Declining mortality rates are probably accompanied by reductions in morbidity, which also impact favorably on the quality of life. The large decline in cardiovascular disease mortality just since 1972 also translates into billions of dollars of economic productivity that the Nation would otherwise lose each year.

*Hypertensive disease mortality is measured by death rates nominally attributed to hypertensive disease as the underlying cause of death in death certificate tabulations, with no regard to the much larger contribution to mortality made by this disease.



Source: National Center for Health Statistics, Health and Nutrition Examination Survey (Ref. No. 41).

Figure 15. Prevalence Rates (%) for Hypertension by Sex and Color, Ages 25 to 74; United States

Acceleration in downward mortality trends, especially for hypertension and stroke, coincided with increased Federal health efforts in the cardiovascular disease area, directed especially to hypertension awareness and therapy. The mortality trends and the health efforts also coincide with increased use of cardiac surgery, medical devices, diagnostic aids, and therapies; with healthier lifestyles, such as proper diet and exercise; and with reductions in risk factor levels, such as cigarette smoking and serum cholesterol levels.

One can focus on differences in mortality trends between certain age, race, sex, and geographic groups in the light of coincident trends in the various prevention and treatment factors. But another point of view would note similarities in the declines

Table 9. Percent of Hypertensive Persons By Awareness, Treatment, and Control Status for Two Definitions of Hypertension, United States, 1971 to 1972 and 1974 to 1975

Awareness - Treatment - Control	Systolic 140+ or Diastolic 90+ or on Antihypertensive Treatment		Systolic 160+ or Diastolic 95+ or on Antihypertensive Treatment	
	1971-72	1974-75	1971-72	1974-75
Total with Hypertension	100	100	100	100
Unaware[1]	65.5	48.2	49.1	32.4
Aware, no treatment[2]	14.2	24.6	14.4	23.9
Aware, treatment, no control[3]	15.9	19.4	20.0	19.5
Aware, treatment, control[4]	4.4	7.8	16.5	24.2

1. Never told by a physician of having hypertension.
2. Told of having hypertension but no medication prescribed for it.
3. Told of having hypertension, now taking prescribed medication for it.
4. Told of having hypertension, now taking prescribed medication for it, and blood pressure is below the cutoff point in the definition of hypertension.

Source: Health Examination Survey, National Center for Health Statistics (Ref. No. 24 and unpublished data for 1971-72).

across age, race, sex, and geographic groups and even across most cause-of-death groups. (Only lung cancer and chronic obstructive pulmonary disease mortality are increasing.) This latter point of view leads one to look to common forces affecting everyone, perhaps forces that affect noncardiovascular diseases as well. These might be, for example, the increased availability of health care services, improved standards of living, advances in health care, and healthier lifestyles.

In 1979, the Surgeon General's national goal was "to improve the health of adults and, by 1990, to reduce deaths among people 25 to 64 years of age by at least 25 percent to fewer than 400 per 100,000."[25] As of 1980, progress towards the latter goal has been ahead of schedule, thanks primarily to the mortality decline for cardiovascular diseases. Projected at current rates of decline, cardiovascular mortality in 1990 can be well below its expected portion of the national rate of 400 deaths per 100,000 persons 25 to 64 years of age.

If the cardiovascular disease death rate of 1978 persists into the future in that the rate does not decline further, aging and increases in the U.S. population will mean that cardiovascular disease deaths will amount to nearly 1,180,000 by 1988. But if rates continue to decline at the rate observed between 1968 and 1978, fewer than 900,000 cardiovascular disease deaths will occur in 1988, with the most occurring by far among the elderly population.

Glossary

Age-adjusted death rate	A death rate that would exist if the age-specific rates of a particular year (or geographic area) prevailed in a population with an age distribution like that of a selected standard population. It is a summary figure that gives at a glance a comparison free of the effects of age differences, and of geographic, race, and sex differences.
Age-arranged death rate	The unweighted average of several age-specific death rates.
All-listed diagnosis	A diagnosis (explaining admission) that is listed anywhere on the face sheet of the hospital record, tabulated in the Hospital Discharge Survey.
Arteriosclerotic-related diseases	Clinical manifestations of the arteriosclerotic process: coronary heart disease, cerebrovascular disease, and other diseases of arteries. Perhaps 20 percent of the cerebrovascular diseases are not caused by arteriosclerosis.
Bed day	A bed-disability day when a person stays in bed for all or most of the day because of a specific illness or injury.
Cardiovascular disease	Includes heart diseases, cerebrovascular disease, rheumatic fever, other diseases of the arteries and veins, and (in some tabulations) congenital anomalies of the heart and circulatory system.
Case-fatality (rate)	The number of deaths among the number of cases of a disease, commonly expressed as a percentage. For heart attacks, deaths within 30 days of the attack are included in a case-fatality rate.
Comparability ratio	The factor applied to raise or lower a death rate from a particular cause so it will be more comparable (in terms of the time trend) to a death rate for that disease tabulated according to a different International Classification of Diseases revision.

Contributing cause of death	Diseases, injuries, conditions listed on a death certificate as apparently contributing to the death along with the underlying cause of death.
Disability	Any temporary or long-term reduction of a person's activity as a result of an acute or chronic condition.
Disability benefits (allowances)	Payments allowed under the Social Security disability insurance program to those who can no longer work due to a specific disease.
Disability day	A day of restricted activity, bed-disability, or work loss.
Economic impact	A measure of the annual effect on the U.S. economy in terms of dollars spent on care and related items attributed to a particular disease (direct costs) and lost productivity measured in wages lost due to illness or death from that disease in that year (indirect costs). Also called "economic costs."
First-listed diagnosis	The diagnosis (explaining admission) at discharge from a short-stay hospital that is listed first on the face sheet of the hospital record, tabulated in the Hospital Discharge Survey.
Heart (coronary) attack	An occurrence of clinical or subclinical manifestations of coronary heart disease other than of solely angina pectoris. That is, a myocardial infarction (overt or unrecognized), an episode of the coronary insufficiency syndrome, or a death from coronary heart disease--sudden or nonsudden.
Hospital discharge	Discharge of a hospital inpatient whether the discharge status is alive or dead.
Hypertension	Borderline hypertension: elevation of either the systolic blood pressure of at least 140 mm Hg or the diastolic blood pressure of at least 90 mm Hg or taking antihypertensive medication. Definite hypertension: systolic 160 or greater or diastolic 95 or greater or taking antihypertensive medication.

Incidence (rate)	The number of occurrences (new or recurrent) in a defined population, of a specified disease event during a specified period of time (usually one year), commonly expressed as a rate per 1,000 persons at risk in that population.
Infant death rate	Number of deaths under 1 year of age in a year divided by the number of live births in that year, expressed per 1,000 live births.
International Classification of Diseases	The coding system developed and revised about every 10 years by the World Health Organization to standardize nomenclature in disease terminology.
Life expectancy	The average remaining number of years of life that a person of a particular age is expected to live, calculated for a particular year by life table methods based on the age-specific death rates of that year. If no age is specified, "life expectancy" means life expectancy at birth.
Limited in activity	Limited or unable to work, keep house, or engage in school or preschool activities.
Morbidity	A measure of the presence or occurrence of illness in terms of prevalence, incidence, limitation of activity, hospitalizations, physician office visits, Social Security disability allowances, or disability days.
Mortality	A tabulation of death certificates by cause of death during (usually) a 1-year period, commonly expressed as a death rate per 100,000 population.
Peripheral vascular disease	Arteriosclerotic diseases other than coronary or cerebrovascular diseases.
Premature death	Death before an arbitrarily chosen age, such as 65, 75, or average life expectancy.
Prevalence (rate)	The estimated number of persons who have a particular disease at a particular point (or period) of time, commonly expressed as a rate per 1,000 persons in the population. Prevalence should be based on physical examinations, but it is often based on health interviews.

Restricted activity day	A day when a person reduces his or her usual activities for the whole of that day because of an illness or injury.
Silent myocardial infarction (MI)	An MI that is diagnosed only by an electrocardiogram (ECG). At the time of the event, the patient was asymptomatic, and neither the patient nor the doctor identified the event as an MI.
Standard error	A statistical measure of variability of an estimate due to sampling from a population, commonly expressed as a percent of the estimate (relative standard error), indicating the percent of error. Not included are errors in accuracy in measuring what the estimate is supposed to measure.
Sudden death	Death within 1 hour of onset of symptoms.
Underlying cause of death	The disease or injury that initiated the train of events leading directly to death, or the circumstances of the accident or violence that produced the fatal injury.
Unrecognized myocardial infarction	An MI that would be diagnosed only by an ECG when the patient was symptomatic but neither the patient nor the doctor recognized the episode as an MI.
Work-loss day	A day on which a person did not work at his or her job or business for at least one-half of the normal work-day because of a specific illness or injury.

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3. Arteriosclerosis

Contents

3. Arteriosclerosis

Arteriosclerosis, which is a synonym for hardening of the arteries, is a term used to describe a group of diseases affecting arteries in a particular way. Atherosclerosis is a specific type of arteriosclerosis that affects large arteries. It is the pathologic condition underlying most cases of coronary heart disease, aortic aneurysm, peripheral vascular disease, and stroke.

A decade ago, the gross and microscopic pathology of arteriosclerotic plaques were recognized to be remarkably varied and complex. Attention had shifted from morphology to the epidemiologic pathology of atherosclerosis and the correlations between lesions in different vascular beds. For studies of this type, there was a classification of lesions that simplified their characterization into fatty streaks, fibrous plaques, and complicated lesions. The valuable International Atherosclerosis Project (1968) had established that the average severity of atherosclerosis in many parts of the world differed widely and that in those places the differences correlated with mortality from ischemic heart disease. This project demonstrated that heart attacks occurred in all populations when coronary atherosclerosis reached approximately the same severity. At the same time, a wide range of severity about the mean was documented in relation to coronary heart disease. Among several other important results, it was found that the fatty streaks of childhood were equally prevalent and severe in both boys and girls and in all countries where they were studied. Fibrous plaques generally appeared first between ages 20 and 30 and in proportion to the prevalence of ischemic disease in the corresponding adult population. Sex differences were observed among whites in the northern hemisphere where males had more extensive coronary atherosclerosis, but both sexes had the same extent of aortic atherosclerosis. The study was able to draw only loose associations with most data on risk factors, environment, and lifestyles because these variables were not generally available for the subjects and had to be inferred from other circumstances.

Each plaque of atherosclerosis in humans can be studied only once under conditions of nature. Consequently, lesion pathogenesis has had to be inferred through the analogy of one kind of lesion to a similar but not identical one. The accepted view of the pathogenesis of human atherosclerotic lesions was that they were preferentially localized and slowly progressive, probably originating in childhood as well as in adult life and manifesting

the general pathological features of a tissue reaction to chronic injury. The differences in appearance among the lesions emphasized lipid content in some, fibrous tissue in others, and various complicating features such as necrosis, inflammation, thrombosis, or calcification in still others. Lesions of the same or different nature might lie on various vessels. Consequently, different pathogenetic pathways were considered likely, and two principal types were accepted, namely, a lipid-induced pathway of injury and repair reactions, and an encrusting thrombus injury and repair pathway with tissue organization. There were, however, many unresolved questions regarding initiation and localization; progression (episodic rather than continuous); origin of the lesion (a single or generic type that diversifies); and the arrest, progression, and regression, or healing. Moreover, while there were circumstances of disease and risk factors that clearly accelerated the pathogenesis of plaques, the plaques themselves appeared not to display any special pathologic features that could be associated with any particular etiology or injury.

Because of such considerations, there was a strong focus on attempts to understand the initial pathogenetic stages of atherosclerosis. In the United States, the emphasis was on lipid aberrations; in Western Europe, particularly in England, it was on thrombosis. There was comparatively little study of the early pathogenetic associations of smoking, hypertension, age, sex, or diabetes. Other correlates such as physical inactivity, obesity, uric acid level, and personality were rarely explored in studies of pathogenesis.

State of Knowledge in 1972

Lipid Accumulation and Lipoprotein Metabolism and Transport

It was generally recognized in 1972 that atheromata include proliferating cells and extracellular matrix materials in addition to lipid, but much more attention was being paid to lipid deposits. It was known that the arterial wall was metabolically active and that it could synthesize the lipids found in plaques, including phospholipids and cholesterol esters. However, its ability to synthesize free cholesterol was so low that the presence of plaque cholesterol could not be explained by in situ origin. Moreover, isotopic studies had shown that cholesterol could enter the intima from the blood. It had also been shown that plaque lipids, particularly triglycerides, phospholipids, and esterified cholesterol, decreased during regression, and there was active interest in the role of various lysosomal enzymes in these processes. Biochemical analysis of vascular tissues was commonly used to detect and quantitate atherogenesis.

By 1972, it was reasonably well established that the cholesterol accumulation in lesions, regarded from Virchow's time as the hallmark of the atheroma, was largely derived from the plasma: that is, endogenous synthesis played a minor role at best. The mechanism of lipid transport into the vessel wall, however, was not understood at all.

Understanding was emerging of the structural and metabolic interrelationships between lipids and lipoproteins and of their specific roles with respect to arteriosclerosis. In 1951, human serum lipoproteins that transport serum lipids were isolated and characterized by ultracentrifugation. It was discovered that elevated plasma levels of the so-called S_f 0-20 lipoproteins (for example, the low density lipoproteins) were associated with coronary heart disease. A role in atherogenesis for the other lipoprotein fractions was not clearly established. In 1966, scientists at the National Heart Institute proposed a classification scheme for the hyperlipoproteinemias, using Roman numerals I through V to identify the five main groups. Types II, III, and IV (but not I and V) appeared to be associated with premature atherosclerosis. This classification, coupled with the availability of paper or agarose electrophoresis of plasma, stimulated considerable interest in the hyperlipoproteinemias, their underlying causes, and their relationships to coronary heart disease.

This seminal work at the National Heart Institute reoriented thinking about plasma lipids to emphasize their "packaging" in rather well-defined groups of lipoproteins. It became clear that lipid transport needed to be understood in terms of how these various classes of lipoproteins were metabolized. Specifically, the entry of lipids into the artery wall might occur in the form of lipoprotein "packages." Intact lipoproteins had been observed in the subendothelial space, but there was little or no characterization of them or information about how they got there.

In the 1950's and 1960's, most efforts to characterize lipoproteins concerned isolation of the various lipoprotein classes, their lipid composition, and atherogenic potential. In the early 1970's, with new procedures and methodologies, study of the apoprotein structure of lipoproteins began. Very low density lipoprotein (VLDL) was known to contain apo B and several smaller apolipoproteins (now known as apo C-I, C-II, C-III, E), low density lipoprotein to contain primarily apo B, and high density lipoprotein predominantly apo A-I and apo A-II with minor amounts of the apo C's. Polymorphism was observed; cofactor roles of apo C-II for lipoprotein lipase and apo A-I for lecithin-cholesterol acyltransferase (LCAT) had been demonstrated. The functional roles of these proteins were not yet understood, particularly their cellular uptake and degradation by receptor-mediated mechanisms. Kinetic studies of apoprotein metabolism were just getting under way, particularly in humans. There was no clear

information about the relative importance of different tissues in lipoprotein uptake. The liver was recognized as the primary source of lipoproteins, and some work in biosynthesis using perfused livers and liver slices was available. Factors regulating plasma lipoprotein levels were poorly understood.

The relationship of diet to plasma lipid levels had been under active investigation for some time. Saturated fat caused serum cholesterol levels to rise when compared to isocaloric amounts of unsaturated fat in the diet. These observations were consistent with descriptive studies showing that in the countries where the populace had a high consumption of saturated fat, the levels of serum cholesterol were higher than in the countries where lower quantities of saturated fat and higher quantities of unsaturated fat were consumed.* These observations led to the recommendation that individuals who had high serum cholesterol reduce their intake of saturated fat and increase their intake of polyunsaturated fat. Concomitantly, reducing dietary cholesterol intake was recommended. Several studies demonstrated that human plasma LDL could be reduced by diets low in saturated fat and cholesterol, and that VLDL was influenced by diet, especially the carbohydrate component. However, precise understanding of the effects of diet and other factors on the levels of the lipoprotein fractions was absent. Moreover, the beneficial effects on vascular disease of diet-induced reductions of blood lipids were unproven.

By 1972, the importance of lipids and lipoproteins in CHD was generally accepted, but the atherogenic mechanisms of elevated plasma cholesterol (or LDL level) were little understood. Much basic information on the levels of cholesterol and the lipoproteins was lacking for the U.S. population. Studies had described the lipoprotein profiles of normal males and females of different age groups, the familial hyperlipoproteinemias, and other disease states. The Framingham Study and the Los Angeles Civil Service Study had provided data on larger populations, but few studies of the average or "normal" blood lipid and lipoprotein levels in large, epidemiologically defined, diverse population groups had been conducted, and the prevalence of the hyperlipoproteinemias in the United States was uncertain.

During the 1960's, methods of triglyceride measurement were sufficiently developed to allow clinical and epidemiological studies. In confirmation of earlier studies, this lipid also appeared to be a risk factor for CHD. Later, the measurement of

*"Serum cholesterol" is used throughout this section to indicate either serum or plasma cholesterol.

LDL and HDL and the application of multifactorial analysis indicated that triglyceride levels are not independently associated with CHD risk.

In the area of therapy for hyperlipidemia, several drugs were available, but their efficacy, safety, and therapeutic value were uncertain. Many trials of cholesterol-lowering by diet or drugs for the primary or secondary prevention of CHD had been conducted, and some had yielded encouraging results. Due to problems in design or in statistical procedures, none could be regarded as conclusively positive or negative. The MER-29 experience of the 1960's had sensitized researchers to assess hypocholesterolemic drugs for potential toxicity. Drugs in use in the late 1960's and early 1970's included: cholestyramine, a bile acid sequestrant; sitosterol, a natural sterol that blocked cholesterol absorption; the hormone d-thyroxine; sex hormones such as estradiol; clofibrate; and nicotinic acid.

The Coronary Drug Project (CDP) had been initiated in 1965 by the National Heart Institute as a randomized double-blind clinical trial to test the hypothesis that lowering blood cholesterol through the use of various drugs would reduce the incidence of heart attacks in individuals who had suffered a previous heart attack. By 1972, the use of estrogen and thyroxine in the study had been discontinued because of a suboptimal therapeutic ratio. The nicotinic acid and clofibrate groups were continued until 1975 when these drugs, too, were reported to be ineffective and not free of toxicity. Thus, in 1972, few hypocholesterolemic drugs were known to be effective, and it was unclear if lowering blood cholesterol was beneficial. Diet responsiveness had been recently quantified in the National Diet-Heart Study project, which concluded that it was feasible to conduct a satisfactory trial of the efficacy of blood lipid-lowering by dietary means in preventing CHD. By 1972, several new trials to test the effects of lipid-lowering by other means were under way or in the planning stage.

Accumulation of Cells

While cells had been recognized as a component of lesions, the 1971 Report of the Task Force on Arteriosclerosis offered a changing view of the cell types involved and a recognition that cellular accumulation was a major aspect of the pathogenesis of lesions. This development included speculation that cellular changes, rather than representing a response, might be an initiating event. In this regard, it was generally recognized that plaques develop in areas of preexisting fibromuscular thickening. The presence of similar patterns of fibromuscular thickening in human populations with differing propensities for plaque formation implied that the thickened intima might provide the ground for focal lesion development.

Other data in support of this viewpoint came from animal studies. There was a remarkable homogeneity among descriptions of the histologic response of arteries to trauma. This response involved proliferation of medial wall smooth muscle cells and their accumulation in a thickened intima. This model, however, was of less interest than the response of the vessel wall to lipid feeding. Smooth muscle cell replication in response to hyperlipidemia had been demonstrated by the use of tritiated thymidine in experimental animals. Here, too, smooth muscle cells had been recognized as a major component of the cellular accumulation in the intima of lipid-fed animals and of the cellular components of human lesions. While hematogenous cells, especially monocytes, also were thought to be present, cells derived from the vessel wall itself raised the issue of the role of abnormal cell growth as a component of lesion formation.

This new emphasis on the cells of the vessel wall was intimately related to studies of metabolic activities of the vessel wall. Studies with isolated smooth muscle cells demonstrated the ability of these cells to synthesize collagen and elastin. Studies of whole vessel wall, however, showed that vascular cells were not involved in de novo sterol synthesis. Isotopically labeled cholesterol had been used to demonstrate that all of the cholesterol in the lesion was derived from plasma lipoproteins. This demonstration implied that the major role of vessel wall cells in lipid accumulation was in lipoprotein transport across the endothelium and in accumulation of the lipid by the cells of the intima. A change in the fatty acid composition of cholesterol esters, however, implied that plaque cells were capable of esterification or reesterification of cholesterol derived from plasma lipids.

Relatively less was known about the role of cells other than the smooth muscle cells. It was assumed that loss of endothelial continuity led to thrombosis over advanced lesions, but direct evidence was lacking. Preliminary studies suggested that hyperlipidemia induced accelerated endothelial turnover. Cells other than smooth muscle cells, notably macrophages, were identified in lesions, but the relative proportions of the different cell types, their sources, and mechanisms of accumulation remained unexplored.

Connective Tissue and Atherogenesis

At all stages of vascular thickening, ranging from the mildest fibromusculoelastic intimal thickening to the most advanced complicated lesion, connective tissue was recognized to be increased in atherosclerotic plaques. Previously dependent on special stains of histologic sections, investigators were verifying the presence of elastin, collagen, and microfibrils by

electron microscopy. Although focal condensations of fibrous tissue, such as the "fibrous cap" of advanced lesions, could be appreciated, quantitation was a problem. Biochemical measurement of the different connective tissue components of lesions was in an early stage of development.

That the vascular smooth muscle cell could be responsible for the synthesis of connective tissue was clear from a variety of animal studies of experimentally produced damage to the wall and of the ensuing repair process. Circumstantial evidence implicated the smooth muscle cell as the major, if not the exclusive, cell type responsible for the fibrous repair. Studies of the normal growth of blood vessels increased the appreciation that the vascular smooth muscle cell is multifunctional. The cell was seen to differentiate to a fibroblast phenotype during intensive connective tissue synthetic activity.

The stimuli for connective tissue accumulation in atherosclerotic lesions were thought to be several: stimulation of connective tissue formation by extracellular lipid (comparison of the sclerogenic properties of fatty acids and various plaque lipid components had shown cholesterol esters, particularly oleate, to be most active); organization of hemorrhage or thrombosis in the plaque; and injury, whether through increased blood pressure or the action of other risk factors. In regard to the latter, the large international autopsy study discussed above did associate prior hypertension with the degree of fibrosis seen in lesions postmortem. The various mucopolysaccharide components of ground substance were also increased in atherosclerotic lesions. Detailed chemical evaluations were just under way. An interaction of lipoproteins with these components was proposed.

The limited work on regression indicated that the connective tissue component of plaques endured despite considerable decreases in the lipid components. This observation suggested that the fibrosis component might be irreversible. Pathological studies had previously suggested that sites of developing fibrosis might be more vulnerable to lipid deposition when the repair reaction and hyperlipidemia occurred concurrently. If fibrosis of an artery segment was induced first, however, the area seemed "protected" from subsequent lipid deposition induced by hyperlipidemia.

In general, evaluation of connective tissue by microscopy lacked quantitation, and even the state of morphometry was relatively crude. The explosive increase in knowledge and methodology of the biochemistry of connective tissue components was just being appreciated by workers in the field of atherosclerosis. For example, whereas an investing basement membrane was seen around vascular smooth muscle cells, the distinction a decade ago among the various collagen types did not have a strong

scientific foundation. Relatively little had been done to characterize and quantitate the mucopolysaccharides found in lesions and to relate them to the pathogenesis of plaques.

An interest in the early changes in plaque formation, the advent of the methods and findings of cellular biology, and the observation of the distinctive behavior of different kinds of cells in plaques were all leading at this time to an emphasis of research on pathogenesis at the individual cell level and to a deemphasis of the study of the plaque as a tissue or community of cells with complex interactions and complications.

The Thrombotic Process

Traditional pathological studies of humans have demonstrated that thrombus often encrusts atherosclerotic plaques, becomes organized by smooth muscle cells and endothelium from the intima on which it lies, and contributes to the bulk of the plaque. In vessels such as the coronary arteries, it may cause occlusion and may recanalize in the process of organization. These phenomena have been described repeatedly, and the process of thrombus accretion has been mimicked in artificial flow tube systems. It had been reported that minced thrombus injected into the pulmonary circulation of rabbits led to fibrofatty plaques in their pulmonary arteries and that diets rich in saturated fats promoted thrombotic tendencies in experimental animals. It was observed in Europe during World War II that heart attacks and other thrombotic disease had decreased in parallel and that subsequently both had increased. There was not a good quantitative understanding of the extent to which thrombosis contributes to the progression of atherosclerosis or of what precipitates either encrustation or occlusive events. Although it was known that fibrin could be detected in fatty streaks, platelets were not demonstrable. However, platelet antigens and fibrin had both been detected in fibrous plaques.

In human pathology, occasional examples of microscopic aggregations of platelets could be found on the arterial intima even in children. It was also speculated that these minute encrustations represented a factor in the initiation of atherogenesis that was propagated by the release from platelets of agents damaging to the endothelium and also by the release of agents favoring further platelet aggregation and activating the blood coagulation cascade. Flow studies in simulated vascular beds had shown that platelet encrustation occurred at sites that atherosclerotic plaques favored.

There were compelling reasons to investigate thrombosis in atherogenesis because of the long established role of thrombotic occlusion as a clinical event, its demonstrable role in the growth

of some plaques, and the question of its role from the beginning. It was apparent that the ab initio hypotheses were primarily concerned with platelet aggregation and release, classical thrombus encrustation, and the countervailing effect of the fibrinolytic system on thrombus formation. Most working hypotheses envisioned a platelet-thrombus system kept in balance by inhibitor and lytic mechanisms. The concept of hypercoagulability was offered as a functional state that might explain premature atherogenesis, arterial occlusion, or both.

In 1972, there was a sophisticated understanding of the blood protein coagulation cascade in vitro and its relationship to genetic hemophilias. Technical methods to handle platelets were available, and the elaborate properties of platelets, their metabolism, and their function were being studied more closely. In particular, the mechanisms of adhesion, aggregation, disaggregation, and release were being identified. It was known that agents such as adenosine diphosphate (ADP) caused platelet aggregation. Collagen had this property and clearly provided a basis for platelets to adhere to intima denuded of endothelium. The experimental technique of balloon denudation of the aortic endothelium in rabbits, with subsequent intimal proliferation, had been developed. Agents such as aspirin, antihistamines, anti-inflammatory drugs, theophylline, and prostaglandins were known to alter platelet membrane reactivity and release. Although this information was scant in 1972, it raised the question of antiplatelet drug therapy for the platelet aggregation aspect of thrombosis in atherogenesis, just as the identification of heparin and coumarin had raised earlier for the protein coagulation aspect of thrombosis.

Work on prostaglandins in relation to platelet aggregation and thrombosis had just begun by 1972. Prostaglandins had been shown to have both platelet-aggregating and platelet-disaggregating properties, and prostaglandin production by platelets had been shown to be inhibited by aspirin, a known inhibitor of platelet aggregation.

Unfortunately, exploration of the hypotheses available in 1972 was severely handicapped by several circumstances. Animals generally are more resistant to arterial thrombosis than are humans, and there was a lack of animal models suitable to study both atherogenesis and thrombosis. Only highly artificial systems were available. There was no knowledge of risk factors, like that for atherosclerosis, for susceptibility to thrombosis. It was uncertain which platelet or coagulation variables should be measured. Thrombosis was not an easily ascertainable endpoint.

In addition to the need for more basic information about the intimate complexities of platelet and coagulation behavior, there were issues directly related to atherogenesis and ischemic

disease. Among the unresolved issues a decade ago were such questions as: Can thrombotic phenomena initiate atherogenesis, or are such events always secondary? In either case, what are the precipitating mechanisms? Are there risk factors for arterial thrombosis? Can suitable animal models for thrombotic atherosclerosis be developed?

Risk Factors

In 1972, there were a number of well-documented risk factor associations with CHD. Cigarette smoking, elevated levels of blood cholesterol, and elevated blood pressure were known to be major risk factors for arteriosclerosis and its clinical manifestations. Several other factors were suspected of increasing risk, including diabetes mellitus, obesity, physical inactivity, and personality type. Although observed primarily in white males, most of these associations had also been identified in women. The 1971 Report of the Task Force on Arteriosclerosis listed 12 risk factors of major interest. The report noted that appreciable numbers of people suffered heart attacks in the absence of an excess of conventional risk factors and postulated that other risk associations remained to be found. It was not known whether risk estimates developed for the population of Framingham were applicable to other populations. The ability to predict future occurrence of CHD or stroke was limited in that the majority of high-risk individuals remained free of disease, and the majority of individuals with disease did not come from the segment of the population considered at high risk.

Risk factor data relating to atherosclerosis were much less common since they had to be obtained from autopsy or angiographic observations. Nevertheless, data suitable for univariate analysis, after stratification by age and sex, showed similar risk associations with severity of plaque for several of these factors. Some of the risk factors, such as age and sex, were innate. Some were diseases in their own right, such as diabetes, hypertension, and gout. Some were reflections of lifestyle, such as smoking and dietary hypercholesterolemia. A genetic influence was expressed through monogenic disorders such as homozygous hypercholesterolemia and suggested by family history data that showed excessive disease in first-degree relatives of heart attack cases.

In 1971, the Task Force on Arteriosclerosis recommended against a large-scale, open, primary prevention trial of dietary intervention and heart attack since such an undertaking was not then considered feasible. It did recommend intervention trials to reduce risk among subsets of high-risk populations. It also offered prudent lifestyle information to the public as an unproven but plausible preventive measure against atherosclerotic disease.

Lipids and Lipoproteins as Risk Factors

In 1972, it was clear from a host of epidemiologic studies that there was a strong association between levels of blood cholesterol and risk of heart attack. Case control studies had demonstrated high levels in CHD patients, prospective studies had established the graded risk of CHD as a function of cholesterol level, and cross-cultural studies had produced consistent results correlating cholesterol levels of different populations with the severity and extent of atherosclerosis and with clinical CHD. Less was known about the correlation between atherosclerosis and blood triglycerides.

As lipoprotein classes were characterized and simpler methods for determining them became available, more refined correlations were made. The clearest correlation was that between CHD and the beta-lipoprotein fraction. As early as the 1950's, the high levels of alpha-lipoproteins (now referred to as high density lipoprotein) in premenopausal women were found to be associated with a very low CHD risk. There were other data, including a prospective study, that showed an inverse correlation between high density lipoprotein and CHD risk. Emphasis on the beta-lipoprotein fraction, however, was so great that the full significance of these observations was overlooked. A low beta:alpha ratio was associated with low risk, but the importance of high alpha was not appreciated.

To move beyond correlations of data to proof of cause and effect, intervention trials were needed. Several first generation trials were completed by 1972. Three dietary intervention studies yielded positive results, but each was flawed in some way. The Medical Research Council study yielded negative findings.

There was consensus that Americans as a group maintained too high a level of blood cholesterol. There was no consensus, however, on what public health measures were appropriate. All agreed that extensive hyperlipidemia should be treated as a significant risk factor.

With some of the major risk factors for arteriosclerosis identified, the way was open for programs that attempted to modify these factors in the hope of reducing morbidity and mortality from this disease. The 1971 task force recommended a series of clinical trials in several areas such as: continuation of the Coronary Drug Project, expansion of the Lipid Research Clinics (LRC) program, and initiation of a clinical trial to intervene on several risk factors simultaneously in order to decrease morbidity and mortality from the complications of arteriosclerosis.

Other issues of general interest in 1972 included questions such as: Is hypertriglyceridemia a risk factor for heart attack

or atherogenesis? What are the mechanisms linking the plasma lipoproteins to the atherogenic process? In other words, how is the "risk factor" linked to the "risk"? Does intervention that lowers cholesterol levels lower risk?

Since elevated serum cholesterol or LDL was associated with enhanced atherogenesis, it was natural to consider whether lowering serum cholesterol--by diet, by drugs acting on the cholesterol synthetic pathway, by drugs known empirically to be hypocholesterolemic, or by drugs or by surgical operations to prevent cholesterol absorption--might prevent atherosclerotic disease or cause it to regress. Such diets, drugs, and procedures were known. They formed the basis for feasibility studies of clinical trials and for experimental therapy, and they were to become the basis for clinical intervention trials, some of which are still ongoing.

Such regimens were also tested in animals. Regression of the lipid component of experimental cholesterol atherosclerosis had been demonstrated in nonhuman primates, but it was difficult to know how the artificially hypercholesterolemic animal model should be compared with humans. More complex and interpretable animal experiments remained for the future. Studies of the effects of these regimens on the metabolism, structure, or function of the plaque in progression or regression were not available.

Hypertension and Atherogenesis

In 1970, hypertension was clearly established as a major risk factor for heart attack, stroke, cardiac and renal failure, and retinal damage. Both actuarial and prospective epidemiological studies left no doubt that there was a continuously decreasing gradient of risk, even to levels of pressure below the normal range. Study of human atherosclerosis at autopsy showed that patients with history or anatomical evidence of hypertension had more advanced and more diffuse atherosclerosis.

There were animal models of hypertension including renal ischemic injury, aortic coarctation, adrenal regeneration, and genetic salt-sensitivity types. In these models, thickening of the aortic wall and coronary arteries was seen with hypertension, but the relation of hypertension to the atherogenesis was not clear. The limited amount of research that had been done usually employed rats or dogs, species in which atherosclerosis is not typical or easily induced. Only in a few rabbit and nonhuman primate experiments had dietary atherogenesis and hypertension been studied together. The work was scant, but enhancement of aortic atherogenesis was seen in the hyperlipidemic animals when hypertension was present. There were limited data suggesting that lipids entered the arterial intima at an increased rate in the

presence of hypertension, perhaps due to stretching of the endothelial lining. Very little was known, however, about the physiologic basis of transport into the vessel wall. Atherosclerotic changes in large arteries due to hypertension alone were not reported. Despite the importance of hypertension as a risk factor, its influence on atherogenesis was not an active field of research.

Smoking and Atherogenesis

Smoking had been identified as a risk factor for heart attack in the 1964 Report of the Surgeon General. Another report in 1971 amplified the association. There were extensive data for men but not for women. Risk was demonstrable for fatal and nonfatal heart attack, including sudden death. Although no clear relationship with the incidence of angina was demonstrable, it was known that angina was more easily induced among angina patients when they smoked. Cessation of smoking was known to be associated with a reversal of CHD risk toward that of the nonsmoker. Arteriosclerotic aortic aneurysm and the intermittent claudication of peripheral vascular arteriosclerosis were known to be increased among smokers. Autopsy studies had more recently found that atherosclerosis of the coronary arteries and aorta was more severe among smokers than nonsmokers. Whole smoke is a very complex mixture of substances, and the pathogenetic mechanisms by which cigarette smoke might enhance atherogenesis were obscure. Two studies in experimental animals, one in rabbits and another in squirrel monkeys, had reported an enhancement of cholesterol atherogenesis by exposure to carbon monoxide. It was also thought that nicotine leads to catecholamine release and thus might influence free fatty acid metabolism or enhance platelet adhesion and hence atherogenesis. Several experiments in which nicotine was given by injection or by mouth, however, yielded a variety of findings that were not conclusive. There were no animal models available to test the effect on atherogenesis of the inhalation of whole smoke in the absence of major stress.

Diabetes Mellitus and Atherosclerosis

Diabetes has long been recognized by epidemiologists as a powerful risk factor for atherosclerotic disease in the Western world. It was known in 1972 that in those subcontinents and countries in which clinically manifest atherosclerosis is uncommon, such as the Middle East, North Africa, and Japan, diabetes per se does not produce clinically significant atherosclerosis. It is a risk factor for both men and women, increasing risk for CHD about three times for men and six times for women, and it is an even stronger risk factor for peripheral vascular disease, gangrene, and stroke. Autopsy studies in the West had

demonstrated that diabetes was accompanied by more severe atherosclerosis. There was a general consensus that the plaques of atherosclerosis in the diabetic were not qualitatively remarkable. There was uncertainty whether there was a microangiopathy of the heart (as in the retina or kidneys) that might also contribute to CHD by increasing liability to heart attack, case fatality, sudden death, and congestive failure. A similar uncertainty existed regarding the role of microangiopathy of the lower limb as a contributor to gangrene in diabetic arteriosclerosis obliterans and its often slow proximal progressive clinical course.

The mechanism by which diabetes affected atherogenesis and clinical cardiovascular disease was not known. A variety of well-characterized animal models of diabetes was needed to investigate basic cellular and tissue phenomena in atherogenesis, thrombosis, and lipid metabolism as affected by the diabetic state. The literature on experimental diabetes as a pathogenetic factor in atherogenesis, however, was both sparse and unsatisfactory.

In diabetic humans, the question of synergism of microvascular disease with macrovascular disease in the occurrence of myocardial ischemia, stroke, and peripheral vascular disease required further multidisciplinary study. The identification of those factors in Western society that are associated with the promotion of atherogenesis by the diabetic state was greatly needed. The means by which diabetes abolishes the relative immunity to coronary atherosclerosis of the white female in Western society was obscure. The questions were unanswered whether such events as stroke, congestive heart failure, or sudden cardiac death were to be attributed solely to vascular disease or to some other component of the diabetic state. The statistical analysis of a major clinical trial finding that certain therapies did not lessen but rather might increase liability to cardiovascular disease among diabetics who had previously had a heart attack was a subject of vigorous controversy. The effects of diabetes on lipoprotein and apoprotein metabolism needed investigation.

Overall, although diabetes was well-known for its ability to affect atherogenesis, study of the details of atherogenesis in diabetes was not an active field.

Obesity and Atherogenesis

In 1972, obesity was known in both actuarial and prospective cohort data as a factor associated with increased all-cause mortality and cardiovascular mortality. Its relationship, however, was a matter of debate; for if other associations of diabetes and hypertension were considered, obesity became only a

weak correlate of CHD incidence. Metabolic studies focused on energy balance, insulin, glucose metabolism, and the induction of obesity in infancy as a reflection of fat cell hyperplasia. It was known that persons who gained weight increased their serum triglyceride levels and that cholesterol turnover was altered among obese patients. Loss of weight was known to reduce hypertriglyceridemia and blood pressure. Animal research offered some genetic models in rodents and some hypothalamic-lesioned hyperphagic models in several species. Simple dietary energy-balance obesity, however, is difficult to induce in laboratory animals, and there was little research on models that simulated the human condition. The investigation of obesity in relation to experimental atherogenesis was not active, and many questions remained.

Physical Inactivity and Atherogenesis

By 1972, several epidemiological studies had reported lesser morbidity and mortality among persons who were physically active compared to persons who were sedentary. About an equal number of studies did not find such results. It was speculated that if an association of inactivity with CHD does occur, it must either be strong or be counteracted only at very high levels of activity. Physical activity was regarded as being difficult to measure. In addition, its standards might differ among persons, and many other variables could confound the interpretation of such studies. Data from autopsies failed to show any association between severity of coronary atherosclerosis and history of physical activity. Some animal studies had been attempted in which animals closely confined to cages and fed cholesterol were compared to animals that exercised on motorized treadmills or similar devices. The experimental designs and interpretations can be criticized for a number of reasons, and the experiments were generally regarded as unsatisfactory from the viewpoint of atherogenesis. Exercise conditioning was known to be associated with a number of changes in risk factors, such as lower body weight, lower blood pressure, lower VLDL and triglycerides, and increased fibrinolysin activity. Clinical trials of the prevention of recurrent heart attack by regimens of exercise were in progress.

Genetics and Atherogenesis

Genetic constitution has long been known to be a component in the development of atherosclerotic disease. The mechanisms and the force of genetic expression in the current U.S. environment and lifestyle have been issues of concern.

In 1972, the role of genetics was addressed by three sets of human data. The first was family aggregation data that found that

first-degree relatives of coronary artery index cases were themselves at several-fold increased risk (two to seven times in one report) compared to the general population. Such data suggest either an environmental or a genetic relationship but do not lead conclusively to either.

From a second set of data (twin studies), concordance rates were found to be higher among monozygotic twins than among dizygotic ones for hypertension and stroke but not for myocardial infarction.

A third set of data related to risk factors themselves. Studies indicated genetic expression in hypertension and diabetes. Simple Mendelian inheritance was recognized in familial hypercholesterolemia and other forms of hyperlipidemia. Epidemiological data that indicated unusual CHD susceptibility of some patients in the absence of conventional risk factors implied a role either for genetics or for unknown risk factors. Equally compelling were similar data that many individuals with heavy burdens of risk factors did not suffer a CHD event, indicating either a genetic constitutional resistance to atherogenesis or the presence of unknown protective "risk" factors.

There were no autopsy data on atherosclerosis suitable for genetic analysis. It was known that both heterozygous and especially homozygous Type II familial hypercholesterolemia is accompanied by severe premature atherosclerosis. The individual plaques, although fatty, are not qualitatively unusual.

In animal research, comparative studies of experimental atherosclerosis clearly indicated strong genetic influences. Species differ markedly in susceptibility, and it was known that within species some strains differ. Most of the information was obtained from pigeons. It was known that strains differed in susceptibility to both spontaneous and dietary cholesterol-induced atherosclerosis. Moreover, it was possible within a strain to breed those that developed hypercholesterolemia of marked or minimal degree on the same dietary intake of cholesterol. No inbred or purebred animals, however, were commercially available for use in research on atherogenesis, such as the commonly available rodents used in cancer research. The response of experimental animals showed much biological variation, and experiments generally required large sample sizes.

Since experience with humans indicated both monogenic and polygenic influences on risk factors and unknown but probably polygenic influences at the level of the vessel wall, genetic studies of all but the simple one-gene or two-gene effects would be complex. It was held likely that an understanding of the mechanism of expression of the simpler disorders would enhance the understanding of the various factors that enter into atherogenesis

and would help identify and characterize its mechanisms. Since the mechanisms of the monogenic effects were unknown, it was recommended that such studies be pursued.

Psychosocial Factors and Atherogenesis

In 1972, evidence suggested that psychosocial factors might increase the risk of heart attack and perhaps other atherosclerotic diseases by elevating other common risk factors, by inducing some independent pathogenetic mechanism, or by affecting a patient's acceptance of health-promoting or medical advice. It was accepted that levels of blood cholesterol, blood pressure, and physical activity, and cigarette smoking, obesity, and dietary consumption of fats all have behavioral components. Blood pressure, for example, increases during periods of anxiety and correlates with measures of unusual social mobility and cultural displacement. The concept of acute psychosocial stress as a precipitating factor in heart attack and sudden death, however, was different from that of chronic atherogenesis and its clinical sequelae.

An association between a coronary-prone behavior pattern and CHD risk was reported as early as 1959. By 1970, substantial prospective data were available indicating a twofold increased liability to CHD in persons classified as having competitive, aggressive, impatient personalities (type A). This association was independent of other conventional risk factors, and while there was controversy about the validity of techniques of assessment, type A behavior was gaining acceptance as a CHD risk factor. Insufficient data were available on similar associations of behavior profiles with stroke and with peripheral vascular disease.

No data existed that confirmed the relation of behavioral factors to atherogenesis per se. Human vessels studied at autopsy were either sampled inadequately or were not correlated with psychosocial data. Animal studies of atherogenesis in relation to spontaneous or induced behavioral change were in an early stage. The field had many unresolved problems, and among them were questions of conceptualization and measurement of the independent variables.

Multiple Risk Factors and Atherogenesis

Epidemiological data clearly showed a synergism of risk factors such that their combined effect on risk was greater than their simple sum. Autopsy data, limited in nature, tended to confirm that atherogenesis was more severe in the presence of known or inferred multiple risk factors, although qualitative

differences in plaques were not apparent. Animal research was limited to studies using combinations of diet, hypertension, and diabetes. Very few studies suggested the existence of sex differences in the response of cholesterol-fed animals. Hormonal effects on cholesterol metabolism were reported. The effect of very young age contrasted with old age of animals had been studied only very rarely. For convenience, almost all experiments were conducted on young adult animals. A few studies of the effect of hypertension on cholesterol-induced atherogenesis showed synergism of risk, and it was accepted that hydrodynamic stresses, of which hypertension was a special class, could localize plaques, enhance atherogenesis, or even act from the beginning. Such data were not extensive.

Clinical Sequelae

In 1972, a major unresolved problem was the prognostic significance of coronary artery plaques or atherosclerosis of other vessels as seen on angiography or at autopsy. Studies of autopsy material had defined, in a broad sense, the association between the location, severity, and kind of vascular lesions found in those dying with old and recent myocardial infarction, stroke, or ischemic limbs. Generally, it was a picture of severe, occlusive, multiple vessel disease although it was common to find an appreciable amount of scatter above and below the average findings and to see equally severe atherosclerotic lesions in patients dying of other causes. Limited amounts of clinically developed angiographic data indicated that in patients with angina pectoris, the prognosis for avoiding future heart attack was good unless there was occlusive disease in more than one major coronary artery.

Available data indicated generally that the severity of the lesions corresponded to the prognosis, but this association lacked specificity and offered little information about the quality of lesions as distinct from their severity. The prevalence of dangerous lesions of the coronary or other arteries in Americans of different age groups was not known, although the data of the International Atherosclerosis Project provided some insights into this question. Risk factors for the acute conversion of dangerous plaques to plaques precipitating clinically manifest ischemic disease were not identified except for a few particular clinical disorders. Since animal experiments in atherogenesis were seldom carried to the point of ischemic complication, there were no findings relevant to plaques. At the same time, animal experiments had provided much data about the relation of artificial arterial stenosis or intraluminal occlusion (generally acute) to the precipitation of ischemic events.

Spasm

Appreciation of the contractile function of large blood vessels susceptible to atherosclerosis dates back to early observations of spontaneous vasomotion of major muscular arteries. Little attention was given to the contribution of active contraction to pathogenesis or to complication of lesions. Proposals that spasm contributes to clinical symptoms did not involve questions of the relationship of sites of spasm to preexistent atherosclerotic disease. Virtually no effort was directed to the study of the relationship of contractile properties of cells to their other activities in the pathogenesis of atherosclerosis. The only vascular systems in which spasm was proposed as a complicating feature of the sudden-occlusion component of atherogenesis was the pulmonary circulation, in which reflex vasoconstriction was proposed by some workers to occur following embolization of a segmental vessel and in the cerebral circulation at sites of hemorrhage or embolism. One study did show that stimulating the aortic smooth muscle to contract had only a small effect on aortic conductance. Studies pertinent to other large vessels involved in clinical syndromes did not exist except for a considerable amount of information about the capability of even large cerebral vessels, under the stress of severe hypertension, to reduce their caliber appreciably.

Progression and Regression of Atherosclerosis

The rate at which lesions progress had been considered to be highly variable. This conclusion was usually based on clinical manifestations. Little was known about the real rate of progression at the tissue level in human disease. At various times, roles had been proposed for sudden hemorrhage, thrombosis, and evacuation of plaque components as complicating events, but the temporal relation of any of these to rate of progression was unclear. It was traditional knowledge that necrosis, development of a gruel-like center, and calcification become prominent as the mass of the lesion increases, but the influence of these alterations on progression of plaque size, in a causal sense, was not known.

Whether lesion progression was best thought of as a repetitive expression of the basic process of atherogenesis, whether another set of events was responsible, or whether a combination of old and new components was involved was not resolved.

Similarly, regression was not understood. It could be thought of either as a simple reversal of all components and steps responsible for progression, or as a healing in some other fashion. The insusceptibility of various plaque components to regression was addressed in a limited amount of work on regression

of lesions in experimental animals. The possibility that necrosis could even be a salutary event with respect to decreased plaque mass was suggested by certain electron microscopic observations of nonhuman primate lesions. Nevertheless, the documentation and quantification of this component and of most components in regression were lacking.

Thrombosis as Precipitating Factor in Clinical Events

It was speculated that platelets could aggregate in small numbers on the intima or in the bloodstream and that because of their known ability to disaggregate before release of platelet contents, such aggregations might be evanescent. This temporary aggregation was offered as a mechanism for microvascular occlusion, myocardial ischemia, and induction of arrhythmias without gross thrombus. The frequent presence of microthrombi and emboli in the coronary vasculature was associated with sudden coronary death. Such events were demonstrated in swine by the introduction of adenosine diphosphate into the coronary circulation. Gross thrombosis of coronary arteries was also associated with sudden death in about one-third of the human cases.

Data from autopsies continued to accumulate on the frequency of thrombosis in cases of established infarction. Little attention, however, was given to classifying infarcts in relation to the frequency or location of thrombi. At this time, scattered reports were appearing to suggest that thrombi were secondary to infarcts. This opinion was in marked contrast to the classically held view that thrombi cause infarcts.

Thrombosis and vasospasm were not thought to be closely associated events, even though earlier investigators had suggested that intramural hemorrhage, which is also associated with the induction of thrombosis, can induce vasospasm.

Diagnosis and Treatment of Atherosclerosis

In 1972, the diagnosis of arteriosclerosis rested primarily on medical history, physical examination, and contrast arteriography. Because of the lack of sensitivity of the clinical examination, most patients' symptoms were detected only after the atherosclerotic lesion had reached an advanced stage, with significant encroachment on the arterial lumen (greater than 50 percent reduction in diameter). In coronary artery disease, electrocardiography was the principal noninvasive method to establish the diagnosis of advanced CHD. In cerebrovascular disease, indirect noninvasive diagnostic techniques were being developed, including periorbital Doppler ultrasound and ocular plethysmography. In peripheral arterial occlusive disease, noninvasive techniques

included Doppler ultrasound and plethysmography to define abnormal pulse waveforms, segmental limb blood pressures, and other techniques that could measure limb blood flow in the presence of advanced arterial disease. Preliminary work had been reported on the use of B-mode ultrasound imaging and Doppler ultrasonic arteriography, particularly in cerebrovascular diseases. The techniques, however, were relatively primitive, and the resolution of their imaging systems was poor. Intravenous angiography had been largely abandoned because of poor contrast in the visualized arterial segments.

The therapy of symptomatic arteriosclerosis in the coronary, cerebrovascular, or peripheral arterial beds involved bypass of the diseased segments or endarterectomy. Arterial prostheses had been developed for the larger arteries, including the aorta and iliac arteries. Most prostheses were either knitted or woven Dacron® or Teflon®, which were suitable mainly for large arteries with high flow. These prostheses proved unsatisfactory in operations distal to the knee. In such circumstances, autogenous vein grafts proved most useful for femoropopliteal or tibial artery reconstruction as well as for coronary artery bypass surgery.

Program Goals Through 1982

Goals established by the Institute in 1972 included:

- Obtain a better understanding of the basic processes of arteriosclerosis, and improve the prevention, diagnosis, and treatment of the process and its sequelae.

- Stimulate the development of sensitive, noninvasive, convenient, and safe diagnostic techniques that can be used to determine arteriosclerotic changes in vessels.

- Define those circumstances that may promote the prevention of arteriosclerosis.

- Establish colonies of suitable animal models, especially nonhuman primates with arteriosclerotic disease, for use in arteriosclerosis research.

Additional goals developed in 1977 included:

- Gain a better understanding of the pathogenetic mechanisms in arteriosclerosis.

- Specify further associated or causal disturbances and associated risk factors for arteriosclerosis.

- Define those circumstances that may promote the regression and/or prevention of arteriosclerosis.

- Develop information on behaviors that promote or inhibit the application of knowledge of the prevention, diagnosis, and treatment of arteriosclerosis.

Research activities in the service of these goals included:

- Expansion of knowledge of the cellular mechanisms of atherogenesis.

- Increased involvement of investigators from the fields of blood coagulation, blood platelet research, and thrombosis to elucidate the effects of platelets and of normal and abnormal plasma constituents on atherogenesis.

- Extension to childhood of pathogenetic studies of antecedents of risk factors.

- Further development of understanding the importance of diet and nutrition in atherosclerosis and its control.

- Development and implementation of a bioassay of cardiovascular disease-inducing ability of less hazardous cigarettes (in collaboration with the Smoking and Health Program of the National Cancer Institute), and investigation of why smoking promotes atherosclerosis.

- Research on diabetes mellitus as a risk factor for, and an important participant in, many aspects and mechanisms of cardiovascular disease.

- Continued multigenerational, longitudinal, and epidemiological studies in the Framingham and other cohorts.

- Promotion of research on the role of local and humoral substances--prostacyclin, prostaglandins, thromboxane, and other prostaglandin stimulators and inhibitors--on vessel reactivity, smooth muscle cell proliferation, and the atherosclerotic process.

- Continued research on the genetics of hyperlipidemia and of other risk factors and their potential role in CHD prevention. This was to include research on the possible monoclonal origin of arteriosclerosis.

- Exploration of the role of intimal smooth muscle cells and platelets in atherogenesis.

- Continued utilization of the nonhuman primate resources developed for research in arteriosclerosis, cerebrovascular disease, and hypertension.

- Search for additional risk factors to elucidate additional causes of premature CHD and other atherosclerotic complications.

Accomplishments Through 1982

Atherogenesis

During the past decade, the progress made in the understanding of atherogenesis is in its factual content and also in the change in concepts concerning the biomedical nature of the disorder. During the 1960's, the risk-factor associations of ischemic disease secondary to atherosclerosis were emphasized, and they led to the multicenter risk-factor intervention trials of the 1970's. Fundamental metabolic mechanisms, lipoprotein structure and function, the thrombotic process, and the reactions of the cells of the arterial wall in atherogenesis were all subjects of active research, but they were overshadowed by interest in risk-factor data that were of great and obvious importance to public health. During the past decade, however, rapid progress in cellular biology has been made in fundamental studies of lipoprotein structure and function, lipid metabolism, and thrombosis, and of their relationship to atherogenesis. In many ways, the 1970's have been the decade of lipoprotein and cellular biology research. One can speculate whether elucidation of basic processes will now lead to a decade of cellular and molecular biology in which research on the fundamental phenomena of atherogenesis will again be evaluated in the whole human and animal organisms.

The LDL Receptor

Cholesterol is essential for cell structure and life. But how do cells get cholesterol from the fluid that surrounds them, and how is the amount in the fluid regulated? The discovery of the existence on the exterior membranes of cells of receptors for LDL has done much to resolve these questions, and it has led to research on related questions about other lipoproteins, about modified lipoproteins, and about the development of intracellular accumulations of fat in atherosclerotic plaques.

Basic research in the 1960's had described how certain cells might have highly specific receptors for certain biologically

active substances (for example, hormones) that allow the cells to receive and respond to them. Against this background, the question of the existence of receptors for LDL was examined in normal patients and in patients with the monogenic defect of homozygous or heterozygous familial hypercholesterolemia. This disorder is associated with exceptionally high levels of circulating LDL-cholesterol, with the highest level occurring in the homozygous state.

With cell cultures of human fibroblasts as the test system, it was found that normal cells have numerous receptors specific for LDL, that cells from homozygotes have very few such receptors, and that cells from heterozygotes have an intermediate number of such receptors. This fundamental observation has improved the understanding of the metabolism of cholesterol, lipoproteins, and apoproteins and has led to a strong appreciation of the possible roles of various cell membrane receptors and of receptor pathophysiology in atherogenesis.

In the past 10 years, it has been learned that cells from many tissues in the body, including those of the artery wall and of organs such as the adrenal gland that have a specialized sterol hormone metabolism, possess receptors that have a high affinity to bind LDL. The lipoprotein is then internalized into the cell, and its protein portion is degraded. The cholesterol portion is freed of fatty acid and then esterified again for storage and use in the cell. The process also has the effects of decreasing the cell's own biosynthetic pathways for making new cholesterol from simple molecules and of decreasing the formation of new membrane receptors for LDL. Through these feedback mechanisms, the cell is thus in control of its cholesterol metabolism.

The finding has fundamental importance for understanding the cellular metabolic economy of the basic building block, cholesterol. It also makes it possible to understand a very important step in the maintenance of levels of circulating LDL cholesterol, the most atherogenic form of lipoprotein. It is now known that about one-half of the degradation or disposal of LDL that occurs in the body occurs in extrahepatic peripheral tissues through this receptor mechanism.

The receptor mechanisms and related phenomena control intracellular cholesterol metabolism so well that excess cholesterol does not accumulate in the cell; yet it is the lipid-laden smooth muscle cells and macrophages that are a hallmark of atherogenesis. Consequently, research has now focused on receptor-mediated processes in which particular alterations in the lipoprotein structure, in the receptor mechanisms, or in both may account for excessive intracellular lipid accumulation and the development of characteristic foam cells.

This research has contributed both factually and conceptually, at a very basic level, to a better understanding of lipoprotein homeostasis and of the pathogenesis of atherosclerosis. Such findings should lead to clinical investigation and application in the next decade. They now allow for classification of certain clinical hyperlipidemic disorders as genetic defects in numbers or properties of receptors. In the future, it may be possible to affect directly or to manipulate the receptors for therapeutic purposes. Basic studies to explore this possibility have just begun.

Growth Factor From Platelets

Atherosclerotic plaques have bulk and occupy space in the vessel wall. Part of this bulk is made up of a large number of cells. The cells increase in numbers by dividing and perhaps also by migration into the plaque from adjacent vessel wall tissue. Until recently, it was not known what the stimulus for cell proliferation was, and a vague nonspecific inflammatory injury-repair reaction was assumed.

A major understanding was gained when experiments disclosed that cultures of smooth muscle cells multiply much more actively if the culture medium contains blood platelets or platelet products. These observations were expanded from cell culture to animal experiments in which it was shown that arterial endothelial denudation in the presence of circulating platelets resulted in smooth muscle cell proliferation at the sites of endothelial loss and in the development of cell-rich, plaque-like lesions. If platelets were inhibited from acting, however, such proliferation was minimized. Subsequent research has identified the platelet factor as a polypeptide. The factor also affects other cells from the vessel wall. Additional growth factors and growth modulators have been identified. Thus, the basic outline of chemical systems for stimulating the cellularity of plaques has been identified.

These findings have had a major effect on concepts of atherogenesis. The recognition that a platelet-derived growth factor can stimulate cells in the arterial intima to heap up like a plaque provided strong support for the idea that endothelial injury followed by platelet adherence and release can initiate atherogenesis. This idea led to the concept of atherogenesis as a platelet-mediated injury-repair reaction. It has gained much acceptance as an important, but not necessarily exclusive, pathogenetic pathway, the other major concept being that of reaction to lipid accumulation. This concept is somewhat different from the older view that thrombi deposited on the intima can be incorporated by healing processes to yield a fibrous plaque on the vessel lining. The two concepts are not mutually exclusive, but the platelet concept is a promising hypothesis for the initiation of

plaques; according to the hypothesis, recurrent episodes of platelet adherence would contribute to plaque enlargement after initiation.

A further result of this research has been a rekindling of interest in the possibility that atherosclerosis might be inhibited by drugs that block the stimulating effect of growth factors on the vessel wall. This concept is in addition to the earlier one that was directed to the prevention of occlusive or mural thrombosis in the presence of preexisting atherosclerosis. Since the cells that multiply also have the capacity to elaborate collagen, elastin, and proteoglycans, and since they can accumulate lipid, it is clear that they can contribute to the bulk of plaques beyond their mere numbers.

This basic research, which has been performed in cell cultures and experimental animals, has utilized principles of cellular biology and protein chemistry. Direct confirmation in humans has not yet been attained.

Collagen and Atherogenesis

Plaques of atherosclerotic tissue harden the arteries because they form a large amount of scar-like connective tissue composed of collagen, elastin, and proteoglycans. These substances are formed chiefly by the smooth muscle cells that proliferate within the plaque and by the endothelial cells on its surface. In some plaques, the connective tissues make up less than one-half of the composition of the lesion; in others, they contribute more, and in still others, they constitute almost the entire bulk of the lesion.

During the past decade, rapid progress has been made in arterial connective tissue biochemistry. From cell cultures, it has been learned that endothelial cells can produce three different types of collagens, heparan sulfate, and elastin, as well as some other substances. Smooth muscle cells also produce three collagens (one of which is different from the products of endothelium), some heparan sulfate, and chondroitin sulfate. From preliminary observations that compare the composition of plaques with the composition of normal artery, it has been found that the proportions of the various connective tissues change so that heparan sulfate and chondroitin sulfate are disproportionately increased in plaques, as are type I and type III collagens. This change in the profile of cell secretory products in the plaque indicates a shift in cell metabolism and implies an altered environmental stimulus.

Connective tissue is important in atherogenesis for several reasons. Bulk is one. Another is that when endothelium is

denuded, collagen provides a potent stimulus for platelet adherence and thrombosis. A third consideration is that these connective tissue proteins interact with endothelial cells to form the basis for endothelial cell adherence or attachment to the artery wall. A fourth consideration is that the tissue may act to trap lipids, and such substances as the proteoglycans may actually complex with lipoproteins such as LDL. The connective tissue proteins may also modulate local cell growth, and protein fragments may be chemotactic toward smooth muscle and other cells. Lastly, since collagen is slow to undergo metabolic turnover after it is formed and since it tends to mature and stabilize with cross-linkages to become scar-like, it has a high degree of permanence. Studies of the regression of plaques that are induced in animals by a cholesterol-rich diet indicate that the fatty components of plaques can largely disappear but that the collagen portions are slow to change and may increase under some experimental conditions.

Platelet Aggregation and Prostaglandins

The theory that thrombosis plays a role in atherogenesis as well as in arterial occlusion existed in the past century. The more modern expression of the notion--the Duguid-Rokitansky theory--was based on the idea that the organization of thrombus deposited on the vessel wall makes a fibrous plaque. This theory is widely supported as a mechanism that contributes to the progression of a plaque, but it has not been widely accepted as a means of initiating plaques. The latter viewpoint, however, has been strengthened greatly by the recent discovery (discussed above) that platelets contain a mitogenic or growth factor that stimulates vascular smooth muscle cells to proliferate to form plaque-like lesions. Results of recent research related to local hormones (called prostaglandins) that affect the interactions between platelets and the vessel wall have emphasized the importance of the interplay of atherogenesis and platelet aggregation (platelet thrombi).

From research related to other matters, it was discovered in 1975 that blood platelets produce and release a substance called thromboxane A_2. The substance is a short-lived but potent agent that causes platelets to aggregate, and it is also a vasoconstrictor. In 1976, a related substance called prostacyclin was found to be a product of the vessel wall. It inhibits platelet aggregation and is a vasodilator. It is the most powerful antiaggregant substance known. It, too, has a short half-life. These two opposing substances suggest a concept of local homeostasis in the interaction of platelets and the vessel wall and also a new concept of the processes of atherogenesis and thrombosis.

It has been determined that both substances derive from arachidonic acid acted upon by cyclooxygenase. Thromboxane synthetase then forms thromboxane A_2 (TxA_2) in the platelet while prostacyclin synthetase forms prostacyclin (PGI_2) in the vessel wall, with about 40 percent being formed by the endothelium. Certain drugs such as aspirin inhibit formation of both substances by blocking cyclooxygenase. Although there is a tendency for low doses of aspirin to inhibit the thromboxane pathway more, it is now known that as little as 40 mg of aspirin every second day will provide 70 percent inhibition of PGI_2 in a few days so that both proaggregation and antiaggregation activities are affected. Prostacyclin has been found to block platelet aggregation but not to affect platelet adhesion to the vessel wall. There is suggestive evidence that atherosclerotic plaques of all types may form less prostacyclin than does normal vessel wall. Nevertheless, a clear demonstration of a role for the prostaglandin system in atherogenesis remains to be found.

The attractiveness of the homeostatic concept of platelet-vessel wall interaction together with the potency of prostacyclin has led to preliminary trials of the substance in various situations where its antiaggregatory or vasodilator effects might have therapeutic value. It appears to diminish platelet aggregation in open heart surgery and to diminish operative bleeding. By producing similar effects in renal dialysis and in the treatment of hepatic failure by hemoperfusion through activated charcoal, it diminishes the usual requirement for heparin. Beneficial effects, some of them of long duration, have been reported in peripheral vascular disease and in Raynaud's disorder. These trials, however, have been of modest size and have not been blinded, so that the interpretation of the results is uncertain. The results need confirmation.

It is of interest that dietary fats may also affect the prostaglandin system. Linoleic acid depresses platelet reactivity. It is the precursor of arachidonic acid, the source substance, but it may also displace arachidonic acid in platelet phospholipids and lower the platelet capacity to form thromboxane A_2. Linoleic acid can also give rise to prostaglandin E_1, which is an inhibitor of platelet aggregation. Conversely, a diet rich in arachidonic acid increases platelet aggregation. Some fish diets are rich in eicosapentaenoic acid, which is the precursor of yet other prostaglandins (the 3-series). This diet may lead to the production of thromboxane A_3 (weakly aggregating) at the expense of A_2. Such a diet can lead to a bleeding tendency.

Lipid Metabolism

The foregoing review of developments of new concepts of atherogenesis is incomplete without an accompanying review of

accomplishments in the field of lipid metabolism and the genetics of lipid transport. Progress in these areas has been dramatic and has touched almost every aspect of lipid metabolism and clinical hyperlipidemia. In most cases, progress and accomplishments have greatly exceeded the expectation of knowledgeable investigators' predictions in the late 1960's.

The two important parts in the Division's program on lipid metabolism are the Lipid Research Clinics program, including the LRC Population Studies and the Coronary Primary Prevention Trial (CPPT); and fundamental and clinical research on lipid metabolism.

Lipid Research Clinics

The LRC program was initiated in 1971. Its major components are a series of population studies, and the CPPT. Among the unique attributes of the LRC population-based studies is the integration of the disciplines of "lipidology," laboratory sciences, biostatistics, internal medicine, cardiology, and nutritional sciences with epidemiology.

Population Studies. Age-specific and sex-specific plasma lipid and lipoprotein distributions (means, medians, and selected percentiles) from over 600,000 participants selected from well-defined North American target populations that included a broad range of sociodemographic subgroups have been published in the LRC Population Studies Data Book, Volume 1, The Prevalence Study. These data showed slightly lower cholesterol and markedly higher triglyceride values than those previously reported for North America. The LRC Prevalence Study is the first large-scale population study where accurate and reliable triglyceride values have been reported. Formerly, a fasting level above 150 mg per dl was the criterion in clinical use to diagnose hypertriglyceridemia. The LRC studies indicate that this value is near the average for middle-aged men and that the upper limit is nearer 300 mg per dl.

Of special interest is the pediatric age group. Both clinic-specific and overall LRC analyses of data on approximately 16,000 participants from under 1 year of age to 19 years have shown that mean plasma cholesterol levels were lower in the late teenage than in the preteenage group. Lipoprotein data demonstrate that the lipoprotein changes responsible for this teenage dip in cholesterol differ according to sex. In the male, an LDL reduction is mainly reponsible, whereas in the female, both HDL and LDL make a contribution. A finding that cholesterol levels were lower than previously reported suggested the need to reduce the cutoff point for hypercholesterolemia in this age group.

A recent and dramatic decline in CHD death rates has occurred in the United States. The possible contribution of secular trends in serum cholesterol to this decline was examined by comparison of the LRC data with that of the Framingham Study, the Tecumseh Study, the Health Examination Survey, and the Health and Nutrition Examination Survey. It appears that in the 1960's, there was a modest decline in serum cholesterol levels (approximately 5 mg per dl in middle-aged adults). Comparison of data from the LRC and the earlier National Diet-Heart studies shows the decline in serum cholesterol to be consistent with changes in dietary fat intake in the 1960's.

Nutrition findings from the LRC Prevalence Study indicate that, for adults in the United States, daily cholesterol intake (at about approximatley 350 to 450 mg) appears to be lower than that previously reported. Also, the data suggest that an increase has occurred in the ratio of polyunsaturated to saturated fats (P:S ratio). The Framingham data from the 1963-1964 and 1967-1970 surveys show P:S ratios of 0.25 and 0.39 respectively, as compared with LRC data that show a P:S ratio of 0.5. These changes are particularly interesting in view of the reported decreases in blood cholesterol levels and cardiovascular mortality rates during approximately the same period.

Food Composition Data. Significant advances have been achieved in the important area of compilation of food composition data, with emphasis on dietary fats. Compiled through Federal interagency collaboration, with the assistance of the food industry, the Table of Food Composition, which is the keystone of the NHLBI dietary data base, was designed to include detailed and current data on fat, fatty acid, and cholesterol content of food. This computerized composition table has the flexibility to permit the inclusion of changes introduced by the food industry, such as altered composition or new products.

This nutrient data base currently contains about 800 food items and 450 recipe items. In response to needs of other investigators requesting information on training and standardization of provisions, the entire nutrition data system has been published.

Collaboration between the NHLBI and the Nutrient Composition Laboratory of the Department of Agriculture (USDA) has also led to significant advances in methods to determine food composition. Data now exist, for example, on the fat composition of a sample of popular "fast foods," which represent a large and growing proportion of the national diet. Analytical data have been compiled for the neutral detergent

fiber and the simple sugar content of ready-to-eat breakfast cereals, the lipid composition and inorganic nutrient content of cooked beef and pork, and the sugar, sodium, potassium, and phosphate content of soft drinks.

Dietary Fat-Plasma Cholesterol Correlations in Israel. Important nutritional findings are also emerging from the LRC in Jerusalem. This LRC has confirmed its initial finding that plasma cholesterol levels differ in native-born 17-year-old army inductees according to the country of parental origin, with the highest in the Western group and the lowest in the North African and Asian group. Preliminary findings also show similar differences in total and saturated fat and cholesterol intake. Polyunsaturated intake, however, showed opposite trends.

Impact of Sex Hormones. The LRC study explored the impact of sex hormone use on lipid and lipoprotein levels. Compared with controls, oral contraceptive users showed increased cholesterol, triglyceride, and LDL-cholesterol and VLDL-cholesterol levels, but HDL-cholesterol levels were similar. The high frequency of use of oral contraceptives, combined with their impact on blood lipid levels, indicate that up to 40 percent of hypercholesterolemia and 60 percent of hypertriglyceridemia in young women could be attributed to oral contraceptive use. Compared with nonusers, menopausal users of estrogen had slightly lower cholesterol and triglyceride levels, but more marked decreases in LDL-cholesterol and VLDL-cholesterol, and a significant increase in HDL-cholesterol.

Epidemiology of Plasma High Density Lipoprotein Cholesterol Levels. In view of the recent reemergence of HDL as a powerful, independent, inverse risk factor for CHD, there is considerable interest in the determinants of HDL levels, especially those that are potentially alterable. In a supplement to Circulation (Vol. 62, Nov. 1980), the LRC program reported the distributions of HDL-cholesterol for populations in diverse settings and correlations of HDL-cholesterol with many factors, including cigarette smoking, obesity, alcohol intake, dietary intake, physical activity, and socioeconomic status.

Among the findings regarding HDL-cholesterol reported for the U.S. population are:

- HDL-cholesterol is positively associated with leanness and physical activity and with estrogen use and moderate alcohol consumption.

- Menstruating women (ages 20 to 50) have higher HDL-cholesterol and lower LDL-cholesterol than men of the same age group. After menopause, LDL levels rise in women and HDL levels remain constant.

- HDL levels differ among blacks and whites. Although there are no significant black-white differences in HDL levels at birth, black children and adults have higher HDL levels than their white counterparts.

- Cigarette smoking is associated with lowered HDL levels, and the levels appear to be progressively lower with greater amounts of smoking.

- Level of education correlates positively with HDL levels.

If HDL is eventually proved to be causally protective against CHD, the LRC data suggest that hygienic modifications of lifestyle can favorably alter HDL levels. This possibility has considerable potential for the nonpharmacologic, public health oriented, primary prevention of CHD.

Lipid Research Clinics Population Studies Data Books. Many specialized analyses of the LRC data are available in the scientific literature. The LRC program also provides the biomedical community with a series of archival documents or data books that present basic descriptive statistics from the study populations.

Volume 1 of the LRC population studies data books, which was published in 1980, presents the aggregate lipid and lipoprotein distributions and other selected variables such as body weight, cigarette smoking, and blood pressure measurements from a random sample of the surveyed populations. These data, especially those on lipids and lipoproteins, are a standard source of information for clinical, epidemiological, and public health purposes.

LRC Family Study. An assessment of the relative importance of genetic and environmental mechanisms is crucial to an understanding of the nature of CHD and other vascular diseases. Knowledge of genetic mechanisms illuminates pathogenesis and helps provide means of identifying individuals at high risk before the onset of manifest clinical disease, and may suggest appropriate means of control. In light of these research needs and the paucity of large-scale population-based genetic studies, the LRC Family Study was deemed an essential feature of the overall population studies design.

Probands were selected from the LRC study population, either randomly or on the basis of hyperlipidemia or a lipoprotein abnormality, and the final data set includes 2,405 probands and 12,468 relatives. The size of this study sample and the diversity of the participants' background make this a uniquely valuable data set, and its importance is enhanced by the inclusion of more than 200 three-generation families. Data being generated and published from the family study elucidate the familial distributions of lipids and lipoproteins and the efficacy of specific analytical methods.

Mortality Followup Study. To test the predictive value of the risk factors and physiological parameters measured in the LRC program, a mortality followup of the study population was instituted in 1978. Baseline data on the population had been accumulated from 1972 to 1975 and contained lipid and lipoprotein values, electrocardiographic data, nutritional information, family history, and data from a battery of clinical tests. Thus, a convenient population was already assembled on which a prospective mortality study could be mounted. This design would allow testing the predictive value of many risk factors and physiological parameters that hitherto had been implicated in heart disease but only in retrospective and cross-sectional epidemiological surveys.

Although this study is still ongoing, it has thus far yielded over 25,000 person-years of observations with over 400 deaths, of which more than 250 were cardiovascular. Vital status of virtually every participant has been ascertained in this study. Results to date have confirmed that HDL is a powerful, independent, negative risk factor for CHD, and that cholesterol, LDL, blood pressure, cigarette smoking, and age are all strongly independent positive predictors. Triglyceride, however, appears not to have any independent predictive value for CHD. The data have also been used to assess the risk of increased cancer incidence in those individuals with low blood cholesterol values. After a 5.5-year followup, no correlation between cancer incidence and blood cholesterol level has yet been detected.

Through the use of samples stored when the original baseline study of participants was performed during the years 1972-1975, a comprehensive survey of a variety of plasma apolipoproteins as risk factors has just been completed and is presently being analyzed.

Lipid Research Clinics Laboratories. An accomplishment of the LRC program is the demonstration that more than a dozen geographically dispersed laboratories using common procedures and reference standards can achieve, over the long term, a

high degree of precision and accuracy for lipid and lipoprotein determinations in large-scale population surveys. In demonstrating that the interlaboratory standard deviation was smaller than the average intralaboratory variation, and in carefully documenting the procedures and standards that must be met in order to achieve such a level of precision, the LRC lipid laboratories have established a precedent for the assurance of quality data. In addition to the LRC Laboratory Methods Manual, which continues to be in demand as a reference document and has been cited regularly, the LRC laboratories have provided, in the scientific literature, extensive documentation of the standardization program. The biomedical community now has easy access to procedures, technology, and results. In 1980, the NHLBI and the Centers for Disease Control established the CDC-NHLBI HDL Standardization Program concerned with standardization of HDL-cholesterol measurements.

Coronary Primary Prevention Trial. The major field study currently being conducted by the LRC program is the Coronary Primary Prevention Trial. The CPPT was mounted by the NHLBI to evaluate the effectiveness of drug-induced cholesterol lowering in the prevention of heart attack and death from CHD. Recruitment of subjects started in 1973 and was completed in August 1976, with followup until August 1983. Participants number 3,810 between the ages of 35 and 59 and have no discernible evidence of existing heart disease or other physical ailments. Their blood cholesterol had to be above 265 mg per dl and the LDL-cholesterol above 190 mg per dl. In this randomized, double-blinded prospective clinical trial, one-half of the subjects receive a cholesterol-lowering drug, cholestyramine, and the other one-half receive a placebo. Both groups are prescribed a cholesterol-lowering diet. The primary endpoints are coronary death and nonfatal myocardial infarction. No significant toxicity has been observed in the study to date. The results of the study should be reported in early 1984.

Fundamental Lipid Metabolism Research

During the past decade, major advances have been made in the understanding of the role of lipids in health and disease and in the development of experimental methods and techniques for investigating the cellular systems and mechanisms concerned with the metabolism of lipids. Among the principal accomplishments are the following:

- Characterization of the structure and function of the plasma lipoprotein transport system.

- Definition and structural description of eight different apoproteins.

- Advances in the knowledge of lipid-protein interactions and in the rates of synthesis of lipid and protein components of lipoproteins.

- Definition of metabolic pathways such as the conversion of VLDL to LDL.

- Utilization of cell culture and clinical studies of genetic disorders and hyperlipidemia to define specific details of receptor-mediated uptake of LDL-cholesterol by the cell membrane.

- Demonstration of the dependence of cellular uptake of cholesterol on specific apoprotein components of the lipoprotein carriers, and clarification of the role of apolipoprotein components as cofactors for enzymes in the metabolism of lipids.

- Recognition of specific apolipoprotein deletions or cell membrane receptor impairments.

- Characterization of the regulation and control of plasma cholesterol levels by lipoprotein receptors in liver and peripheral tissues.

- Development of experimental animal models for relating hyperlipidemia to atherogenesis and coronary artery disease.

- Delineation of the pathways in the synthesis of lipid-derived prostaglandins.

- Identification of the bioregulatory nontransport functions of lipoproteins in the organism.

Specialized Centers of Research: Arteriosclerosis. A program of Specialized Centers of Research (SCOR) in Arteriosclerosis began in 1970. Many of the SCOR's have been involved in characterization of biochemical-genetic disease relationships, studies of dietary and drug control of lipids, and the development of diagnostic instrumentation for the assessment of lesions. The animal and tissue studies of arteriosclerosis have included experimental arteriosclerosis research (including nonhuman primates, other mammals, and nonmammalian species), investigations of lipid-lipoprotein metabolism, and the measurement of diet and drug effects on lesion progression and regression.

Basic laboratory investigations performed under the aegis of the SCOR's have focused on characterization of lipoproteins, apoproteins, and their interactions with lipids, as well as on the metabolic processes of the various lipids and lipoproteins. A major focus of the SCOR program continues to be on lipoproteins and the metabolism of lipids associated with hyperlipidemia and arteriosclerosis.

A recent achievement of two centers has been the identification, in humans and rats, of two forms of the major protein component (apoprotein B) of LDL with apparently different sites of synthesis (liver and intestine). A diet-drug regimen (colestipol-niacin) has been developed for the treatment of individuals with heterozygous type II familial hyperlipidemia. The treatment reduces serum cholesterol levels by 40 percent, normalizes the LDL-cholesterol level, increases the level of HDL-cholesterol, and reduces xanthomas.

Familial Hyperlipoproteinemia. One of the major advances that occurred in the past decade was the elucidation of the genetics and biochemical defect in familial hypercholesterolemia (FHC), one of the most common genetic abnormalities with a marked predisposition to premature CHD. The basic discovery was of a specific receptor for LDL in normal human skin fibroblasts in cell culture. This receptor bound human LDL and facilitated its metabolism by the cell. The uptake of LDL-cholesterol by the cell turned off cholesterol synthesis in the cell and reduced the LDL level in the culture medium and, presumably, in the in vivo blood levels.

FHC homozygote fibroblasts lacked this receptor activity. These cells continued to manufacture cholesterol in the presence of excess LDL in the culture medium. Cells from heterozygotes showed levels of activity intermediate between those from homozygotes and those from normal individuals. Thus, the biochemistry of FHC can be explained in terms of the failure of the cells to take up LDL from the blood and of unregulated cellular synthesis of cholesterol despite adequate dietary intake and elevated blood cholesterol levels. In the homozygote, these circumstances predispose to atherosclerosis at an early age.

These initial observations were expanded during the past decade. Of particular interest is the hypothesis that plasma cholesterol levels are controlled by the number of LDL receptors on somatic cells and that blood cholesterol levels can be altered in vivo by increasing the number of extrahepatic receptors in the organism. Certain drugs (such as thyroid hormone or the biliary sequestrant cholestyramine) or dietary cholesterol can apparently increase receptor number.

Unfortunately, such an approach has had limited success because there is a compensatory increase in the net synthesis of cholesterol by the liver when LDL receptor levels are increased, and hence, blood levels of LDL tend to remain the same. Recently, the discovery of inhibitors of 3-hydroxy-3-methylglutaric coenzyme-A reductase (HMG Co-A reductase), the rate-limiting enzyme for cholesterol synthesis, provides a means of preventing this concomitant increase in the synthetic rate of cholesterol when the number of LDL receptors is increased by pharmacological agents.

Hence, an exciting new approach to the control of elevated blood cholesterol levels appears at hand. Questions about potential toxicity of HMG Co-A reductase inhibitors, however, remain to be answered, and clinical trials testing the efficacy of this approach are needed before it can be applied in the treatment for elevated blood cholesterol levels or prevention of premature CHD and arteriosclerosis. These observations and theories have stimulated highly innovative studies in lipid metabolism as related to atherosclerosis, and offer major breakthroughs in this area.

Type III Hyperlipoproteinemia. In 1975, investigators reported the specific deficiency of E-III, one of the "isoforms" (components separable by isoelectric focusing) of apolipoprotein E in VLDL of subjects with type III hyperlipidemia. It was suggested that the lack of E-III represented the basic defect predisposing to the lipoprotein abnormalities in type III hyperlipoproteinemia. This deficiency was reported to be genetically determined.

More recent work using two-dimensional gel electrophoresis has shown that the apo E isoforms are not missing in type III hyperlipoproteinemia but are merely shifted to more acidic isoelectric points. It was further shown that individuals have either one of two apo E isoform patterns, designated alpha and beta. These apo E subclasses are genetically determined and are the result of three common alleles at a single genetic locus. The apo E subclass beta IV appears to be associated with type III hyperlipoproteinemia. It has been estimated that the apo E subclass beta IV (homozygote for the beta IV apo E allele) would have a frequency in the population of 2 to 3 percent.

Other investigators have determined the amino acid sequence of the apo E present in type III homozygotes (designated as E2/E2) and found it to differ by one amino acid (cysteine replaces arginine) from the E3/E3 homozygote or by two amino acids (2 cysteines replace 2 arginines) from the E4/E4 homozygote. This finding is the second reported instance of an amino acid replacement causing a metabolic impairment.

It is not yet clear whether the apo E subclass beta IV can alone produce type III hyperlipoproteinemia or whether factors determined by other genetic loci are also required. In this respect, there have been reports of probands that completely lack apo E and of a proband that has a normal apo E but apparently has an apo E receptor defect. Both of these patients exhibit classical clinical symptoms of type III hyperlipoproteinemia. There is a need to establish the prevalence of the apo E isoforms and to determine the contribution of these isoforms to CHD risk.

Apo C-II Deficiency. The discovery of a new lipoprotein disorder, apolipoprotein C-II deficiency, has opened a new avenue for the investigation of metabolic defects in hypertriglyceridemia and has clarified the role of the apo C-II polypeptide in human plasma. The elevated triglyceride levels result from the lack of apo C-II, an essential cofactor for lipoprotein lipase, which is the enzyme that hydrolyzes triglycerides to free fatty acids and monoglycerides. Because apo C-II deficiency is an inborn error of metabolism, it was possible to explore its genetics by examining the immediate family of the proband. It was found that the characteristic was transmitted as an autosomal recessive trait. Even though apo C-II deficiency is an extremely rare disorder, its discovery and the elucidation of its metabolic features have added significantly to the knowledge about lipid and lipoprotein metabolism.

Normotriglyceridemic Abetalipoproteinemia: Absence of the B-100 Apolipoprotein. Low density lipoproteins and the triglyceride-rich lipoproteins of human serum each contain proteins of high molecular weight. They are called apolipoprotein B. They had previously been thought to be identical. Investigators have isolated four species of apolipoprotein B that have unique molecular weights and amino acid compositions, and they have assigned numerical designations in a centile system to these species. One, which they term B-100, predominates in LDL and VLDL, and it is also present in chylomicrons from thoracic duct lymph or plasma. Substantial amounts of two large proteins designated B-74 and B-26, which appear to be complementary fragments or constituents of the B-100 protein, are found in the low density lipoproteins of many individuals. Another distinct protein, B-48, is a major and constant constituent of chylomicrons from thoracic duct lymph or plasma.

The recognition of the heterogeneity of apolipoprotein B has been quickly followed by the description of a new hypolipidemia. In the two genetic forms of abetalipoproteinemia, which are recessive abetalipoproteinemia and homozygous hypobetalipoproteinemia, all lipoproteins that normally

contain apolipoprotein B are absent from plasma. Recently, a new disorder has been described in which normal LDL and VLDL are absent but in which triglycerides are absorbed from the intestine and chylomicrons are present in plasma. The underlying molecular defect appears to be selective deletion of the hepatogenous B-100 apolipoprotein. The B-48 apolipoprotein found in chylomicrons is spared. These findings suggest that the two species of apolipoprotein B are under separate genetic control and that LDL is not normally derived from chylomicrons.

Epidemiology

Since 1972, the DHVD has supported a number of population-based genetic studies including components of the Framingham Heart Study, the Framingham Offspring Study, the NHLBI and Hamilton Twin Studies, the Family Study of CHD in Finland, the Homocystinuria Family History Study, and the High Blood Pressure in the Young Program. These family studies have shown that CHD tends to develop preferentially in certain families and that genetic factors are known to influence the levels of some risk factors. Familial aggregation of CHD was confirmed in a Finnish population in which the occurrence of disease in first-degree relatives of affected and healthy men was compared. CHD was more frequent in fathers, brothers, and sisters of affected men than in relatives of healthy men. Increased familial aggregation of disease was most marked when the index case was young. Progress has also been made in assessing the contribution of genetic factors to lipid levels. Familial resemblance in total cholesterol, LDL, HDL-cholesterol, and VLDL-cholesterol levels is consistent with a heritable influence on these lipid fractions, or possibly with environmental influences acting early in life.

The Framingham Heart Study, which began in 1950, is a national resource. This program has established the significance of risk factors for the development of various forms of cardiovascular disease. These risk factors include cigarette smoking, elevated serum cholesterol, blood pressure, blood glucose, ECG abnormalities, and type A behavior. The Framingham study also permitted restudy of the populations based on newly recognized biochemical indices of risk factors such as lipoprotein fractions. Relationships between HDL-cholesterol, LDL-cholesterol, and atherosclerosis are being clarified. HDL-cholesterol has an inverse relationship with the incidence of CHD; levels are higher in women; and they are related positively to very modest alcohol consumption and physical activity and negatively to obesity and smoking. The importance of other risk factors, including physical inactivity and acculturation to a Western lifestyle, is coming into sharper focus.

Progress has also been made in extending knowledge of risk factors in middle-aged men to older and younger age groups, women, different geographic areas, and ethnic groups. The Framingham risk factor profile has been validated in other comparable populations in the United States and also in low-risk populations in Honolulu and Puerto Rico. Conventional risk factors have been given more definition, and additional risk factors have been identified. Use of oral contraceptives as well as the menopausal state, for example, are associated with an increased incidence of atherosclerotic disease in women.

There are some serious limitations to the use of current risk factor profiles. Some high-risk subjects do not develop CHD whereas some low-risk subjects do. Although groups of subjects can be classified according to levels of risk, it is not possible to predict which individuals in the group will develop disease.

Geographic variations in risk factors and their relevance to variations in morbidity and mortality from CHD and stroke have been investigated in comparisons of the Framingham, Honolulu, and Puerto Rican populations. Although relationships between risk factors and disease incidence hold with each population, differences in the occurrence of disease between the populations are not due entirely to differences in levels of risk factors. CHD rates are lower in Honolulu and Puerto Rico than in Framingham even after established risk factors have been considered. Stroke morbidity and mortality are higher in Japanese living in Japan than in Japanese living in Honolulu.

Time trends in risk factors were a major focus of the Framingham Offspring Study, which showed lower levels of cigarette smoking, blood pressure, and cholesterol in the descendents than in the original cohort. However, the offspring were more obese.

During the past 10 years, autopsy findings in the Framingham and Honolulu populations have been related to risk-factor levels during life. Systolic blood pressure was correlated with heart weight and left ventricular muscle thickness in both sexes and with coronary atherosclerosis and critical coronary narrowing in men, but age was the only significant correlate with coronary atherosclerosis in women. Obesity was correlated with heart size, and heart weight and coronary pathology were correlated in men. Correlations between clinical data and autopsy findings tended to be greater when clinical measurements were made early rather than shortly before death.

Instrumentation

Technological development has led to three major advances in the noninvasive or minimally invasive diagnosis of atherosclerosis: ultrasound, subtraction radiography, and nuclear magnetic resonance (NMR).

Real-time B-mode ultrasonic scanning has been a major advance in the diagnosis of atherosclerotic lesions, particularly in the carotid and femoral arteries. Several institutions have developed high-resolution real-time scanners that provide longitudinal and transverse cross-sectional views of large peripheral arteries. The current resolution limit (less than a millimeter) permits identification of small plaques or arterial ulcerations. Such lesions may be difficult to detect by contrast arteriography, and they are missed by those noninvasive instruments sensitive to lesions that cause a reduction in pressure or flow. Several instruments, now commercially available, have been used principally for noninvasive detection of extracranial carotid occlusive disease. A multicenter prospective validation of the instruments is now under way. A parallel investigation using animals is designed to evaluate these devices as research tools. It is probable that real-time scanners will play a major role in epidemiologic studies of the prevalence and natural history of carotid occlusive disease. Further development of these instruments may lead to better range and resolution for detecting lesions in deep-lying arteries such as the coronary and renal arteries. Ultrasonic techniques applying echo-tracking methods have also been applied for defining arterial wall thickness and distensibility in order to document alterations in the vessels of atherosclerotic monkeys prior to the development of visible lesions.

Considerable advances have been made in Doppler ultrasound techniques, in terms of imaging of the vascular lumen as well as of improved processing of the Doppler flow signals through spectrum analyzers. Doppler ultrasonic arteriography provides images similar to contrast arteriography. In addition, the flow velocity information can provide sensitive detection of moderate or advanced atherosclerotic plaques and possible information about arterial wall roughness.

Real-time B-mode scanning combined with Doppler ultrasound, the so-called duplex scanner, has led to the most sophisticated form of ultrasonic vascular diagnosis thus far. This device has led to highly accurate noninvasive assessment of extracranial carotid occlusive disease. Although B-mode scanning alone provides the most sensitive detection of minor plaques or ulcerations, the instrument may not distinguish between advanced arterial stenosis and total arterial occlusion. This distinction can be important in devising appropriate surgical therapy.

Doppler ultrasound is capable of differentiating between these two lesions. Several instruments offering combined high-resolution B-scan and Doppler techniques are now commercially available.

The second major technological advance in the diagnosis of atherosclerosis is the development of the minimally invasive technique of subtraction radiography. Several programs have investigated computer methods to enhance the contrast of arteries visualized through the intravenous injection of contrast media. Several technical approaches have been undertaken, including digital subtraction techniques, combined analog and digital subtraction methods, a linear diode array and moving slit technique, and energy subtraction methods. Intravenous arteriography has provided images of the quality approaching that of intra-arterial contrast arteriography in a variety of vascular systems, including extracranial and intracranial vessels, aorta, and visceral and peripheral arteries. Refinements in image detail and accommodation for motion artifacts may permit imaging of coronary arteries. The use of the intravenous route avoids many of the risks of intra-arterial injections of contrast agents. Further improvements in contrast media may permit improved images without the complications of conventional contrast media. Although the rapid acceptance of this technology by the vascular surgery profession connotes its use as a replacement for noninvasive techniques, the method will in fact complement current noninvasive techniques that emphasize physiologic information. Furthermore, noninvasive techniques will continue to provide useful information for followup of patients.

Nuclear magnetic resonance systems have been developed for both detection of blood flow and imaging. The technique involves the detection of energy emitted by atomic nuclei responding to a low-level radio frequency field superimposed on the patient who has been placed in the center of a system of magnetic fields. Experiments have included studies of animal arteries in vitro. Current image resolution is around 1 to 2 mm and is obtained over a period of 2 to 4 minutes. At present, NMR is a useful research tool. In the future, the technique not only may permit three-dimensional imaging of living structures but also may yield data concerning the composition and metabolism of these tissues.

The DHVD sponsored a Workshop on Noninvasive Techniques for the Assessment of Atherosclerosis in January 1980, which brought together the leading authorities on all current and future techniques in noninvasive and minimally invasive assessment of atherosclerosis, including diagnostic ultrasound, x-ray arteriography, nuclear magnetic resonance, positron emission transaxial tomography, and radioisotope and microwave technologies.

Prevention

The Multiple Risk Factor Intervention Trial

In response to the 1971 recommendations of the Task Force on Arteriosclerosis, the Institute launched the Multiple Risk Factor Intervention Trial (MRFIT). Its primary purpose was to determine whether a special risk factor intervention program directed over a 6-year period to the reduction of elevated serum cholesterol, elevated diastolic blood pressure, and cigarette smoking in men at high risk of death from CHD (but still free of clinical evidence of CHD) would result in a significant reduction in CHD mortality, nonfatal myocardial infarction, cardiovascular mortality, and mortality from all causes. In 1972 and 1973, 22 clinical centers supported by a coordinating center, a central laboratory, a standardization laboratory, two ECG centers, and a drug distribution center became operational. The study randomized 12,866 men aged 35 to 57 to intervention and nonintervention ("usual care") groups. A variety of techniques of group counseling and individual instruction was applied to achieve changes in dietary patterns and reduce serum cholesterol. Multiple individualized approaches to smoking cessation were applied to the smokers, and a stepped-care approach to high blood pressure control was employed. Efforts in smoking cessation and blood pressure lowering were very successful, while success in reducing serum cholesterol proved more difficult to achieve. The "usual care" men also modified their risk factors to some extent. This modification reflected dietary and other secular changes in the general population. Risk-factor change observed after 4 years of intervention was published in 1981. The trial ended in February 1982, and publication of the morbidity and mortality data and of the complete risk-factor reduction data is anticipated in late 1982.

The Program on the Surgical Control of the Hyperlipidemias

A trial was initiated in 1974 to study whether surgical reduction--that is, by partial ileal bypass--of serum cholesterol in patients with myocardial infarction will reduce CHD mortality. As of 1982, the study has enrolled some 450 patients at four clinical centers, with 1,000 patients as a design goal, and it is scheduled to end in 1989 after a 5-year followup period for all patients. This Program on the Surgical Control of Hyperlipidemias (POSCH) has reported the partial ileal bypass operation to be safe, lasting, and effective in reducing serum cholesterol levels. The potential benefit of marked lowering of lipids by this method will be ascertained by quantitative angiographic measurement of coronary atherosclerotic plaques in addition to assessment of clinical endpoints.

Preventive Cardiology

The Chicago Heart Association Nutrition Education Project (also referred to as the Heart Saver Program), which was organized in 1972 in three different health care settings, attracted a mix of racial, ethnic, and socioeconomic groups. This educational project taught hyperlipidemic men and women to change their food habits in order to achieve serum cholesterol lowering. At the completion of between 6 and 9 months of the project, the special care group had significantly greater decreased serum cholesterol, decreased intake of calories, dietary cholesterol, and percent of calories from fat and saturated fat, and increased percent of calories from polyunsaturated fat than the regular care group.

The University of Chicago's Nutrition Education Project, which was active from 1972 to 1974, utilized an "educational diagnosis" in instructing patients in a fat-modified diet. The educational diagnosis depended on the assessment of three independent instructional features: the amount of structure, the mode of teaching, and the kind of language preferred by the patient. The data suggest that patients preferring high structure in the "symbolic" mode had a greater serum cholesterol reduction than other diagnostic groups.

The Nutrition-Behavioral Research Conference held in April 1975 brought together practicing nutritionists, interested physicians, and consultants from the behavioral sciences to define progress made to date in nutritional-behavioral research, advise the Institute regarding remaining areas of needed research, and suggest ways to disseminate knowledge and techniques from the behavioral sciences to practitioners conducting programs that promote more healthful dietary patterns. The proceedings of the conference were published and distributed widely (DHEW Publication No. (NIH) 76-978).

A particular result of this Nutrition-Behavioral Research Conference was the Model Workshop on Nutritional Counseling in Hyperlipidemia for Dietitians and Nutritionists. Its objective was to provide to a select group of nutritionists basic information on hyperlipidemia, behavior modification, and communication skills.

The Diffusion of Innovative Nutrition Counseling Skills, another model workshop program, brought together nutritionists, local practicing physicians, and behavioral scientists for 2-day regional workshops at which nutrition counselors could be encouraged to improve their counseling skills in the area of cardiovascular disease prevention and control. In this program, the NHLBI collaborated with the American Heart Association (AHA), taking advantage of AHA's administrative network of affiliates and

chapters as a means of greater diffusion of innovative dietary counseling methods.

The Chicago Heart Health Curriculum Program, initiated in 1978 and scheduled to end in 1982, is following 6th-grade students in city schools to ascertain the effect of risk-factor intervention on the development of cardiovascular disease. The program goes a step further than cognitive learning modification and attempts to make attitudes, value judgments, and behavior consistent with the development of a healthful lifestyle.

State of Knowledge in 1982: Atherogenesis

Receptor Mechanisms

In 1982, there is an intense interest in receptor-mediated mechanisms in atherogenesis. The mechanisms relate both to systemic metabolic phenomena and to local events in the region of the plaque.

After the discovery of the low density lipoprotein receptor on mesenchymal cells (fibroblasts), there was a rapid elucidation of how cells manage their cholesterol economy by the feedback regulation of cholesterol synthesis and by the "up" or "down" regulation of receptors. A major related finding was that such mechanisms play a potent role in degrading LDL and in establishing the circulating levels of cholesterol in the blood. The LDL receptor mechanism does not explain the development of foam cells in plaques.

Currently and into the near future, there will be much interest in a variety of specific (high-affinity) and nonspecific lipoprotein receptors in the liver, the adipose tissue, the mesenchyme in general, and the endothelial and smooth muscle cell, and the monocyte-macrophages in plaques. In parallel, there are many opportunities to understand the structure-function aspects of apoproteins that determine their ability to bind lipids and to be recognized by receptors. Research utilizing one and two gene defects affecting receptors or apoproteins is particularly promising.

It has also become apparent that native lipoproteins may undergo posttranslational modifications that lead on the one hand to failure of normal receptor recognition but on the other to recognition by other less specific receptors. Investigation of posttranslational modifications in lipids may serve to clarify many features of lipid accumulation in and removal from plaques.

Overall, there are many opportunities to understand and possibly control a variety of receptor-lipoprotein interactions at the level either of the receptors or of the lipoproteins, with the view of controlling lipid metabolism and atherogenesis.

Endothelium

The endothelium provides the cellular interface at which the circulating blood and the arterial intima meet. It acts as a doorkeeper to the inner aspect of the vessel wall. Until recently, its role in atherogenesis was speculative. The discovery of the platelet-derived growth factor (PDGF) for vascular smooth muscle cells gave impetus to the idea that endothelial denudation could play a prominent role in atherogenesis by initiating platelet adhesion and release of PDGF. Denudation was also perceived as allowing the macromolecules from the blood to have free access to the intima.

The original concepts have become more complex. Endothelium has been found to have a variety of functions, some of which are local in their effects and some of which are systemic. The concept of endothelial injury has been expanded to include concepts of endothelial dysfunction that may influence atherogenesis. Concepts of endothelial repair and maintenance are also appearing.

There are many relevant endothelial functions that can be explored. Among other functions, the endothelium produces von Willebrand factor, prostacyclin, and a glycocalyx. These properties can influence platelet-endothelial cell interactions. Their role in atherogenesis offers challenges for research. It has been found that exposure of native LDL to endothelium modifies the lipoprotein so that monocyte-macrophages accumulate it avidly. How endothelium does this and what it means in atherogenesis remain to be elucidated. The permeability of endothelium for macromolecules in small vessels has received much attention, but little is known about it in larger arteries. It is an important field for clarification since permeability affects the influx of macromolecules such as lipoproteins or fibrinogen into the intima. During the next decade, these and many other opportunities to relate the endothelium to local and systemic effects relevant to atherogenesis exist for fundamental research scientists.

Cell Proliferation

It has been known for many years that mitotic activity occurs in the cells of atherosclerotic plaques. The process occurs in smooth muscle cells, monocyte-macrophages, and endothelial cells. The observation a decade ago that platelets contain a protein that is a potent mitogen for vascular smooth muscle cells provided a

strong stimulus to investigate the factors that might stimulate mitosis in all the cell types found in plaques, the factors that might modulate growth, and the chemotactic phenomena as well. The repair of endothelium by mitosis, as well as the cellularity of plaques due to smooth muscle cell division, have been of particular interest.

Currently, it is known that platelet-derived growth factor affects fibroblasts, glial and 3T3 cells, and smooth muscle cells, but that endothelium does not require it. The stimulated cells form more high-affinity receptors, protein, and glycosaminoglycans. Endothelial cells can grow in culture in plasma-derived serum in the absence of exogenous growth factors, although such factors may enhance the culture. Cell contact may be a critical factor modulating endothelial cell growth. It is of interest that endothelium may condition smooth muscle cell growth due to the degree of permeability of endothelium to growth stimulants such as LDL from hyperlipidemic plasma and other factors in plasma. There is also some evidence that endothelial cells may elaborate growth inhibitors or stimulants.

The central role of cell proliferation in atherogenesis is beginning to be clarified by fundamental research on the molecular mechanisms that may be responsible. However, much more needs to be learned about the growth factors, the stimuli for their activity, their inhibitors, and the more subtle modulators of these phenomena. Control of these processes may offer a means to inhibit much of the atherogenic process.

Plaque Matrix

The cells of atherosclerotic plaques can elaborate an abundant matrix. The matrix occupies space and contributes to the bulk of plaques. A fairly complete body of knowledge of the various types of collagen, proteoglycans, and glycosaminoglycans that can be present in the matrix has been developed. Information is also available about the amounts and proportions of the various matrix substances that are found in normal intima compared to plaque. The elaboration of these substances has been followed in cell culture. It has been observed that matrix components may calcify, complex with lipoproteins, and modulate cell proliferation.

Knowledge of these substances, their posttranscriptional modifications, and their roles in atherogenesis is primitive. Little is known about mechanisms and about the stimuli that cause smooth muscle cells or endothelial cells to secrete matrix components. Moreover, since these components are slow to regress after plaque formation, an understanding of their genesis may have particular practical importance. Clearly, there are many

opportunities in the coming decade to increase the knowledge of this important aspect of plaque development.

Thrombotic and Coagulation Processes

That thrombosis and coagulation phenomena can contribute, to a very important degree, to plaque progression and complication has been appreciated for many years. Nevertheless, little concrete qualitative or quantitative information is available. Except for the understanding of platelet-derived growth factor, it remains an open question whether or to what degree such processes contribute to the early pathogenesis of plaques.

In the field of hematology, much detail has been worked out concerning the pathways of blood coagulation, thrombosis, and endothelium-blood interface phenomena. Nevertheless, very little of this information has thus far been found to have application to atherogenesis, and it is a relatively inactive field of research in spite of its obvious significance and importance. The area provides many opportunities for research, although the field is constrained by lack of convenient animal models.

Natural History of Atherosclerosis in Humans

Knowledge of the natural history of atherosclerosis in humans developed largely after World War I and culminated in such epidemiological and geographic studies as those of the International Atherosclerosis Project and the WHO Five Cities Studies--studies that used greatly simplified definitions of atherosclerosis and that made macroscopic rather than microscopic observations on only a few arterial beds.

Currently, there are detailed gross, microscopic, and fine-structure descriptions of the variety of changes that can be found in atherosclerosis. Point prevalence data exist on simple gross classes of lesions and on age and sex associations, drawn from epidemiological cohorts, for the aorta, for coronary and cerebral arteries, and to a very limited extent, for other vessels. Some univariate and multivariate analyses of risk factors and disease have been made, but as yet they are limited. There are also some biochemical and histochemical data, but they too are limited. A variety of possible pathogenetic mechanisms are identified, but there is little firm qualitative and quantitative data on the evolution of plaques. There is a lack of adequate antemortem or postmortem vascular maps of atherosclerosis in different vascular beds in terms of types of lesions at the gross, microscopic, histochemical, and chemical levels; and also at the levels of incidence, prevalence, evolution, and risk or clinical associations. It should be noted that contrast angiography does not

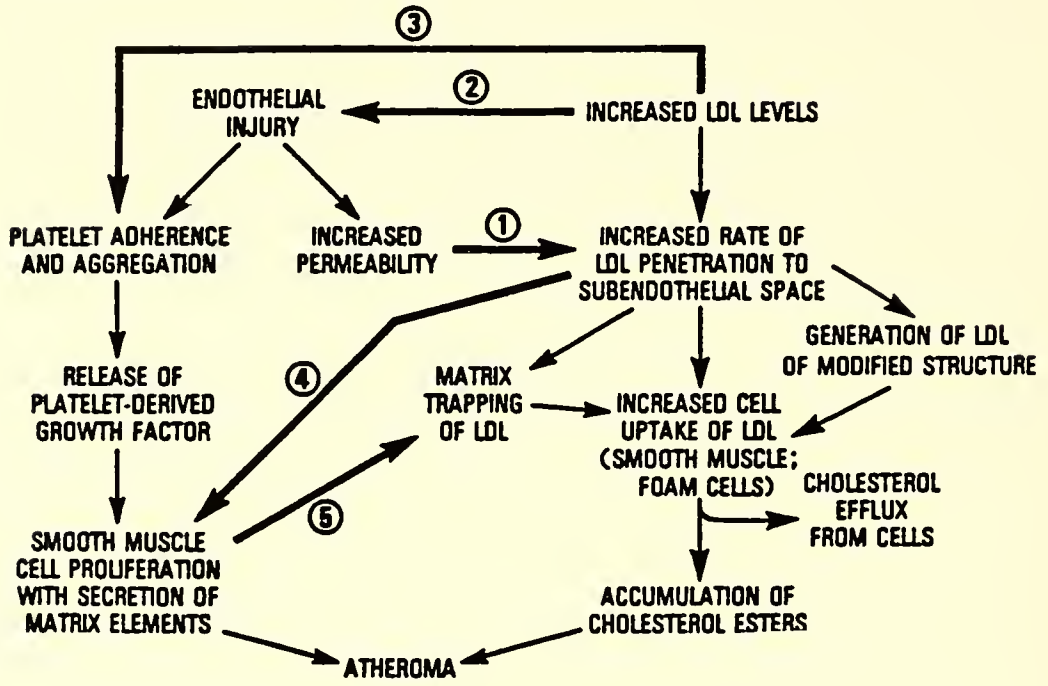
display atherosclerosis but rather displays the column of blood in the artery as distorted by the inner aspect of plaques. Contrast angiography per se is therefore not useful in the study of the natural history of atherosclerosis. Techniques such as B-scan ultrasound or nuclear magnetic resonance that can image plaques as such may be of value in the near future.

Since the natural history of atherosclerosis is the ultimate reference subject to which all other research on the disease must be referred, scientists are presently in the position of conducting much research at the most fundamental and applied levels without a clear or demonstrable understanding of its relevance to the human disorder.

It is necessary to upgrade and modernize the understanding of the natural history of atherosclerosis with the use of modern quantitative techniques similar to those being used for other research in this field.

State of Knowledge in 1982: Lipoprotein Metabolism

The lipid hypothesis, which has been under investigation for many years, was widely accepted at the beginning of this decade. The hypothesis, however, does not necessarily entail a precise definition of the steps by which hyperlipoproteinemia initiates or contributes to the atherogenic process. There was a tendency to consider the lipid (or infiltration) hypothesis as antithetical to or, at best, parallel to the other leading hypothesis--endothelial injury and thrombosis. During the past decade, however, advances have shown several ways in which the two hypotheses are actually intimately related to one another (see figure 16). The lipid hypothesis is usually explicated in terms of ways in which the lipid accumulation in the artery wall comes about, as shown by the series of events on the right side of the schema in figure 16. Elevated lipoprotein levels, however, may be atherogenic in ways that do not necessarily relate directly to accumulation of lipids in the artery wall. For example, studies in cell culture and some in vivo studies have suggested that LDL could cause endothelial cell injury that can initiate the sequence of events (as shown on the left in figure 16) that are envisioned as leading to lesion formation as a response-to-injury. In addition, there is evidence that patients with hyperlipoproteinemia have platelets that are more sensitive to aggregation-inducing factors such as adenosine diphosphate. Finally, it has been shown in cell culture that LDL from hyperlipidemic serum can induce an increased rate of growth of smooth muscle cells over and above that caused by platelet growth factors and can thus contribute to the characteristic proliferation of smooth muscle cells seen in arterial lesions. These processes are not totally independent of the lipoprotein



Source: Adapted from D. Steinberg, Metabolism of lipoproteins at the cellular level in relation to atherogenesis. In Lipoproteins, Atherosclerosis, and Coronary Heart Disease (N.E. Miller and B. Lewis, eds.), Elsevier, Amsterdam, 1980. With permission.

Figure 16. Schema to Indicate the *Endothelial Injury Hypothesis* and the *Lipid or Infiltration Hypothesis* of Atherogenesis and the Overlaps and Interactions Between Them

pattern. The several discrete processes that have been investigated in individual laboratories are now beginning to show potentials for interactions, and in some circumstances, a "unified" hypothesis of atherogenesis may emerge.

Lipoprotein Structure and Function

The plasma lipoproteins are widely recognized as risk factors for atherosclerosis. The major function of the plasma lipoproteins is the transport, to and from tissues, of two classes of extremely hydrophobic lipids, triglycerides, and cholesterol

esters. In normal human physiology, triglycerides are a source of energy, whereas cholesterol derived from cholesterol esters is a structural component of membranes and a precursor of steroid hormones and bile acids. The apoproteins are determinants of lipoprotein binding by specific receptors on cell surfaces. An additional function of the apoproteins includes their serving as cofactors for certain enzymes involved in lipid and lipoprotein metabolism.

Regulation of Plasma Lipoproteins

The plasma profiles of the lipoprotein and apolipoproteins reflect the direct control by the genome and the indirect influence of physiological (for example, hormones), environmental (for example, diet), and pathological (for example, diabetes and other diseases that affect lipid metabolism) factors. Abnormalities in plasma apolipoproteins have been found as a consequence of genetic variation and under a variety of pathological conditions. Since the properties, functions, distribution in plasma, and metabolism of the lipids and lipoproteins are subject to regulation at several levels, the potential exists to reduce the pathological consequences of lipoprotein abnormalities by appropriate alterations in exercise, smoking, and drugs.

Heterogeneity of the Lipoproteins

A wide spectrum of lipoprotein particles is present in human plasma. It has been possible recently to identify three to five subpopulations of differing particle size within the HDL class and from five to seven subpopulations within the LDL class. This heterogeneity is most likely a consequence not only of the processes involved in the synthesis of the lipoproteins but also of the catabolic processes by which the lipoproteins are transformed or degraded after their entry into the bloodstream. During catabolism of the triglyceride-rich lipoproteins (chylomicrons and VLDL), there is a progressive reduction in particle size, accompanied by the transfer or reorganization, or both, of some of the apolipoproteins associated with these lipoprotein species. The particle sizes of lipoproteins produced by such catabolic processes fall either within the size range of the original lipoprotein class or of an entirely different class. Transient elevations of "remnant" particles produced during degradation of triglyceride-rich particles after a lipid-rich meal can also contribute to the heterogeneity of the plasma lipoprotein spectrum. The presence of apo B and apo E on the surface of such "remnants" accounts for their avid interaction with high-affinity cell-surface receptors and their subsequent internalization by arterial smooth muscle cells.

Heterogeneity of the Apolipoproteins

A dozen or more different apolipoproteins, considerably more if one considers their polymorphism and mixed dimers, are associated with the human plasma lipoproteins. These include apolipoproteins A-I, A-II, A-IV, B, C-I, C-II, C-III, D, E, F, G, Lp(a) polypeptide, proline-rich protein, threonine-poor amyloid proteins, beta 2-glycoprotein-1, and HLA antigens. The amino acid sequences of A-I, A-II, C-I, C-II, and C-III have been determined. Their distribution among the different classes of lipoproteins (chylomicrons, VLDL, LDL, and HDL) differs characteristically. Thus, apo B is the predominant protein of the LDL, chylomicrons, and VLDL, but the proportion of apo C's and apo E is considerably increased in the chylomicrons and VLDL. Normally, apo A-I and apo A-II together account for about 85 to 90 percent of the HDL protein.

Polymorphism and Genetic Variants

Many of the apolipoproteins, including A-I, A-IV, C-II, C-III, D, and E, exhibit polymorphism. The significance of polymorphism of apolipoproteins has not been elucidated. Because it seems to occur in all individuals, polymorphism of the apolipoproteins could be a ubiquitous determinant of lipoprotein metabolism. Small differences in primary structure or composition or in net charge could significantly affect virtually every lipoprotein property, including the affinities of apolipoprotein for lipids, for enzymes that metabolize the lipoproteins, and for cell receptors; the exchange of apolipoproteins and lipids among different lipoprotein particles and between lipoproteins and cell membranes; and the metabolism of the lipoproteins.

Functions of the Apolipoproteins

Knowledge of specific physiological functions of the apolipoproteins is incomplete. Apo C-II was found to activate lipolysis of chylomicrons and VLDL by lipoprotein lipase. The activity of lipoprotein lipase is modulated by apo C-III counteracting the activation by apo C-II. However, the in vitro lipolysis of triolein by hepatic lipase is stimulated about threefold by apo A-II, which is an HDL apoprotein, and markedly suppressed by apo C-II, which is present in HDL as well as VLDL. Apo A-I, which is the major HDL apoprotein, is also involved in the metabolism of HDL. It is a cofactor for lecithin-cholesterol acyltransferase, which is a liver-derived enzyme in plasma that preferentially esterifies the cholesterol moiety of HDL. The important role of LCAT in lipoprotein structure and metabolism is evident from the gross abnormalities that occur in LCAT deficiency.

Several studies have demonstrated the role of the apoprotein moiety in binding the lipoproteins to specific receptors of cell membranes and platelet membranes. For example, the LDL receptor of most cells binds the apo B-containing lipoproteins, including VLDL, intermediate density lipoprotein, LDL, and Lp(a) and apo E-containing lipoproteins. Liver contains an additional receptor that recognizes apo E-containing HDL but not LDL. HDL's that do not contain apo E (or apo B) are taken up by a separate receptor pathway, presumably specific for apo A-I and/or apo A-II. The lipoproteins differ in the number of receptors bound per lipoprotein particle: VLDL can bind four to nine receptors per particle and hence they and their remnants are most avidly bound. The apo E-containing HDL_C binds four receptors per particle and is also more tightly bound than LDL. Modification of LDL by endothelial cells (but not by fibroblasts) causes a marked increase in the uptake and degradation of the lipoprotein by macrophages that degrade native LDL slowly by nonspecific pathways. The modified LDL, taken up by a specific macrophage receptor that is different from the receptor for native LDL, may be an important source of lipid in the foam cells of atheromata. This area of lipoprotein-endothelial cell interaction should receive continued study during the next decade.

Disorders of Lipoprotein Metabolism

Environmental factors play a major role in determining the distribution of lipid levels in a given population. It is becoming increasingly clear, however, that the genetic makeup of the individual determines the wide range of responses to the effects of the environment. At the upper and lower extremes of the distribution, many individuals are found with major gene defects affecting lipoprotein metabolism. Studies of several of the familial disorders have been extremely valuable in revealing specific functions of enzymes and structural proteins in lipoprotein metabolism. Low levels of plasma cholesterol have gained increasing interest since an increased total mortality has been described among men with the lowest levels of total plasma cholesterol in some population studies. The complexities inherent in this association warrant long-term monitoring of trends. In many instances, the pathophysiology of abnormal lipoprotein levels needs further study.

Elevated High Density Lipoproteins

Increased plasma HDL cholesterol levels are associated with a reduced cardiovascular risk. Elevated HDL levels may be due to a familial genetic trait and are associated with regular exercise, moderate consumption of alcohol, or consumption of estrogens by women. On the other hand, lower HDL levels are found in

individuals who smoke, are sedentary, or are obese. The higher levels of HDL are usually associated with increases in the less dense HDL fractions referred to as HDL_2. Further heterogeneity of HDL has been defined and may, in part, be due to increased lipoprotein lipase activity. However, the basic biochemical mechanisms that control HDL production and clearance are virtually unknown. The negative association of vascular disease with HDL levels may be a product of increased cholesterol transport from peripheral tissues to liver, but this hypothesis awaits confirmation. No prospective studies have been conducted with interventions that are designed to change HDL and to determine the impact on future vascular events. Whether HDL reduces risk or is simply a marker in persons with reduced cardiovascular risk, is not known.

Program Goals 1982 to 1987

- Advance the understanding of the basic pathogenetic mechanisms of atherosclerosis at the tissue, cellular, and molecular levels, using all suitable mechanisms and techniques, including those of cellular and molecular biology.

- Enhance the knowledge of the causal mechanisms and associated risk factors that play important roles in atherogenesis.

- Improve the understanding of the natural history of arteriosclerosis in all vascular regions in humans, utilizing modern methods of research and reassessing, with modern techniques, existing older studies.

- Improve the understanding of the epidemiology of arteriosclerotic disease, improve data-gathering capability and analytic methods, and improve predictive capability for all populations.

- Develop improved minimally invasive and noninvasive methods for detection of atherosclerosis in various regions of the vascular system.

- Expand investigations to ascertain the effectiveness of therapeutic interventions to reduce or prevent atherosclerosis.

- Elucidate the roles of behavior in relation to the etiology, pathogenesis, treatment, and prevention of arteriosclerosis and related diseases.

Research Activities 1982 to 1987

- An increase in information, in all age groups, on the genetic factors and risk factors for atherogenesis, their mechanisms of action, and their modification by therapeutic interventions.

- An expansion of studies of the contributions of diabetes and hypertension to atherosclerosis.

- Further study of the relationship of platelets and prostaglandin metabolism to atherogenesis.

- Investigation of the role of thrombosis as a phenomenon contributing both to plaque growth and to luminal occlusion and of the circumstances that precipitate thrombotic occlusion of atherosclerotic arteries.

- Continuation of research on the structure, function, and metabolism of apoproteins and lipoproteins utilizing clinical investigations of lipid disorders and other perturbations of lipid handling.

- Further study of the factors that may promote regression of plaques, and study of the nature of the regression process in early and late lesions in animals and humans.

- Continuation of support of the Specialized Centers of Research in Atherosclerosis.

- Expansion of investigation of pharmacologic, nutritional, and other modifications that may influence lipid metabolism, and an investigation of the apparent benefits of estrogens on cardiovascular morbidity and mortality in postmenopausal women.

- Surveillance systems in selected communities to monitor long-term trends in nonfatal and fatal atherosclerotic disease.

- Elucidation of the pathophysiological links of behavior to atherosclerosis, coronary heart disease, and stroke, and confirmation of these links by trials that ascertain the effectiveness of defined health practices in promoting optimal cardiovascular health.

- Improvements in the capabilities of various noninvasive or minimally invasive systems that image the vascular wall, lumen, or circulation. This activity includes development of methods that will detect major compositional differences in the makeup of plaques or vascular occlusions.

4. Hypertension

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As used in this report, the term hypertension includes the group of disorders that are manifested by the presence of elevated blood pressure in the systemic arteries. The qualifying term primary or essential hypertension is used generally to refer to the most common form, for which the cause or causes are yet unknown. Primary hypertension of unknown cause is responsible for about 95 percent of the high blood pressure found in the U.S. population. Various "secondary" forms of hypertension due to specific diseases of the kidney, tumors of the adrenal gland, congenital narrowing of the aorta, obstruction of renal arteries, toxemias of pregnancy, and other causes have been identified. These secondary forms are estimated to comprise less than 5 percent of hypertensive disorders.

State of Knowledge in 1972

The view that hypertension is a multifaceted problem in which numerous neural, humoral, genetic, and environmental factors might play interdependent and compensatory roles continued from the 1960's into the 1970's. Hypertension was thus regarded as the result of complex interactions of control systems for physiological and pathophysiological phenomena. This view was compatible with the response of essential hypertension to empirical therapy with drugs, which exhibited three quite different modes of action. These were diuretics to reduce blood volume, sympatholytics to reduce nerve action on vessels, and vasodilators to dilate the vessels. In many instances, the drugs were more effective when taken together--an observation that led to the sequential addition of drugs of different classes to obtain the best clinical effect.

In 1972, it was thought very unlikely that a single cause would explain all cases of essential hypertension. For many investigators, the working concept was that one or more mechanisms expressing genetic and environmental interaction became quantitatively abnormal and self-reinforcing or circuitous, ultimately damaging the vessels irreversibly. It was strongly suspected that a genetic-environmental interaction from the consumption of excess dietary sodium was a basis for essential hypertension in some genetically predisposed individuals. Psychosocial stress was not regarded as a major factor at this time. Some investigators

continued to search for qualitatively abnormal factors or a single unifying abnormality that could account for all essential hypertension. Most research, however, sought to elucidate mechanisms of blood pressure control (especially the renin-angiotensin-aldosterone axis) in order to understand their place among the interacting factors, to assign them significance for clinical disease and therapy, and finally to assign them etiological significance for the classification, treatment, and prevention of essential hypertension or prehypertensive states.

In 1972, hypertension was regarded as a major, treatable disease and public health problem. Treatment of essential hypertension was empirical rather than specific since essential hypertension remained without known cause. It was held that prevention was of the utmost importance so that lifelong treatment could be avoided, but in the absence of etiological information, prevention was not possible. Clinical investigation of unusual biochemical and physiological sophistication was current, and animal models of considerable variety and potential for application were available. The complexity of the mechanisms of known or suspected involvement in the control of blood pressure was beginning to engage interdisciplinary biomedical research interest. Earlier studies of hypertension and its pharmacology had already had a major influence in establishing the discipline of clinical pharmacology, and research questions of interest in this complex disorder were emerging in other disciplines.

Epidemiology and Natural History

The World Health Organization has proposed definitions for hypertension since 1959. In 1962, it convened an expert committee to recommend a further classification for arterial hypertension. Extending some of its earlier definitions, the committee recommended two categories: normal blood pressure for adults was defined as a systolic blood pressure of less than 140 mm Hg and a diastolic blood pressure of less than 90 mm Hg, and abnormal blood pressure as a systolic equal to or higher than 160 mm and a diastolic of 95 mm or higher. Additional classifications of three stages of severity related to the absence or presence of evidence of organ damage were also recommended. This system was a useful standardization of terminology for purposes of research. Physicians continued to use their own criteria, however, in deciding whether a patient's high blood pressure warranted treatment.

By 1972, many clinical and epidemiological studies had established that high systolic or diastolic blood pressure is a major risk factor for coronary heart disease, stroke, congestive heart failure, renal failure, and retinal damage. Life insurance studies had shown that mortality among men and women at any age

was directly related to their level of systolic or diastolic blood pressure even down into levels that were previously considered normal. Epidemiological studies had further extended these findings and established a direct association of high blood pressure with morbidity and mortality from these disorders. Moreover, interactions of the higher levels of blood pressure with other risk factors were found to further increase the risk of morbidity and mortality from coronary heart disease, stroke, cardiac failure, and renal failure.

Advances in drug therapy of hypertension had been made possible by the introduction in the United States of ganglionic blocking drugs and natriuretic agents, and also hydralazine, reserpine, guanethidine, and methyldopa. They were used alone or in combination. Mortality from hypertension had declined by 1972, and both mortality and incidence of accelerated hypertension had decreased. As a result of therapy, the distribution of causes of death had changed, and congestive heart failure, formerly the dominant cause, ranked behind myocardial infarction, uremia, and stroke. Morbidity such as retinal exudates, hemorrhages, and papilledema became rare under treatment. A beneficial effect of therapy on the incidence of coronary heart disease was not established, although it was clear that hypertension was a major risk factor for myocardial infarction and for atherosclerosis per se.

Evaluation of the efficacy of antihypertensive drugs in the reduction of morbidity and mortality from hypertension had been markedly advanced by the controlled clinical trials initiated in the 1960's by the Veterans Administration Cooperative Study investigators. Their studies had shown a significant reduction in morbidity and mortality for middle-aged men with baseline diastolic blood pressures averaging 105 to 114 mm Hg. No significant difference had been found among the men with diastolic blood pressures of 90 to 104 mm Hg although the trend favored the treatment group. These promising results automatically raised the question of the efficacy of antihypertensive treatment in women and in the broad range of severity of high blood pressure in the general population.

In 1972, the public was largely unaware of the benefits of treatment of high blood pressure, and the majority of persons with high blood pressure were unaware of their condition. Epidemiological studies revealed a high prevalence of the disorder, particularly among black individuals, and the Health Examination Survey of 1960-1962 provided data on national prevalence for adults of 18 to 79 years of age in the civilian population. Furthermore, hypertension was generally considered in terms of elevation of diastolic blood pressure. Systolic hypertension of the elderly and its associated risks were not fully appreciated.

Etiology and Pathophysiology

Because cases tended to occur more often in some families than in others, a genetic or familial component was generally accepted in 1972. Essential hypertension was viewed clinically as a chronic disease that usually had its onset after age 30 but rarely developed after age 50, with a course of 20 or 30 years. The disease resulted in major morbidity or mortality by age 50 or 60, possibly through a mechanism of pressure-induced damage to blood vessels. About 1 percent of the cases were known to evolve into accelerated or malignant hypertension and to progress rapidly to death over a course of a year or two. In 1972, the issue of essential hypertension in children was largely unexplored.

Physiological studies of the maintenance of normal blood pressure had found that the regulation of the blood pressure is a complex neural and humoral process. In 1972, there was much interest in the renin-angiotensin-aldosterone-sodium-water balance axis, both for modulation of blood pressure and as a possible causal chain for essential hypertension. Renin had been reported in 1940 to induce formation of a substance that raises blood pressure. Angiotensin was identified later. In 1960, injections of angiotensin were reported to increase aldosterone secretion. Technical problems of measurement of these substances, present in minute amounts, were a matter of urgent concern in 1972. A dependable assay for angiotensin I became available just as the decade began. In addition, sympathetic arousal or sensitivity and catecholamine metabolism, including its central nervous system modulation, were of interest.

Brain peptides such as enkephalins, substance P, and somatostatin, to mention a few, were found to be localized in brain areas involved in cardiovascular control. Furthermore, neuropeptides were reported to modify an animal's thermoregulation, and a few were capable of altering catecholamine metabolism, release, and uptake. Finally, information was available that some brain peptides act as releasing factors for hypothalamic hormones. Stimulating the biosynthesis of angiotensin II in the brain, for example, stimulated hypothalamic receptors to increase drinking behavior. Receptor stimulation also led to the release of antidiuretic hormone (ADH) and adrenocorticotropic hormone (ACTH), as well as to enhanced release of adrenergic transmitters. This cascade of factors, which also includes the release of sodium-retaining aldosterone, was thought to lead to an increase in blood pressure that was slow in onset and long-lasting.

Many such mechanisms were conceived to be acting on the fundamental hemodynamic systems for the maintenance of blood pressure in the arterial circulation; namely, the blood pressure as a product of cardiac output, and the resistance to runoff

through the arterioles to the venous circulation. Any factor that could affect either cardiac output or the resistance bed was a candidate for investigation as a cause of either essential hypertension or secondary hypertension. The major factors considered were blood volume, venous and arterial compliance, neurogenic activity, renal pressor systems, and adrenal steroids. It was generally recognized that vascular reactivity is elevated in both clinical and experimental hypertension.

Research on animals, initially physiologic in nature, was given a pathological focus with the development of models of renovascular hypertension in 1934. Other models were added including renal parenchymal, adrenal hyperplastic, salt-sensitive (Dahl) rat, and eventually hereditable models of hypertension in rats such as the spontaneously hypertensive rat (SHR). The salt-sensitive model was believed to result from a genetic-environmental interaction. All except the genetic ones could be regarded as analogous to secondary hypertension rather than to essential hypertension. The animal models, however, were of immense value for the study of the mechanisms of changes in blood pressure, autonomic influences, and the effects of acute and chronic hypertension on the heart, arteries, and arterioles. They were also important in the development and evaluation of drugs.

While there had been searches for abnormal substances as causal factors in the development of hypertension, none had been found. Instead, it was found in experimental animal models and in secondary hypertension in humans that substances normally present were identified in unusual amounts and that normal mechanisms involved in the maintenance of blood pressure were quantitatively rather than qualitatively disturbed. Thus, hypertension was viewed as a disease of circulatory regulation rather than a response to an abnormal substance or agent. Attention was thus turned to attempts to demonstrate similar quantitative biochemical differences in essential hypertension in humans. These attempts were largely unsuccessful. By 1970, however, quantification of renin activity in essential hypertension had identified high, normal, and low values among patients and suggested that essential hypertension might be subject to meaningful classification.

Hypertension and Atherosclerosis

Study of human atherosclerosis at autopsy showed that patients with a history or with anatomical evidence of hypertension have more advanced and more diffuse atherosclerosis. Thickening of the coronary arteries was also seen with hypertension, but the relation to atherogenesis was not clear. The limited amount of research that had been conducted usually employed rats or dogs, species in which atherosclerosis is not typical or easily induced. Only in a few rabbit and nonhuman

primate experiments had dietary atherogenesis and hypertension been studied together. The work was scant, but enhancement of aortic atherogenesis was seen in the hyperlipemic animals when hypertension was present. Some limited data suggested that lipids entered the arterial intima at an increased rate in the presence of hypertension, but very little was known about the physiological basis of transport into the vessel wall. Atherosclerotic changes in large arteries due to hypertension alone were not reported. Despite the importance of hypertension as a risk factor, its influence on atherogenesis was not an active field of research.

Clinical Considerations

By 1972, the ease of diagnosis, the strength of the data on risk factors in prospective epidemiological studies, the prevalence of the disorder established by surveys, and the growing awareness of the effectiveness of treatment all acted to make hypertension a public health issue as well as a medical one.

The clinical diagnosis of both primary and secondary hypertension involved indirect serial determinations of systemic blood pressure by cuff sphygmomanometry in physicians' offices. The diagnosis of renovascular hypertension, one of the secondary forms, rested primarily on contrast arteriography, although indirect methods included rapid-sequence intravenous excretory urography, split renal function studies, and determinations of renal vein renin. Although medical therapy of hypertension predominated, patients in whom renovascular hypertension was identified were considered for endarterectomy, for bypass of the renal artery stenosis--using either autogenous vein or artery (internal iliac) grafts or artificial prostheses--or for nephrectomy.

The most frequent examples of secondary hypertension had been found to occur in association with diseases of the renal arteries or the parenchyma of the kidney, tumors of the adrenal medulla or cortex, congenital narrowing of the aorta, the toxemias of pregnancy, and some disorders of the central nervous system. As a result of better diagnostic techniques and of improvements in surgical treatment, the percentage of patients with secondary hypertension who had been cured increased markedly. Associations had been made with other rare diseases such as acromegaly, pseudoxanthoma elasticum, acute porphyria, hyperparathyroidism, some renal tumors and mineralocorticoid disorders, and renoprival states in patients on long-term dialysis. It had been recognized that contraceptive steroids caused hypertension in some users.

Program Goals Through 1982

In the 1972 National Program, the overriding long-range goal was to prevent hypertension. A shorter-term goal was full utilization of available treatment. This latter was of interest to several components of the Division of Heart and Vascular Diseases. It was proposed that basic studies of the etiology and pathogenesis of hypertension, enlisting information from epidemiology and other disciplines, address the long-range goal. A second approach was to develop new knowledge about the pharmacology of hypertension, new drugs, and diagnostic and monitoring instrumentation. In 1977, there was special emphasis on etiology, pathogenesis, and methods and techniques for research. A further in-depth assessment of hypertension research by an Institute-sponsored Task Force on Hypertension in 1978 resulted in the identification of a broad range of new research opportunities and the objective of increasing interdisciplinary research in the field.

Activities planned by the Institute in the 1972 National Program were:

- Research on the etiology and pathogenesis of hypertension, including its epidemiology, in many of the individual and specialized laboratories working on this problem.

- Clinical trials of antihypertensive therapy in mild and labile hypertension.

- Evaluation of new pharmacologic approaches to the treatment of hypertension that utilize existing research centers and pharmacologic expertise, with emphasis on new drug formulations.

- Motivation of all adults to have their blood pressure checked annually, and encouragement of those found to be hypertensive to obtain proper therapy.

- Dissemination of current knowledge of antihypertensive drug management to general practitioners and to specialists from whom individuals with high blood pressure seek therapy.

- Continuation of the Hypertension Information and Education Program to expand public and professional knowledge of the dangers of high blood pressure and the benefits of effective treatment.

- Establishment of an education research program for testing hypotheses that will lead to effective educational methods for increasing awareness of the problem, defining

cost-effective methods of delivering patient care and patient education, and increasing patient compliance.

In 1977, the following goals were identified by the Institute:

- Emphasize research on etiology and pathogenesis of hypertension.
- Encourage the development of improved methods and techniques for all aspects of hypertension research.
- Identify important new areas for research emphasis through the Hypertension Task Force activities.
- Broaden the interdisciplinary base for contributions to hypertension research by attracting scientists who traditionally have not been involved in this field, or those unaware of the magnitude of their potential contributions if their efforts were directed toward this area of research.
- Complete the Hypertension Detection and Followup Program.
- Implement effective models of high blood pressure control on a communitywide basis.

Accomplishments Through 1982

Drug Therapy

The development of drugs during the past two decades has made long-term control of hypertension possible. Some patients, however, have significant side effects from all available agents. In addition, the treatment of many patients with very severe hypertension is often only marginally effective.

Some important new antihypertensive drugs were introduced for clinical use during the past 10 years. Many beta-adrenergic blockers have become available, and they have been widely used. Other new agents have included clonidine, which is a centrally active alpha-2 receptor agonist, and prazosin, which is a peripherally active alpha-1 receptor antagonist.

The treatment of severe and refractory hypertension has been enhanced by the introduction of the potent vasodilator, minoxidil, which has proven of value as a third-step drug in accelerated hypertension, particularly if associated with renal failure.

Of importance to an understanding of the mechanisms of hypertension and the control of refractory hypertension has been the introduction of drugs (such as captopril) that inhibit the conversion of angiotensin I to angiotensin II. These drugs are often effective in treating patients with severe hypertension. They also offer promise for the management of patients with refractory congestive heart failure and of those in clinical states associated with severe vasoconstriction such as scleroderma or Raynaud's syndrome.

A new class of vasodilator drugs, calcium-channel blockers, also has been developed. At present, they are used largely in the treatment of angina pectoris, but they also have an antihypertensive effect and may prove useful in treating hypertension.

Sodium

Evidence continues to accumulate that an important relationship exists between sodium and human hypertension. When human hypertensives are fed a diet with a very low sodium content, their blood pressure usually becomes lower and frequently enters the normal range, and when human subjects and some animals with the hereditary susceptibility to hypertension are fed a high salt diet, their blood pressure usually rises, often into the hypertensive range. Thiazide diuretics often lower the blood pressure of hypertensives close to or within the normal range. In addition, studies of unacculturated societies have shown a strong correlation between the amount of sodium in the diet and the incidence of hypertension. In such societies, blood pressure does not appear to rise with advancing age although other variables cannot be ruled out. Many different animal species, including rats, dogs, chickens, pigs, and monkeys, develop hypertension if they are fed a high salt diet.

The mechanisms by which sodium contributes to the elevation of arterial pressure are still only partially understood. In the past 10 years, however, evidence has accumulated to support the working hypothesis that some human hypertension requires two separate features, a genetic susceptibility for it and a high salt intake.

The Autonomic Nervous System

Basic and clinical research has somewhat improved the understanding of the role of the peripheral sympathetic nervous system in the development or maintenance of hypertension. These accomplishments have been made possible in part by the development of sensitive techniques for the measurement of plasma catecholamines. Increased levels of plasma norepinephrine have been demonstrated

in certain experimental animal models of hypertension and have been found in selected patients with essential hypertension, and a significant correlation has been observed between the levels of blood pressure and plasma norepinephrine. Plasma norepinephrine also has been shown to be sensitive to changes in sodium balance. Interrelationships between blood pressure, sodium, and the sympathetic, renin-angiotensin, and prostaglandin systems have also been demonstrated experimentally, with angiotensin II appearing to potentiate adrenergic vasoconstrictor reactions and prostaglandins of the E series appearing to have the opposite effect. In humans, increased blood pressure responses to stressful stimuli in association with evidence of enhanced peripheral sympathetic activity and increased renal renin release have been found not only in hypertensive subjects but also in normotensive children of patients with essential hypertension. These basic and clinical investigations have provided further evidence of the importance of the sympathetic nervous system in hypertension and have demonstrated the close interrelationships among the various physiologic systems involved in blood pressure regulation.

Major basic research advances have occurred in the molecular characterization of adrenergic receptors. In the past decade, adrenergic receptors have been studied directly with the use of radiolabeled ligands of known receptor agonists and antagonists. Specific alpha-1, alpha-2, and beta receptors have been characterized and quantified in plasma membrane fractions obtained from a variety of animal and human cells and tissues. These receptors have been shown to be involved in the mediation of adrenergic responses. They appear to be in a dynamic state and to be regulated or influenced by adrenergic agonists and antagonists as well as by certain hormones and antihypertensive drugs. These techniques and findings have added appreciably to the understanding of the physiological mechanisms regulating adrenergic function and have provided new methods by which studies of regulation of adrenergic function in disease states such as hypertension can be conducted. Furthermore, they offer promise for the development of specific molecular approaches to influence adrenergic function and blood pressure.

Significant new information has also been obtained regarding the role of sympathetic nerve endings in neurotransmission. Previously, such nerves were thought to be concerned primarily with the synthesis, storage, release, and inactivation of norepinephrine. This concept has been expanded considerably in the past decade. There is new emphasis on the receptors that mediate the action of the transmitters. Alpha and beta receptors were previously defined on the basis of pharmacological characteristics. Subsequent work determined the relation between beta-adrenergic stimulation and activation of adenyl cyclase in cell membranes. Specific alpha and beta presynaptic and postsynaptic receptors have since been identified. Presynaptic

alpha-2 receptor stimulation has been shown to inhibit the release of norepinephrine. Postsynaptic alpha-1 stimulation, in contrast, has been found to enhance the response of effector organs. The sites of action of various adrenergic agonists and antagonists also have been clarified by the new studies. Central alpha agonists such as clonidine have been found to act at presynaptic receptor sites, while such agents as phenylephrine, methoxamine, phentolamine, and prazosin affect primarily the peripheral alpha-1 sites. Such studies provide a basis for the future development of new and specific medications for lowering and raising blood pressure.

The Central Nervous System

A major advance in hypertension research over the past decade has been the recognition that the brain is critical in maintaining the elevated blood pressure in a number of forms of the disease. The evidence includes the findings that: a number of drugs useful in lowering high blood pressure work through centers in the brain; chronic hypertension with many of the features of the human disease can be produced in animals by interference with transmission through very restricted areas of the brain, in particular a nucleus of the lower brain stem, the nucleus tractus solitarius; hypertension produced in animals by interfering with kidney function, by producing brain lesions, or by disturbing salt and water metabolism can be abolished by discrete lesions placed in regions of the hypothalamus; in some patients, hypertension occurs in response to a distortion of the lower brain stem by tumors or arterial abnormalities, and when the defects are surgically corrected, blood pressure returns to normal levels; and the brain is a major target organ for the cardiovascular actions of angiotensin II, a hormone secreted by the kidney that is often present in excessive amounts in hypertensive patients.

Studies of the function of the central nervous system in cardiovascular control have benefited from the application of techniques of contemporary neuroscience. For example, the use of new methods for mapping the distribution of central pathways through which the brain controls blood pressure has revealed specific brain areas delegated to cardiovascular control. These areas are discrete and are frequently ones that also subserve the regulation of hormones and primitive behaviors such as feeding, drinking, or aggression.

Important progress has been made in identifying the neurotransmitters that are the chemical messengers produced by neurons within these networks. Of particular interest has been the discovery that a variety of peptides formerly believed to function only as hormones secreted by the gut, pancreas, kidney, or pituitary gland are localized in nerve tracts in the brain,

particularly in those regions involved in blood pressure control. For example, peptides of the endorphin family as well as insulin, glucagon, and components of the renin-angiotensin system have been found in the brain. The relationship of these agents to control of blood pressure is unknown. Studies of other traditional transmitters such as the catecholamines have also added new knowledge. Notable has been the discovery that epinephrine-containing neurons appear to have an important role in control of blood pressure by the brain.

Investigation of another peptide hormone, vasopressin, has begun to raise questions about the relevance of this substance to hypertension. Over the past 10 years, there has been increasing evidence that under certain circumstances, vasopressin can be important in directly regulating arterial pressure and that disturbances of the content of vasopressin, not only within the pituitary but also within central tracts, may occur in strains of rats with spontaneous hypertension. Recent studies have also raised the prospect that certain forms of experimental hypertension are partially dependent upon the release of vasopressin.

The Renin-Angiotensin System

Evidence for the active participation of the renin-angiotensin system in hypertension has continued to accumulate. The development of four pharmacological probes that act to block the renin system at different control points has markedly facilitated investigations. The probes include beta receptor blocking drugs, which act by inhibiting renin; saralasin, a specific antagonist of angiotensin II; teprotide, the nonapeptide angiotensin I converting enzyme inhibitor; and captopril, the orally active converting enzyme inhibitor. The development of these antagonists has provided important new tools for analyzing the participation of the system in individual hypertensive patients and for finding surgically correctible forms of hypertension due to renovascular or adrenocortical pathology in instances in which renin patterns are specifically abnormal. At the same time this research helps define a new approach to drug therapy.

An important finding of the past decade has been that 90 percent of the total circulating renin in human plasma occurs in an inactive form. This inactive form of renin has been tentatively called prorenin because a large body of circumstantial evidence now suggests that it is likely a precursor of active renin. The demonstration that prorenin is a true prohormone interconvertible to renin in vivo, however, is not yet absolute. Acid treatment and low temperature have both been found to activate prorenin. Acid activation appears dependent on the presence of Hageman factor and plasma kallikrein. Moreover, highly purified renal

kallikrein also appears capable of activating inactive renin to the active form after prior acidification. The discovery of prorenin has relevance to two major aspects of hypertension research. From a methodological standpoint, many older methods of measuring plasma renin activity employ techniques that inadvertently convert inactive renin to an active form and thus can lead to gross error in the assessment of the truly active renin value in plasma. From a theoretical standpoint, the site of origin of prorenin and its role as a precursor for active renin seems of considerable importance for understanding the fundamental nature of the renin system.

Vascular Smooth Muscle and Cell Membrane Changes

The final common mechanism responsible for the elevated arterial pressure of hypertension is an increase in vascular resistance. For this reason, effort has been made to characterize the nature and the cause of the vascular change responsible for this increase. Evidence has accumulated that either humoral or neurogenic factors may be responsible for initiating the increase in total peripheral resistance. These factors may operate as trophic influences altering the intrinsic sensitivity of the vascular smooth muscle cell. Recently the possibility that there may be an intrinsic change in the vascular smooth muscle has prompted extensive studies of the function of this tissue at a cellular and molecular level in normotensive and hypertensive animals.

Many laboratories have reported that the calcium-sequestering mechanism as evaluated by uptake of calcium into subcellular fractions may be deficient in vascular smooth muscle of hypertensive animals. There is also evidence that the electrogenic sodium-potassium pump of the plasma membrane that influences the membrane potential of the cell may be abnormal in hypertension. The most promising evidence that has been developed in the past decade is that the plasma membrane of the vascular smooth muscle from spontaneously hypertensive and deoxycorticosterone (DOCA)-hypertensive rats is more permeable to various ions than is the plasma membrane of vascular smooth muscle from normotensive rats. Relevant to this finding is the recent observation that the red blood cells from spontaneously hypertensive rats and also from human beings with essential hypertension have similar properties of abnormal permeability. The hypothesis has evolved that genetic hypertension in rats or essential hypertension in humans may be the reflection of a generalized membrane abnormality that can be easily studied in the red blood cell but that has significant influence on arterial pressure by increasing sensitivity and reactivity of vascular smooth muscle, with the result that blood vessels are narrowed.

Epidemiologic Findings

As recognized in the 1972 National Program, the etiology of hypertension is extraordinarily difficult to define. Substantial progress nevertheless has been made through epidemiologic studies during the 10-year period. Three accomplishments merit special attention and emphasis.

One area of accomplishment has been the clarification of the heritability of blood pressure. In the NHLBI Twin Study, 514 pairs of white male veteran twins have been studied since 1972, with the major finding that the variance of the distribution of blood pressure of individuals within a population is, in part, genetically determined, with an estimated heritability of 0.64 for both systolic and diastolic blood pressure. This important finding has been supported in the Framingham Offspring Study. In that project, a high correlation of blood pressure was observed between parents and offspring and between siblings, while no such correlation was found between spouses and adopted relatives.

These studies have made a unique contribution to understanding the relative influences of genetic and environmental factors in the etiology of blood pressure, and they emphasize the need to study blood pressure in a familial context. To assess the influence of heredity on factors that regulate arterial blood pressure, for instance, studies have been conducted of sodium loading and depletion in monozygotic and dizygotic twins; normotensive first degree relatives of essential hypertensives; and age, sex, and race-matched normotensive control subjects. Evidence was found supporting a genetic influence on plasma renin activities, on plasma aldosterone concentrations, and on the natriuretic responses after sodium loading. A heritable influence on plasma and urinary norepinephrine after sodium loading was also demonstrated. Relatives of hypertensives differed from controls in that they had higher blood pressures, greater renin values, and relatively sluggish natriuretic responses. Since renin and fractional sodium excretion were inversely correlated in all subject groups, it is possible that the heritable influences observed in sodium excretion were mediated by the renin-angiotensin-aldosterone system.

The second area of achievement has been the demonstration of the importance of "tracking" and body size in the determination of blood pressure even in the earliest years of life. These observations came from the Program on High Blood Pressure in the Young, which was initiated to explore the roots of hypertension in adolescence or earlier. A major finding was that blood pressure "tracks" over time (that is, the rank order of blood pressure levels tends to be maintained over the years in both younger and older age groups). Current blood pressure is thus the single best measure for predicting future blood pressure among both

children and adolescents. Body weight is the major independent correlate of blood pressure. Young adults who were fat children tend to have higher blood pressures than young adults who were not fat, regardless of the levels of blood pressure and fatness of their parents. Changes in blood pressure over time correlate directly with changes in weight.

The third area of accomplishment deals with the more sensitive detection of cardiac target organ response to hypertension. In the Framingham cohort, echocardiography was more sensitive than the electrocardiogram for identifying cardiac abnormalities. Left ventricular hypertrophy, for example, was detected in 9 percent of the Framingham cohort by echocardiography but in only 3 percent by standard 12-lead electrocardiography. Such hypertrophy was correlated with the level and duration of hypertension. Use of this potentially more sensitive tool for assessment of the relationship of target organ damage to hypertension should help extend knowledge of the pathogenesis of hypertensive heart disease.

Clinical Trials

The increasing development before 1972 of drugs to reduce blood pressure stimulated the need for scientific evaluation, through randomized clinical trials, of their effectiveness in the therapy of hypertension. In the Veterans Administration Cooperative Study on Antihypertensive Agents, clinical trials in 1967 and 1970 produced convincing evidence of the ability to reduce mortality by antihypertensive drug therapy among men who had severe and moderately severe hypertension. The potential broader applicability of such findings to the general population in both sexes and in the black population was not known.

The Public Health Service Hospitals Cooperative Study, which was completed in 1976, addressed the effects on cardiovascular complications of treating mild hypertension over an average followup period of more than 7 years. Almost 400 subjects between 21 and 55 years of age with diastolic blood pressures between 90 and 115 mm Hg, who were free of evidence of cardiovascular complications, were studied in a randomized double-blind trial at six clinical centers. Treatment assignment was either to a diuretic, chlorothiazide (500 mg twice daily), together with rauwolfia (100 mg twice daily), or to identical placebo tablets. Although the size of the sample was small, although there were relatively few events, and although a high number of patients were lost to followup, the study provided some indication in the drug-treated group of a reduced rate of development of electrocardiographic findings of left ventricular hypertrophy and left ventricular ischemia. Over the study period, events of myocardial infarction,

stroke, and death were too few to prove significant benefit of drug therapy.

A special panel convened by the Institute in 1970 to assess the need for additional clinical trials in hypertension recommended:

> The first priority need is to determine the effectiveness of antihypertensive therapy in reducing morbidity and mortality from hypertension in the general population. Such studies should include both sexes, all races in a community, and younger adults as well as middle age ranges.

Hypertension Detection and Followup Program

After intensive review, the Institute proceeded to undertake a major population-based clinical trial in communities with high prevalence of high blood pressure. The primary objective of the Hypertension Detection and Followup Program, initiated in 1971, was to determine the effectiveness of intensive antihypertensive therapy in reducing mortality associated with elevated blood pressure in the general population. An important component of this program involved behavioral elements related to the identification of factors that enhance adherence to therapy and to the assessment of personal attitudes toward hypertension. Between February 1973 and October 1974, 10,940 hypertensive persons of 30 to 69 years of age were randomized into stepped-care (SC) or referred-care (RC) groups within 14 centers and by entry diastolic blood pressure (90-104, 105-114, and 115+). After 5 years of the study, 78 percent of the SC participants were taking medication and 65 percent had achieved blood pressure levels within the normotensive range, which was at or below the HDFP goal for diastolic blood pressure.

Throughout the trial, control of blood pressure was consistently better for the SC than the RC group. This difference in degree of control was least for white women; it was less for whites than for blacks of the same sex. For white men, black men, and black women, and for the age subgroups of 50 to 59 and of 60 to 69, 5-year all-cause death rates were substantially lower, by 15 to 28 percent, for SC subgroups compared with the RC subgroups.

The central finding of the HDFP was a statistically significant reduction in 5-year all-cause mortality, which was the primary endpoint of the study, both for the SC group overall (16.9 percent) and for SC participants with mild hypertension (90 to 104) at entry (20.3 percent). The reduction in mortality found in black men and black women was particularly striking. The overall

reduction of all-cause mortality among black men was 18.5 percent and among black women 27.8 percent.

The 1980 Special Public Health Award from the Albert and Mary Lasker Foundation was presented to the NHLBI for the HDFP, which proved the lifesaving value of treating persons with high blood pressure. To assure adequate data tapes and records with appropriate indices and guides for future use by the scientific community, the Data Coordinating Center of the HDFP will continue mortality followup and data analysis through June 1985.

The Impact of Hypertension Information (IHI) was an ancillary study in three of the HDFP communities to determine if there had been any effects on the status of hypertension resulting from the HDFP as well as from other massive efforts in the United States between 1973 and 1978 to detect and treat those with high blood pressure. The three clinical centers assessed changes, over the 5-year period, in blood pressure distribution, degree of awareness, and level of treatment in the population by interviewing a new sample from the same census tracts of the community as screened initially in the HDFP. For black men, a 21 percent reduction in uncontrolled treated hypertensives was obtained, for black women 27 percent, for white men 22 percent, and for white women nearly 36 percent. The decrease in the proportion of uncontrolled hypertensives was consistent for nearly all age, race, sex, and clinical center subgroups.

Other Trials

The Multiple Risk Factor Intervention Trial, initiated in 1972, was designed to determine whether a reduction in mortality from coronary heart disease and total mortality can be achieved by a reduction of the combined risk factors of high blood pressure, high blood cholesterol, and cigarette smoking in men at high risk of developing coronary heart disease. (This study is described in more detail in Section 3, "Arteriosclerosis," page 109.) The results of this study are to be released in late 1982.

The NHLI-VA Propranolol Drug Study, which began in 1973, was a double-blind study conducted in seven VA hospitals to determine whether propranolol alone or with hydrochlorothiazide or hydralazine reduces arterial blood pressure as effectively as the commonly used combination of reserpine and hydrochlorothiazide, and to assess the incidence, severity, and gravity of side effects from treatment with propranolol. Measurements of dynamic factors such as systolic time intervals were also made. The patients were males of 18 to 59 years of age whose mean of three diastolic blood pressures (DBP) was greater than 90 and less than 110 mm Hg at each of two clinic visits. By the end of December 1974, 450 participants were randomized into the study. Of the randomized

participants, 332 completed a minimum of 6 months of followup and treatment. Results obtained at 12 and 18 months of followup were similar to those observed at 6 months. It was concluded that in this population, propranolol and propranolol with hydralazine were less effective than the standard regimen (reserpine and hydrochlorothiazide) in achieving control of blood pressure.

The NHLI-VA Pilot Clinical Trial in Mild Hypertension, which began in 1974, was a double-blind study conducted in four VA hospitals to test the feasibility of conducting a larger controlled clinical trial to determine whether antihypertensive therapy for persons with mild hypertension would result in reduction in the incidence of myocardial infarction in persons from 21 to 50 years of age. By the end of 1975, 1,026 participants with diastolic blood pressure of 85 to 105 mm Hg had been randomized into the study. A stepped-care regimen of drug therapy that used chlorthalidone and reserpine was followed.

The study revealed an average drop in diastolic blood pressure of almost 11 mm Hg in the group receiving active therapy and less than one-half of that in the placebo group. Once established 6 months after randomization, the new pressure levels persisted almost without change throughout the study. There was no significant difference between the two groups in the incidence of major morbid events. A total of eight active and five placebo subjects developed myocardial infarction or died suddenly. There was, however, an excess of apparently new arrhythmias among the active drug subjects (27 in the active group versus 8 in the placebo group). Finally, there were twice as many side effects and 20 times as many chemical abnormalities among the active than among the placebo subjects.

The clinical centers in this trial terminated activity in December 1976 and the Coordinating Center in June 1977. An Ad Hoc Mild Hypertension Committee was appointed by the NHLBI to review the study data and make recommendations for future studies. The committee supported the idea of a mild hypertension clinical trial and offered the following conclusions and recommendations:

- The mild hypertension question is important.
- More definitive information is needed for efficacy and side effects from drug treatment of mildly hypertensive patients.
- It is feasible to design a protocol for the study.
- A population of suitable patients is probably available.
- There would be major problems keeping sufficient patients in the study since the control group would be more likely

to be treated as time goes on and the treatment regimens would be subject to change.

- The projected cost would be $36 to $100 million to follow 10,000 randomized patients for 6 years. The committee felt that the ultimate cost would probably be closer to $100 million.

Despite the acknowledged importance of determining the efficacy of drug treatment of mild hypertension and the feasibility of designing such a study, the committee recommended against undertaking a new clinical trial of mild hypertension therapy. The expected difficulty of keeping the control group from undertaking treatment over time and the high cost for such a study were considered too great to warrant a clinical trial. Instead, the committee recommended continued support for the Hypertension Detection and Followup Program in which about 70 percent of study participants were in the mild hypertensive range.

The Systolic Hypertension in the Elderly Program (SHEP), initiated in 1980, is cosponsored with the National Institute on Aging. This pilot study, involving five clinical centers, is to assess the feasibility of conducting a full-scale trial of the effects of treating isolated systolic hypertension in persons over the age of 60. Five hundred subjects are to be randomized into a double-blind stepped-care program of antihypertensive treatment. The effectiveness and tolerability of chlorthalidone as a step-one drug (25 to 50 mg per day) and of three step-two drugs--reserpine (0.1 to 0.2 mg per day), hydralazine (50 to 100 mg per day), and metoprolol (100 to 200 mg per day)--will be evaluated. The psychological, psychiatric, and social effects of the treatment program will also be studied.

The success of various recruitment strategies, the acceptability of the overall program, and an important behavioral component will be assessed. Initial results are expected in the summer of 1983. Proposed endpoints for a full-scale trial are incidence of stroke and all-cause mortality.

The Hypertension Prevention Trial (HPT) began in the summer of 1981. This is a study designed to determine the feasibility of dietary intervention as a means of primary prevention of hypertension. Eight hundred men and women, aged 25 to 45, who have high-normal diastolic blood pressure (80 to 90 mm Hg) and who are at least 10 percent overweight are being recruited at four clinical centers. They will be randomly allocated in equal numbers to one of five intervention groups: sodium restriction (70 mEq per day), sodium restriction and potassium supplementation, caloric restriction for weight control, sodium and caloric

restriction, and no dietary modification (control). All participants will be followed for a minimum of one year. The results of this study, expected in 1984, will determine whether a large-scale trial of this approach to the prevention of hypertension is warranted.

Demonstration, Education, and Control Programs

National High Blood Pressure Education Program

In the late 1960's and early 1970's, when the Veterans Administration study provided the first real evidence that controlling severe and moderate hypertension markedly decreased morbidity and mortality, the importance of hypertension as a public health problem became increasingly apparent. A large number of Americans were failing to receive needed treatment. "Half-by-half-by-half" became the descriptor for this phenomenon--namely, one-half the hypertensives were being detected, one-half of these were being treated, and one-half of the latter were truly under control. In brief, only one in eight hypertensives had adequately controlled blood pressure.

Because of the need to increase the awareness of physicians and patients of the need for effective long-term control of hypertension, the Institute established the National High Blood Pressure Education Program (NHBPEP) in 1972. The strategy it adopted, by extensive use of the national media, was to educate the public to accept and expect testing for hypertension and long-term treatment for its control, and to coordinate an ever growing coalition of federal agencies, professional, voluntary, and trade organizations, state and local public health departments and diverse community programs in their efforts to identify and to bring and maintain under control the maximum number of Americans with uncontrolled hypertension.

In the years since then, the number and proportion of hypertensives detected, treated, and controlled has risen steadily. Statistics on physician appointments and prescribed medications show an increased number of persons seeking therapy and increased treatment by medical practitioners.

The Pilot Evaluation Studies of Community High Blood Pressure Control were initiated in 1978 to determine ways to establish practical models of high blood pressure control that would be acceptable in communities with a high prevalence of the disorder. The program was designed to facilitate a cooperative relationship of existing resources to make a total community approach to high blood pressure education, detection, treatment, and followup more effectively reach the total hypertensive population in a defined

community. Three rural (Georgia, Kentucky, and North Carolina) and two urban (Berkeley, California, and Detroit, Michigan) programs were established, and baseline surveys have been completed. A final 5th-year survey will be conducted to measure changes in blood pressure control that have occurred during the period of this community-oriented intervention.

The Statewide Coordination Project for Demonstration of High Blood Pressure Control was established in 1978 as part of a congressional mandate "to conduct, assist, and foster research, investigations, experiments, and demonstrations relating to the cause, prevention, and methods of diagnosis and treatment of heart...disease." Seven states (California, Connecticut, Georgia, Maine, Maryland, Michigan, and South Carolina) were funded to determine the impact of coordination of resources and activities on high blood pressure control over 5 years. Baseline household surveys were conducted, coordinating councils were established, educational intervention activities were undertaken, and evaluation strategies were developed. A cooperative workshop fostered the participation of representatives from all seven states in sharing common and divergent elements of their surveys and working toward developing methods for assessment of changes. Repeat household surveys are under way or planned for the last year of each project. The last project will be completed in 1983.

The Black Health Providers Task Force on High Blood Pressure Education and Control was established in October 1977 to obtain a consensus of the role of black health care providers in the detection, treatment, and management of hypertensive patients. Over a period of 18 months, the task force discussed current education and control activities, determined feasible interaction and cooperation among black health providers, and identified barriers to care and high-risk segments of blacks not being reached by current control efforts. The task force recommended that a 20-year effort be undertaken to bring uncontrolled high blood pressure among black Americans under control. Two major objectives were suggested:

- Among blacks with DBP 105 mm Hg and above, attain effective control (DBP less than 90 mm Hg) among a net of 50 percent or more of hypertensive black Americans within the 5-year period 1981 to 1985.

- For persons in the 90 to 104 mm Hg range, attain better levels of control and awareness by reducing the percentage of black Americans in each of the following categories: undetected hypertensives, detected hypertensives not in treatment, and detected hypertensives in treatment but not under control.

The task force completed its work in 1979, and two documents resulted from this effort--one, the report of the task force itself, and the other, the response of the NHLBI to the task force report.

The NHLBI-HSA Five-Site Demonstration Project for High Blood Pressure Control responded to two main concerns of the Black Health Providers Task Force--namely, that a community organizational structure within an underserved community is essential to improving the control of high blood pressure over time, and that a demonstration at community sites where primary health care providers function in expanded roles should be undertaken. The NHLBI and the Health Services Administration (HSA) agreed to a joint effort to support high blood pressure control-demonstration research at five community health centers over a 5-year period. The undertaking also provided the Institute with an opportunity to evaluate the use of HDFP methods in an existing clinical setting rather than in a research setting. Such an action represented a major step of translation of clinical trial outcomes (such as HDFP) into the U.S. health care system. The sites selected and funded in 1981 through an interagency agreement with the Bureau of Community Health Services, HSA, were two urban (primarily black), two rural (primarily black), and one rural (primarily Hispanic).

In 1978, three programs were funded to determine the feasibility of high blood pressure control in the worksetting, the endpoints being changes in health status at the end of a 24-to-30-month period of study. All the participants in the Demonstration of High Blood Pressure Control in the Worksetting Program have collected and analyzed data on screening, referral, and followup activities. It was found that age and percent overweight are good predictors of high blood pressure. Control of high blood pressure was similar by race but better for women than men. Younger workers had greater lability of blood pressure. For those on treatment, the more aggressive the followup procedures, the greater the blood pressure control. These results demonstrated the feasibility of successful control of blood pressure in the worksetting.

Instrumentation

For the ambulatory patient, the Institute has supported the development of automatic blood pressure measurement systems that increase objective out-of-clinic documentation of the results of therapy and improve patient compliance. Support has also been extended for the development of an automatic implantable blood pressure controller.

There remains a definite need for improved instrumentation for the sensitive and specific detection of renovascular stenosis. Currently, most techniques are indirect, relatively insensitive,

and nonspecific. Although contrast arteriography remains the definitive method for establishing a diagnosis of renovascular hypertension, this invasive technique cannot be used for mass screening of patients. It is estimated that up to 5 percent of patients with hypertension have renovascular stenosis that can be significantly improved or cured either by surgery or by newer methods such as transluminal balloon angioplasty. In addition, such treatment of renovascular hypertension can lead to preservation of renal mass and lessen the risk of chronic renal failure. It is anticipated that Doppler ultrasonic techniques and intravenous angiography may both have increasing importance in the screening of hypertensive patients for renovascular disease.

A Consensus Development Conference on Improving Clinical and Consumer Blood Pressure Measuring Devices was held in 1979 with the primary purpose of developing a common terminology for proposed national voluntary guidelines for the use and manufacture of mechanical and electronic blood pressure measurement devices. The topics addressed included scope of labeling, performance requirements, test methods of validation procedures for either automated or nonautomated sphygmomanometers, and needs of special patients such as children and the elderly. Proposed standards for nonautomated, electronic, and automated sphygmomanometers are now at the stage of public review and comment.

Nutrition

The Division has provided a wide array of technical support services for the nutritional aspects of hypertension including a symposium at the American Dietetic Association annual meetings in 1980 entitled "Current Nutrition Issues in Hypertension." Topics addressed were physiological facets of hypertension, epidemiology of hypertension, management of hypertension, significance of hypertension in children and adolescents, preferences for salt and sugar, sodium in food processing, and the FDA perspective on sodium and sugar.

The Dietary Intervention Study of Hypertension (DISH), which began in five centers in 1980 as an outgrowth of the HDFP, is assessing the effect of dietary change on blood pressure after withdrawal of medication in patients whose blood pressure had been normalized by pharmacological means over a period of 5 previous years in the HDFP. Four groups are being compared: continued medication; discontinued medication, with no dietary modification; discontinued medication, with reduction in sodium and moderate increase in potassium; and discontinued medication, with dietary program to encourage weight loss in those whose weight exceeds 20 percent ideal weight. Results of this study will be reported in late 1983.

The NHLBI issued a program announcement in 1981 to focus attention upon dietary sodium and its role in the prevention and management of hypertension. The objective was to encourage the submission of scientifically meritorious applications concerning a broad range of investigations, including physiological, clinical, preventive, and therapeutic research. Such research should provide further knowledge of direct importance in the prevention and management of hypertension in definable subgroups of persons.

Biobehavioral Research

In 1978, the Working Group on Compliance With Antihypertensive Regimens was convened to summarize the work of compliance studies supported by the NHLBI. Major observations were published in "Patient Compliance to Prescribed Antihypertensive Medication Regimens: A Report to the National Heart, Lung, and Blood Institute."

The NHLBI has supported studies of the efficacy of biobehavioral approaches such as biofeedback and relaxation to treat hypertension. Investigations are under way to determine the applicability of these techniques to mild hypertension.

In 1980, the Working Group on Behavioral Approaches to the Treatment of Hypertension reviewed available data and recommended encouragement of research on nonpharmacologic approaches to treatment of hypertension. In 1981, the DHVD issued a program announcement entitled "Biobehavioral Approaches to the Treatment of Hypertension" to develop and focus research interest in this area. The Working Group on Biobehavioral Factors in the Development of Hypertension reviewed the state of knowledge in the area of behavioral influences on the development of hypertension. The DHVD further reviewed this area and issued a request for applications (RFA) in 1982 to study behavioral aspects of genetic and developmental factors in the etiology and progression of essential hypertension in animal models.

State of Knowledge in 1982

Hypertension continues to be the most common of all cardiovascular diseases and also continues to be a major public health problem. The recent decline in the death rate from coronary heart disease at a time when the treatment of hypertension has improved considerably suggests the possibility that hypertension treatment and control may be an important contributing factor.

The scientific community continues to perceive hypertension as a multifactorial problem in which neural, humoral, genetic, and

environmental factors play interdependent and compensatory roles--a disorder of regulation rather than a reaction to some abnormal substance. While these changes vary with the initiating factor, the duration of hypertension, and the vascular bed, they are believed to result ultimately in an increase in vascular reactivity and in vascular resistance.

The factor responsible for the increase in total peripheral resistance appears to be a functional change in the contractile activity of the vascular smooth muscle. It has been demonstrated that this change is associated with an abnormality in the vascular smooth muscle cell membrane. Vascular resistance, and hence arterial pressure, may be returned to normal by antihypertensive measures that reduce the level of contraction of the vascular smooth muscle. This sequence can occur even in the presence of persistent vascular structural abnormality.

In studies of the pathophysiology of hypertension, there has been a rapid increase in appreciation of the importance of genetics. There is now agreement that heredity plays an important role. A variety of animal models of inherited hypertension has been developed that has proved useful in laboratory studies. The hypothesis has evolved that genetic hypertension in the rat, or essential hypertension in humans, may be the reflection of a generalized membrane abnormality. Such an abnormality could exert a significant influence on arterial pressure by increasing vascular smooth muscle sensitivity and reactivity and thereby cause a narrowing of the blood vessels. A promising start has also been made in the application of biochemical genetic approaches to studies of the defect or defects underlying the role of inheritance in human hypertension. However, there are still several opportunities for research that uses genetic breeding techniques in laboratory studies with animal models of hypertension. Biochemical genetic studies in humans are still in an early stage.

The degree of neural control in the maintenance of high blood pressure is more fully appreciated. Substantial progress has been made in localizing blood pressure control centers in the brain and in mapping pathways and identifying neuropeptides and other neurotransmitters that exert significant influence on blood pressure regulation. Considerable evidence is now available to indicate that sympathetic nervous system activity is altered in many patients with essential hypertension and that the vascular smooth muscle is hyperreactive to sympathetic stimulation in certain hypertensive patients. Whether these abnormalities precede or appear as a consequence of the hypertension is uncertain. Plasma norepinephrine levels have been studied extensively, and they appear to be elevated in a relatively small subfraction of hypertensives. The role of epinephrine, either centrally or peripherally, in essential hypertension has not been defined

although recent data would suggest that epinephrine may be important. Further research in this field requires substantial improvements in the methodology for studying sympathetic function and neural catacholamine metabolism.

The molecular nature of adrenergic receptors has been partially characterized along with the mechanism by which they mediate adrenergic responses. The demonstration of specific alpha and beta receptors in circulating blood cells may provide a new tool for clinical investigations involving the direct assessment of adrenergic receptors in hypertensive patients subjected to physiological and pharmacological manipulations. Determination of changes in these receptors that may be present in human or experimental hypertension needs to be pursued.

Research continues on two classes of vasoactive substances, the prostaglandins, and the kallikrein-kinin system. Several new prostaglandins have been discovered, of which two, prostaglandin E_2 and I_2, appear to influence the secretion of renin and thereby control the level of angiotensin II. In addition, prostaglandin I_2, also known as prostacyclin, has been identified as a powerful dilator of small arteries and as an inhibitor of platelet aggregation. Kallikrein, which is an enzyme present in large amounts in the kidney, elaborates kinins, which dilate small arteries and induce prostaglandin secretion. How these substances fit into the increasingly complex scheme is only beginning to be understood and merits intensive study in the coming decade.

Several lines of evidence suggest that the normal kidney exerts some type of antihypertensive action. Transplantation of normal kidneys into hypertensive humans and rats often brings the blood pressure down to normal levels. In recent experiments, there has been evidence that a vasodilator substance emerges from the kidneys and reduces blood pressure when the stimulus causing hypertension has been removed. Interstitial cells in the inner medulla of the kidney secrete vasoactive agents that reduce blood pressure when these cells are implanted under the skin of animals. These cells may exert an antihypertensive action in their natural locus in the kidney.

Dietary factors are still believed to exert a significant influence on blood pressure. The leading candidate is sodium since it favors blood pressure elevation in a sizable proportion of hypertensives. Animal studies and some data about humans with high blood pressure support the concept that potassium may play a protective role--the higher the dietary potassium-to-sodium ratio, the lower the blood pressure. Finally, dietary calcium and dietary proteins and amino acids appear to influence blood pressure, although the mode of action of these nutrients has yet to be determined.

Obesity also appears to play a role in hypertension. Among hypertensives, blood pressure correlates positively with weight. One hypothesis holds that elevated blood pressure is related to the excess sodium intake that occurs in such patients, but some subsequent studies have demonstrated that weight loss without sodium restriction results in a significant decrease in blood pressure. Thus, in clinical practice, weight reduction has become an important nonpharmacological approach to blood pressure control in the mild hypertensive and a supplement to pharmacological treatment in all hypertensives.

Investigators are beginning to elucidate the psychological contributors to the development of high blood pressure. Evidence for a "hypertensive personality" is meager, and what there is has not proved useful in furthering behavioral research. Certain characteristics, however, including increased anxiety, anger, and lack of assertiveness in interpersonal situations, have been correlated with augmented cardiovascular activity. Further research is needed to clarify the relationship of such characteristics to hypertension and to determine whether their presence precedes blood pressure elevation, whether they are subject to change, and if so, whether such change modifies the hypertensive's cardiovascular response to stress.

Knowledge of the natural history of essential hypertension has expanded considerably in the past 10 years. A substantial "tracking" of blood pressure has been observed from infancy, through adolescence, and into adulthood. The tracking suggests that a baby in the upper decile of blood pressures tends to stay in the rank through childhood, adolescence, and adulthood. Those with low blood pressure in childhood also tend to maintain low blood pressure throughout life. Thus, the beginning of adult hypertension may be established in childhood, although the merits of treatment of the young in preventing the complications of the disease are untested.

Essential hypertension tends to run in families, and there is a pattern of circulatory alteration as an individual hypertensive progresses from youth to middle age. In many teenagers and young adults, the high blood pressure is supported more by an exaggerated cardiac output than by an abnormal narrowing of the arterioles, which is present to a lesser extent; however, the pattern later becomes reversed with the narrowing of the arterioles the most prominent mechanism.

It has become established that the elevated arterial wall stress of hypertension results in hypertrophy and hyperplasia of the vascular smooth muscle cell and in an increase in deposition of collagen, elastin, and glycosaminoglycans. Reversal of hypertension results in a decrease in vascular smooth muscle water

and protein content, but the increased fibrous proteins persist and can lead to irreversible structural change in the vessel.

The means for better diagnosis have also advanced in the past decade. Differential renal vein renin measurements have become a basic tool for evaluating the relative contribution of each kidney in patients suspected of having curable renovascular hypertension.

By 1982, the large NHLBI multicenter trial, the Hypertension Detection and Followup Program, and studies in other countries provided important information on treatment of mild hypertension. Although the design of the HDFP precluded a placebo group, it became evident that systematic sequential pharmacologic therapy significantly reduced mortality. These findings have led to greater awareness of mild hypertension and have encouraged its treatment.

In the early 1970's, the belief that systolic hypertension constitutes a health risk was not widespread. Epidemiological evidence gathered since then has indicated that systolic blood pressure, particularly in the elderly, is harmful. What levels of systolic pressure should be treated and by what means is not yet established.

By the middle 1970's, clinicians used drug combinations more frequently. Thus, the concept of "stepped care," which is the sequential addition of drugs of different classes to obtain the best clinical effect, was developed as standard treatment. This method of care continues to be the standard in the early 1980's.

Several new drugs have been added to the armamentarium in the past few years. A variety of beta adrenergic blockers, for instance, are now widely used as antihypertensive medications. Other new agents for the treatment of mild and moderate hypertension include the drug clonidine, which acts in the brain on central alpha receptors, and prazosin, which blocks peripheral alpha receptors. The treatment of severe or refractory hypertension has been enhanced by the introduction of the potent vasodilator minoxidil. The new class of vasodilator drugs, calcium-channel blockers, though of primary benefit in the treatment of angina pectoris, may also prove useful in selected hypertensive cases. Of particular importance to understanding the mechanisms of hypertension and the control of refractory hypertension has been the introduction of inhibitors of the conversion of angiotensin I to angiotensin II. These drugs are quite effective in treating patients with severe hypertension, and they may prove useful for the management of patients with refractory congestive heart failure and patients with severe vasoconstriction secondary to scleroderma or Raynaud's disease.

Program Goals 1982 to 1987

- Expand further fundamental research on the etiology and pathogenesis of hypertension including investigations of neural, humoral, genetic, and environmental factors, with emphasis on interdisciplinary approaches.

- Investigate in all age groups the influence of familial, genetic, and environmental factors in the determination of blood pressure levels in order to establish the relative importance of the multiple factors that contribute to the development of high blood pressure.

- Continue to develop and refine noninvasive technologies for measurement of blood pressure and other relevant parameters related to hypertension that can be used as needed for the evaluation of the health status of persons with high blood pressure.

- Continue to improve pharmacological and nonpharmacological methods for the long-term management of hypertension, and evaluate for each their relative roles in terms of benefits as well as risks. Continue the study of the benefits and risks of blood pressure reduction in elderly individuals with systolic hypertension.

- Continue the improvement of control of high blood pressure in the population, especially in segments of the population where the disease is prevalent, with demonstration and education activities.

- Continue research and development programs that attract and sustain high caliber hypertension research investigators to maintain progress against this disease.

Research Activities 1982 to 1987

- Expansion of understanding of genetically mediated hypertension by study of the relationship between biochemical variables and elevated blood pressure in animal models of hypertension and by verification of the hypothesis that genetic hypertension represents a generalized membrane abnormality that may influence arterial pressure by increasing vascular smooth muscle reactivity.

- Expansion of current understanding of the regulation of normal blood pressure and the modulation of elevated blood pressure by the central and autonomic nervous systems, the

chemical mediators that they elaborate, and the vasoactive hormones that they release.

- Continued support of investigations of the humoral mechanisms and humoral receptors involved in blood pressure regulation and hypertension.

- Further study of the biology of renin including development of more useful probes that will permit more precise tracking of the fate of renin and other vasoactive hormones throughout the complex of interacting blood pressure control systems.

- Study of the kidney's nonexcretory antihypertensive function in addition to continuation of study of the various control mechanisms of the body that affect renal excretion of sodium and water.

- Expansion of the scope of basic and clinical studies of the influence of dietary proteins, amino acids, calcium, sodium, potassium, and other food substances on the metabolism of vasoactive substances and on the development of hypertension.

- Further expansion of the currently limited data base on natural substances that have blood pressure-lowering activity.

- Continuation of the Hypertension Prevention Trial and augmentation of current clinical investigations and clinical trials that assess the effect of nonpharmacologic control of body weight and sodium intake on borderline or mild hypertension.

- An intensified search for better drugs that can be applied to the management of persistent significant blood pressure elevation.

- Modification of existing minimally invasive diagnostic techniques to permit accessible and reliable means of identifying individuals with secondary hypertension.

- Continuation of support of the Specialized Centers of Research in Hypertension.

- Continuation of the study of the treatment of systolic hypertension in the elderly, including the Systolic Hypertension in the Elderly Program. Undertake a full-scale trial as early as possible if the feasibility program is successful.

- Support for demonstration and education research projects for modifying hypertensive risk factors, particularly in the very young and in various settings, through public and professional education.

- Identification of opportunities, in the juvenile hypertension population, for research in basic science, clinical applications, and risk factor modification.

- Continuation of identification and treatment of all hypertensives, through the efforts of the National High Blood Pressure Education Program, with emphasis on particular groups (such as minority groups and those with impaired access to health care) that have high risks of hypertension or its sequellae.

5. Cerebrovascular Disease

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5. Cerebrovascular Disease

The term cerebrovascular disease includes stenosing or occlusive disease of the cerebral arteries (thrombosis or embolism) as well as hemorrhagic diseases of the brain (most commonly, hypertensive cerebral hemorrhage; less often, subarachnoid or parenchymal hemorrhage from rupture of an aneurysm or arteriovenous malformation). The clinical expression of disease resulting from either occlusion or hemorrhage is a stroke, which is broadly described as the sudden appearance of a focal neurological deficit, most often paralysis.

Thrombosis usually obstructs a cerebral vessel already narrowed by progressive arteriosclerosis. Emboli can arise from ulcerated plaques in the carotid arteries or from the heart lining or valves. Some of these embolic events now appear to be preventable.

State of Knowledge in 1972

It was the general view in 1972 that atherosclerosis in the vessels of the neck and brain was not qualitatively different from that in the aorta or coronary arteries. It was, of course, recognized that there are peculiarities of location, that the onset of disease occurs there later in life than it does in the aorta, and that, except for hypertension and age, risk factor associations are weaker than those for coronary artery disease. There was one special circumstance, however: plaques at the bifurcation of the carotid artery were recognized to be particularly liable to surface encrustation with platelet-rich thrombi. Such lesions were recognized as a source of emboli and a basis for transient ischemic attacks. Nevertheless, the lesions were generally regarded as being of lipid rather than platelet origin. There was no clear consensus concerning the effect of hypertension on arterial rupture although there were detailed descriptions of the vessels from autopsies of hypertensive patients and stroke victims. An association with atherosclerosis was usually postulated, but spasm and aneurysm formation on small arteries were also being discussed as the basis for hemorrhagic stroke. Saccular intracranial aneurysms of the circle of Willis were well recognized and treated as a cause of subarachnoid hemorrhage. Their origin was commonly held to be congenital, and

their rupture was held by some to be due to the superimposition of chronic hypertension and atherosclerosis.

Not all investigators agreed. The role of vascular spasm in exacerbating brain injury following subarachnoid hemorrhage was a matter of debate. Contrary to previous views, the prevailing opinion was that hypertension did not enhance the circulation through sclerotic vessels and that hypertension was dangerous and should be controlled. There were, however, questions about the risk of rapid induction of control and about the value of the treatment of hypertension to prolong survival after a stroke. Methods for studying the regional perfusion of the brain were available. There were discussions concerning the role and importance of vascular disease as a cause of senile dementia but no clear resolution of the issue.

In 1972, studies such as the Framingham Heart Study had established the main risk factors for stroke: age, hypertension, diabetes, and at young ages, elevated lipids. There was less certainty about a sex difference and the effect of smoking. Such studies were affected by the relative diagnostic difficulty in separating hemorrhagic stroke from atherothrombotic stroke. By 1972, much of the previous uncertainty had been resolved, and it was apparent that the majority of strokes in the United States were atherothrombotic or ischemic strokes.

At that time, the Institute was supporting only a small number of studies dealing directly with the blood supply to the brain. These included studies of venous and arterial anatomy, the geographic pathology of atherosclerosis, hemodynamics at bifurcation points, risk factors, noninvasive diagnosis, saccular aneurysms, and secondary effects arising from other disorders of the circulation. In general, the assumption was that all data from studies of atherosclerosis were applicable to the cerebrovascular bed. Other vascular or hematologic causes of cerebrovascular disease were not being actively investigated.

Among the issues in 1972, a need was perceived to focus research on cerebrovascular atherosclerosis and other cerebrovascular diseases. There was a need for improved methods of diagnosis, preferably by noninvasive means. The diagnosis of cerebrovascular disease was primarily dependent on history, physical examination, and contrast arteriography. Most noninvasive diagnostic techniques were indirect and assessed altered pressure or flow dynamics in branches of the ophthalmic artery. In 1972, early work was reported on Doppler ultrasonic arteriography and real-time B-mode ultrasonic scanning; however, image resolution and the accuracy of these diagnostic techniques had not been established.

Development and characterization of animal models of cerebrovascular disease were needed for experimental testing of hypotheses. The relationship of vascular disease to senile dementia and to loss of cerebral function as well as the pathogenesis of cerebral hemorrhage needed clarification.

Evidence existed that platelet-fibrin emboli from lesions in the extracranial circulation are responsible for many cerebral ischemic events. It was also known that several drugs, among them aspirin, are able to inhibit platelet aggregation. It was therefore considered important to assess the potential benefits of these drugs in reducing the frequency of transient cerebral ischemic attacks and strokes.

Program Goals Through 1982

The overall goal recognized in the 1972 National Program for cerebrovascular disease was to:

- Decrease the incidence of stroke through studies of the pathology and pathogenesis of cerebrovascular disease.

In 1977, additional specific goals were established including:

- Gain further basic understanding of the pathogenesis of cerebrovascular disease.
- Encourage increased research activity exploiting the recently developed animal models of cerebrovascular disease.
- Develop noninvasive instrumentation to facilitate the diagnosis and observation of disorders of the large vessels supplying the brain.

Accomplishments Through 1982

From 1972 to 1978, there was a dramatic decline in death rates from cardiovascular disease, particularly in the case of stroke (over 37 percent). During this time, the effectiveness of antihypertensive drug therapy in reducing mortality from stroke as part of the overall effects on all-cause mortality was studied in the Hypertension Detection and Followup Program. Comparison of cerebrovascular disease morbidity and mortality rates in the stepped-care and referred-care groups showed that the 5-year reported stroke incidence rate in the SC group (1.9 per 100) was 45 percent lower than that found among the RC group (2.9 per 100).

(More extensive discussion of the HDFP data can be found under "Accomplishments" in Section 4, "Hypertension," pages 138-139.) These significant reductions in stroke rates among SC were experienced for all race and sex groups, all diastolic blood pressure strata, and all ages regardless of evidence of long-standing hypertension.

Epidemiologic studies of stroke have been complicated by the difficulties of specific diagnosis and a lack of objective criteria for proper classification. Because the incidence of stroke is lower than that of coronary heart disease, especially in the young, prospective studies are difficult without a relatively large sample and long followup.

The Framingham Study remains the prototype of a prospective study of stroke. The incidence, distribution by type, fatality rate, and extent of disability have been described in detail. The incidence of thrombotic stroke and myocardial infarction have been compared among men and women. A system for careful surveillance of stroke in the Framingham Cohort, including detailed clinical examinations in the hospital by senior staff neurologists, has added considerable strength to the study design. The relationship between major risk factors and stroke has been carefully analyzed. The strong association between systolic and diastolic blood pressure levels and risk of stroke is well described.

The possible association of stroke with isolated systolic hypertension in the elderly has recently been reported in a publication from the Framingham Study. Carotid bruits were monitored, and their association with both total cardiovascular disease mortality and stroke was evaluated. The bruits apparently represent the stigmata of generalized arteriosclerosis rather than a specific risk factor for stroke.

The Framingham Study has also demonstrated the marked increase in stroke risk associated with left ventricular hypertrophy, previous myocardial infarction, congestive heart failure, and atrial fibrillation.

The association between lipoproteins and strokes remains unclear. The Framingham Study has provided the best data set in the United States, but analysis has been limited by the small number of cases, especially in the young. Lipoprotein levels, however, are apparently not a strong risk factor for stroke, especially when compared to levels associated with myocardial infarction. Other risk factors such as cigarette smoking, diabetes, and vital capacity have also been related to stroke, although the relationship between cigarette smoking and stroke remains unclear.

A second major prospective study has attempted to determine the reasons for the remarkable differences in stroke and myocardial infarction mortality and morbidity between Japan and the United States, the Japanese having much higher death rates from stroke and lower rates from myocardial infarction than the Americans. In this study, the incidence and mortality of stroke and of myocardial infarction have been compared among Japanese men living in Japan, Hawaii, and California. The highest stroke mortality and the lowest coronary heart disease mortality were found in Japan. With the data of this study, the relationship between high blood pressure and stroke can be verified. The geographic variations in the levels of blood pressure, however, do not seem to correlate with the variations of stroke incidence or mortality; that is, the highest blood pressure levels were found in California, and lower levels in Japan. Postmortem studies have added to the clinical evaluations in the Hawaii and Hiroshima populations. The relatively small sample sizes and length of followup have limited further evaluation of the risk factors in these studies; however, continued followup of these cohorts may determine the reasons for the differences in stroke incidence and mortality in Japan as compared to that in the United States.

A third area of interest relates to descriptive epidemiology. The downward trends in strokes were presented and discussed in the Proceedings of the Conference on the Decline in Coronary Heart Disease Mortality. Geographic variations in stroke incidence in the United States have also been observed.

Given the limitations of stroke diagnosis and its relatively low incidence compared to the incidence of myocardial infarction, the epidemiologic studies have been very efficient. The great efforts to ensure accurate diagnosis in the Framingham studies represent a milestone for epidemiological research on stroke. The aging of the Framingham Cohort has resulted in a marked increase in the number of cases of stroke available for study. Prospective evaluation of the risk factors and also of markers of carotid arterial disease is now possible and should contribute substantially to the future understanding of stroke, especially in the older population.

The multicenter Study of Aspirin in Transient Ischemic Attacks was completed in 1975. A total of 178 patients, both men and women, with transient ischemic attacks were enrolled at 10 centers and assigned to aspirin (650 mg twice daily) or to placebo. This clinical trial provided evidence that regular use of low-dose aspirin reduced the frequency of strokes and recurrent transient cerebral ischemic attacks in people with cerebrovascular lesions. This was the case for patients who were operated on as well as for those who were not, and for females as well as for males. No significant difference in mortality between the two groups was observed. As a result of this and other studies, an

embolic cause of cerebral ischemic attacks is generally accepted, and aspirin as an effective therapy has become widespread.

Another clinical trial now in progress may provide additional information on the ability to decrease the incidence of stroke through reduction in elevated systolic hypertension. The Systolic Hypertension in the Elderly Program is a pilot study to assess the feasibility of conducting a full-scale clinical trial on the effect of treating isolated systolic hypertension in elderly subjects. An endpoint of the full-scale study, if implemented, will be stroke incidence. (Additional details of this study can be found in Section 4, "Hypertension," page 141.)

Many of the accomplishments in diagnostic instrumentation resulting from DHVD support have led to improved methods of diagnosing extracranial carotid artery occlusive disease. The major advances have included real-time B-mode ultrasonic scanning, Doppler ultrasonic arteriography, combined B-mode and Doppler instruments (duplex scanners), and intravenous arteriography. The carotid bifurcation has been a particularly appropriate site for the use of ultrasonic imaging because of its relatively superficial location and the frequent localization of disease at the bifurcation. Ultrasonic arteriography has been most useful in the asymptomatic patient with atypical or nonlocalizing symptoms. Patients with transient ischemic attack or stroke have been screened with these devices, but contrast arteriography is usually required to establish the diagnosis and to select appropriate therapy.

Intravenous arteriography has only recently been applied to patients with cerebrovascular disease. The advantage of this technique is that it provides information about not only the extracranial cerebrovascular arterial system but also the major intracranial vessels. This technique could eventually replace intraarterial arteriography in the followup of many patients who have undergone medical or surgical therapy, even though it still carries a small risk of allergy to contrast material, and its expense and complexity preclude its use for routine mass screening and followup procedures. It is likely that some form of hemodynamic assessment of extracranial carotid arteries will remain a useful method to screen patients for hemodynamically significant carotid occlusive disease. In addition, further refinements of Doppler ultrasonic flow information, including the development of real-time spectrum analyzers, may provide increasingly sensitive information about cerebrovascular flow in health and disease.

During the decade, progress was made in improving the understanding of the pathogenesis of cerebrovascular disease. The spontaneously hypertensive rat strains were developed by selective breeding in Japan, and a substrain of these, the stroke-prone spontaneously hypertensive rats (SHR-SP) became available for

research. Other models such as nonhuman primates with aortic coarctation and cerebral hypertension were also employed in conjunction with cholesterol feeding, but such research models were few. More recently, animal models have come into somewhat greater use and may provide a better insight into the vascular changes attributable to subacute or chronic hypertension and synergism of hypertension with elevated serum cholesterol.

Progress in differentiating senile dementia of Alzheimer's type from that thought to be due to vascular disease was substantial, but as might be expected, the advance has posed more clearly focused questions for vascular disease issues as well as for Alzheimer's disease. As a result of studies during the decade, the view that senile dementia is predominantly a vascular effect was changed to the view that vascular disease is the basis for considerably less than one-half of cases of such dementia. In the changed view, a correspondingly greater role was attributed to senile dementia of Alzheimer's type. The latter condition, which is of unknown etiology, is accompanied by focal degeneration of the brain. It has become a subject of major research interest. There does not seem to be a vascular component, but it should be noted that senile dementia of Alzheimer's type (and other dementias) can coexist with dementia of vascular origin.

Cerebral hemorrhage is usually an abrupt event without premonitory signs. While several risk-factor associations are known, cerebral hemorrhage is difficult to study and many aspects of its pathogenesis are obscure.

State of Knowledge in 1982

The arteries that supply blood to the brain--the carotids, the vertebrals, the circle of Willis, and the main distributing and penetrating vessels--are subject to two common disorders and several uncommon ones. Atherosclerosis and hypertensive disease are the major disorders, and there has been the general view that research findings on these subjects in the aorta or coronary arteries is applicable to cerebrovascular disease. This remains the case today although there is increasing acceptance of the view that the cerebral arteries have some properties that indicate regional modification of the basic systemic atherosclerotic process in the aorta or coronary arteries.

Nevertheless, little attention has been given to research on the pathogenesis of cerebrovascular atherosclerosis. The vessels are seldom studied in experimental models, even as incidental observations from experiments directed to the aorta or coronary arteries. Very little research on humans or on experimental animals has been focused on the question of why the vessels fail

in structure or in function in arteriosclerosis, thromboatherosclerosis, and hypertensive vascular disease.

The decline in cardiovascular and cerebrovascular diseases mortality has accelerated during the past 10 years, with evidence of two significantly different slopes, one from 1968 to 1980 and a steeper one from 1973 to 1978. The most striking decline in cardiovascular mortality during the past decade has been in cerebrovascular diseases. This trend coincided with the National Program for the control of hypertension. In clinical trials of the control of hypertension, a decrease in stroke morbidity and mortality occurred in all treated hypertensives regardless of age, race, sex, and level or duration of blood pressure elevation. A finding based on the limited sets of data available from prospective studies shows that cigarette smoking appears to be correlated with the incidence of atherothrombotic stroke in men but not in women and that blood lipid levels in those under 60 years of age are related significantly to stroke only in men. Two areas needing close study concern the relative risk for cerebrovascular disease among women using the new "low estrogen" oral contraceptives and the relationship of diabetes to the development of cerebrovascular diseases.

The surgical therapy of intracranial berry (saccular) aneurysms and subarachnoid hemorrhage has been markedly improved, and studies of the value of extracranial-intracranial vascular anastomosis have shifted from clinical investigation to a formal prospective clinical trial.

An interesting observation from prospective studies in Japan is that, contrary to Western experience, communities exist in which there is an inverse relationship between blood cholesterol and stroke. The hypothesis has been offered that a relative deficiency in dietary protein in these communities might be a more basic correlate of both the low cholesterol and the liability of the vasculature to fail. The concept proposes a new idea for examination--namely, that there is a level of protein nutrition that establishes the health of the cerebral vessel wall. A stroke-prone, spontaneously hypertensive rat model has become available for research, and this model is being used in testing the foregoing hypothesis.

Diagnosis of vascular syndromes has been clarified, particularly diagnosis of the relative frequency of thromboatherogenesis and hemorrhage in the precipitation of stroke. In addition, the older view that most strokes were hemorrhagic changed upon the finding that most are ischemic. The clinical diagnosis of the type of stroke has been greatly aided by computer assisted tomography (CAT scan). The diagnosis of transient ischemic attacks (TIA) has become more precise and more clearly focused. The view that TIA's were thromboembolic in nature

provided a basis for several prospective clinical intervention trials in which antiplatelet drugs such as aspirin were evaluated. Although some benefit accrued to certain types of patients in some studies, some controversy and unexplained findings remain.

During the decade, an attempt was made to define the role of cerebrovascular disease (generally understood as multifocal ischemic disease) in the incidence and prevalence of chronic dementia. Results have brought about a change of opinion about the statistical importance of vascular disease in relation to dementia. The role assigned today to vascular disease in dementia is a considerably decreased one, whereas the role of senile dementia of Alzheimer's type has increased. Presently some 15 to 20 percent of such conditions are thought to relate to ischemic disease. Both may coexist in some patients.

In 1982, noninvasive detection of extracranial carotid occlusive disease is being accomplished in many clinical centers throughout the country. Because of the relatively superficial location of the carotid artery and the frequent localization of atherosclerosis to the carotid bifurcation in the neck, such disease is amenable to detection by noninvasive techniques of carotid evaluation, including B-mode ultrasonic scanning, Doppler ultrasonic velocity analysis and Doppler arteriography, and duplex scanning employing both B-mode and Doppler technology. The minimally invasive technique of intravenous digital subtraction radiography permits definition of aortic arch, vertebral artery, and intracranial cerebrovascular lesions in addition to those in the carotid artery.

Program Goals 1982 to 1987

- Improve the fundamental understanding of the nature of lesions of the vessels of the head and neck that lead to stroke with a view toward improving the diagnosis, prediction, treatment, and prevention of cerebrovascular disease.

- Continue to conduct epidemiological studies of risk factors of cerebrovascular disease.

Research Activities 1982 to 1987

- Expansion of knowledge of risk factors currently known to be associated with cerebrovascular diseases, and investigation of the importance of the level of protein nutrition to vascular integrity.

- Improvement of methods for the diagnosis of vascular disease of the head and neck with emphasis on the diagnosis of atheromatous ulcers of the carotid bifurcation.

- Increase in the understanding of the cardiac and circulatory antecedents of those cases of stroke seen in systemic hypotension or in embolism.

- Refinement of knowledge of regional peculiarities of atherosclerotic and hypertensive disease as they affect the cerebral vessels, and of vascular occlusion, leakage, or rupture as they affect the central nervous system.

- Refinement of knowledge of atherosclerosis of the carotid artery bifurcation with particular attention to the natural history, the occurrence and fate of atheromatous ulcers at the bifurcation, and the importance of platelets and thromboembolic phenomena.

6. Coronary Heart Disease

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6. Coronary Heart Disease

"Coronary heart disease" is a generic term used to identify several cardiac disorders resulting from inadequate circulation of blood to local areas of heart muscle. This deficiency is nearly always a consequence of focal narrowing of the coronary arteries by atherosclerosis. The limitation of blood flow to the heart muscle restricts the supply of oxygen and nutrients to the heart and also the removal of metabolic wastes, and is called ischemia. When ischemia reaches a critical stage and the needs of the heart can no longer be met, symptoms or clinical events occur. The most common of these are angina pectoris, myocardial infarction (heart attack), and sudden death.

State of Knowledge in 1972

In 1972, CHD was, as it is today, the leading cause of death and disability in the United States, with an enormous cost to society in terms of medical expenditures and human suffering, disability, and death. No effective cure was then in sight, no proven preventive regimen was known, and treatment was largely palliative. Many promising avenues, however, were opening as a result of extensive studies of the atherogenic process and of lipid and lipoprotein metabolism related to it. A large body of scientific literature existed, and there was a strong impetus to learn more about the subject, especially in the areas of etiology, prevention, and treatment.

Further research was also needed to resolve basic unanswered questions, the most fundamental of which was why coronary heart disease ultimately manifests itself as the triad of angina pectoris, heart attack, and sudden death. While it was clear in 1972 that ventricular fibrillation, which is a chaotic disturbance of heart rhythm, is the cause of most cases of sudden death, no drugs or other effective treatments were available to prevent this condition, except under intensive medical care in the hospital setting.

In 1972, information from the Framingham Heart Study on many aspects of the risk factors of CHD was available, but there was still a need for further basic research. Refinement and quantification of known CHD risk factors were of major concern. (A detailed discussion of CHD risk factors can be found in Section 3,

"Arteriosclerosis," pages 76-84.) The U.S. decline in CHD mortality, which began in the late 1960s, was only beginning to be appreciated.

The diagnosis of CHD was inferred by history, physical examination, and electrocardiography, and confirmed by intraarterial coronary arteriography. Radionuclide imaging techniques had been developed for visualization of blood flow and were only beginning to be applied as a means of measuring coronary flow and myocardial function. Echocardiography had been used to view the cardiac chambers, but image resolution was relatively poor, and the data were analyzed by qualitative inspection.

Coronary artery bypass surgery was practiced in 1972 as a treatment for angina pectoris, but its value, compared with medical management and in terms of effects on the life span and the quality of life of the patient, required further research and assessment.

The high frequency of out-of-hospital deaths from coronary heart disease contrasted sharply with lives saved through in-hospital systems of emergency cardiac care. The contrast highlighted the need to understand more clearly the etiology and pathogenesis of malignant arrhythmias and to provide for the resuscitation and rapid transport of sudden death victims to hospitals. There was a need for a broad scope of investigations to elucidate the fundamental mechanisms associated with ischemic myocardium and reduction of infarct size. There was also a need for studies to develop interventions to protect ischemic myocardium and to enhance myocardial repair, including experimental studies of the physiology and biochemistry of ischemic myocardium and myocardial scar formation. In addition, it was considered important to investigate and evaluate, at the laboratory level, methods for quantifying the size of ischemic, infarcted, and scarred myocardium. Methods for measuring the amount of ischemic myocardium at risk as well as the amount that undergoes necrosis were needed in order to test more reliably the effect of therapeutic interventions designed to limit infarct size. Intensified research, both clinical and fundamental, was clearly critical to developing a better understanding of the cause and course of CHD and for improving diagnosis and treatment.

Program Goals Through 1982

To decrease mortality and disability from CHD, the Institute established, in 1972, the following goals:

- Develop a better understanding of the mechanisms leading to symptomatic CHD.

- Develop improved methods for the diagnosis and treatment of CHD.
- Establish guidelines for the use of coronary artery surgery in the treatment of various forms of CHD.
- Develop and assess emergency medical care methods for heart attack victims.
- Develop and assess prophylactic drug treatment to prevent sudden cardiac death.
- Improve the recognition and assessment of latent coronary artery disease and overt CHD.
- Improve the therapy and quality of life of patients with acute myocardial infarction and patients with chronic ischemic heart disease.
- Develop methods of reducing the incidence of recurrent myocardial infarction.
- Improve rehabilitation of patients with CHD.

Accomplishments Through 1982

The Division of Heart and Vascular Diseases routinely monitors national morbidity and mortality statistics related to CHD. This effort was intensified in 1973 when an analysis showed that the coronary death rate had not continued its epidemic rise above the 1963 level. The upward trend, evident primarily in men, had abated for virtually all groups regardless of age, sex, or ethnic background. A discontinuity of data created by the Eighth Revision of the International Classification of Diseases (ICD) in 1968 temporarily confused the picture. Subsequent analyses over the next 5 years, however, showed that the upward trend was dramatically reversed and that a real and steep decline was in progress. Geographic distribution of mortality rates of CHD has been recently shown to include state-specific trends. It has been found, for instance, that the decline of CHD mortality reflects discernible regional differences. The lowest rates of disease are clearly in the western states; the highest are concentrated in Appalachia and the Southeast.

At the NHLBI Conference on the Decline in Coronary Heart Disease Mortality in 1978, evidence was presented that primary preventive measures, changes in lifestyle, and improved medical care all contributed to the decline, although their relative contributions were unknown. This conference and other reports

indicated that the decline amounted to 25 percent between 1968 and 1978 and that it contributed substantially to improved national life expectancy, with as many as 200,000 deaths being averted each year. Analysis of mortality data from the World Health Organization (WHO) revealed that the United States now ranked about seventh or eighth highest in coronary mortality compared to second highest ranking in 1969 among 27 industrialized countries. European nations were still experiencing a rising coronary death rate.

To interpret further the decline of the coronary death rate and its epidemiologic implications, important focus has been placed on trends in incidence of myocardial infarction, hospitalizations, case-fatality rates, sudden deaths, and CHD mortality trends by age, racial group, sex, geographic area, occupation, and socioeconomic status. The decline in mortality has been seen in both sexes, in all ages, and in all ethnic groups. The striking regional differences in CHD mortality, within and between countries, have led to studies of environmental factors as well as the known major and minor CHD risk factors and differences in medical care.

Upon recognition of the need and opportunity in this area and the recommendations from several advisory groups, the NHLBI in 1981 began pilot studies for a communitywide strategy of surveillance of both mortality and morbidity. The surveillance data will be obtained from existing hospital and mortality records.

Fundamental Studies of Myocardial Ischemia and Infarction

Laboratory studies have provided insight into the mechanisms that underlie damage to ischemic myocardium. In vivo experiments in the dog have disclosed a number of metabolic and structural events that accompany severe ischemia. It is believed that profound metabolic changes are responsible for the transition to irreversible ischemia and cell death. Irreversibility occurs earliest in the subendocardial region where collateral blood flow is minimal. Coronary artery ligation, in the absence of reperfusion, results in a wavefront of necrosis that begins at the subendocardium and ends at the subepicardium. Myocytes in the subepicardial region, where collateral flow is greater, can be salvaged by reperfusion. In both zones, the onset of ischemia is followed, within seconds, by a number of identified metabolic events including activation of anaerobic glycolysis, progressive loss of the cellular pool of high energy phosphates (ATP), and loss of membrane integrity. Irreversible injury to the myocardium includes almost complete depletion of ATP, membrane defects, and swollen, calcium-loaded mitochondria. Of the many hypotheses proposed to explain the transition to irreversibility, the current hypotheses focus on loss of membrane integrity.

During the latter part of the decade, a new concept--the reversible contractile dysfunction following ischemia--arose from study of ischemic insults that are not of sufficient severity or duration to produce myocardial necrosis but that do produce prolonged, postischemic ventricular dysfunction. The severity and duration of these postischemic changes are a function of the duration and severity of the ischemia and also a function of the condition of the myocardium at the onset of the ischemic episode. It has been postulated that repeated episodes of such reversible contractile dysfunction lead to chronic left ventricular dysfunction and possible progression to myocardial scarring and ischemic cardiomyopathy.

The design of improved diagnostic and therapeutic strategies for patients with chronic coronary disease hinges on a clear understanding of these metabolic and structural sequelae of prolonged ischemia and an increased knowledge of the role of collateral vessels. As noted in the report of the NHLBI Working Group on Arteriosclerosis, the importance and function of the coronary collateral circulation in humans are rather controversial. Human studies, using coronary arteriography, disclose considerable variability in the extent of collateral development within groups of patients exhibiting similar degrees of obstruction of major coronary arteries. The factors responsible for differing rates of development of collateral vessels in different individuals are largely unknown at this time.

Infarct size is inversely related to the extent of existing collateral vessels. In evaluating the efficacy of various therapeutic maneuvers that could limit necrosis, an important new consideration is that of relating necrosis to the area at risk. The latter is a function of the collateral circulation, which is highly variable between and among species.

Many basic studies have identified drugs that may be effective in protecting ischemic myocardium, including adrenergic blocking agents, anti-inflammatory agents, and calcium antagonists. Progress has been made in clarifying the basic mechanisms of action of these agents, which may act on myocardial cellular membranes and subcellular organelles, may alter cellular biochemical or physiological processes, or may cause beneficial electrophysiological or hemodynamic changes.

The final expression of activation of the parasympathetic and sympathetic limbs of the autonomic nervous system includes receptor binding of catecholamines and acetylcholine. These receptor sites are imbedded in the membranes of effector cells such as smooth, cardiac, and skeletal muscle cells. Much progress has been made in characterizing receptors, and several have been isolated. The density of available receptors is dynamic, and, therefore, the effect of a given level of autonomic nervous

traffic is quite variable. Purification of receptors will permit precise measurement of receptor density under a variety of physiologic and pathophysiologic conditions. The significance of this accomplishment is that it permits more detailed understanding of the physiology of effector cell function and a more practical approach to drug design.

Methods using nuclear imaging, computerized tomographic, ultrasonic, and electrocardiographic techniques have been developed for detecting or quantifying ischemic myocardium in animal models. More recently, several new laboratory techniques have been developed that may allow assessment of specific biochemical disruptions during myocardial ischemia. Among them are nuclear magnetic resonance (or NMR), positron emission tomography (PET), and electron probe microanalysis. These technologies provide information concerning the effects of ischemia upon myocardial high-energy phosphate stores, metabolic intermediates, and transmembrane ion gradients.

Many different types of animal models and protocols have been developed for use in assessing interventions with potential to limit infarct size. A recent NHLBI study, Animal Models of Protecting Ischemic Myocardium (AMPIM), attempts to define and better evaluate these models in order to reduce the variability and improve the comparability of results obtained in different laboratories.

Thrombus formation in coronary vessels can occur during the acute stages of myocardial infarction. Efforts to break up the clots by the use of agents that activate plasminogen, such as thrombolysin or streptokinase, may be beneficial in restoring blood flow and in reducing the extent of myocardial injury.

Basic investigations have emphasized the importance of platelet aggregation and thrombus formation in the coronary arteries in the development of ischemic heart disease. Increased coronary vasomotor tone without structural disease of the vessels may also cause myocardial ischemia. Prostacyclin (PGI_2) and thromboxane A_2 (TXA_2) are important metabolites of arachidonic acid and are believed to be important in preserving an appropriate balance between coronary artery constriction/dilation and platelet aggregation/disaggregation.

Studies of variant angina have led to a greater appreciation of the role of coronary spasm in syndromes such as unstable angina and in some cases of exertional angina, myocardial infarction, and sudden death. Coronary vasoconstriction and angina induced in response to a cold stimulus may be mediated through alpha-adrenergic receptors. Although initially thought to involve atherosclerotic vessels, it is now clear that spasm can occur in vessels that are free of atherosclerotic disease. Spasm may

explain cases of anginal pain accompanied by electrocardiographic changes but unaccompanied by antecedent increases in indices of myocardial oxygen demand. Severe rhythm disturbances occur during episodes of spasm and may be responsible for some cases of sudden death.

Investigators have recognized the importance of examining the long-term consequences of acute myocardial ischemia and infarction, including the processes of healing and repair, recovery of function, myocardial wall thinning, and aneurysm formation. These concepts are being pursued in animal models.

Diagnostic Technology and Therapeutic Devices

Improvements have been made in tests used for the clinical detection and diagnosis of heart disease that are of low risk to the patient. Many techniques are minimally invasive; they include echocardiography, nuclear imaging, and computerized tomographic x-ray techniques. Because they are minimally invasive or noninvasive, they allow diagnosis in situations that in the past were either uncertain or required cardiac catheterization.

Echocardiography, both M-mode and two-dimensional, provides an assessment of heart anatomy with the use of sound waves reflected from the heart and great vessels. Refinements in real-time B-mode ultrasonic scanning have led to improved visualization of cross-sectional images of the heart. This development has been important for evaluating patients with ventricular wall dysfunction, aneurysm, and mural thrombosis.

An appreciation of the different results obtained from application of standardized treadmill exercise tests with electrocardiographic recording in different populations has considerably enhanced the diagnostic specificity of this test. The sensitivity of the test and its specificity are highly dependent upon the pretest likelihood of disease in the patients examined. The accuracy of exercise testing has been enhanced by concurrent assessment of myocardial perfusion with a radiopharmaceutical imaging technique (thallium-201).

For many years, the clinical diagnosis of myocardial infarction was aided by scrutiny of evolving changes in serial electrocardiographic tracings and sequential changes in a variety of serum enzyme levels. Many of the latter, although exhibiting considerable sensitivity, lacked specificity. The development, during the past decade, of a reliable means of measuring isoenzymes of creatine kinase--specifically CK-MB--has provided the biomedical community with the most specific means of detecting myocardial necrosis. Furthermore, elucidation of the relationships between pathologically measured infarct size, myocardial CK

depletion, and total amount of CK that appears in the serum in the wake of an infarction, has provided a minimally invasive means of estimating infarct size. This relationship, however, may be altered by very early reperfusion.

Infarct sizing with infarct-avid radiopharmaceuticals (technetium-99 pyrophosphate) or with perfusion scanning (thallium-201) is relatively inaccurate and cannot be applied to all patients with myocardial infarction. These limitations stimulated development of a new, precise, three-dimensional infarct-sizing technique--positron emission tomography. The latter incorporates two technological advances: positron-emitting metabolites, and precise coincident photon detectors. Although this technology is not now widely available, its application provides a reference standard for other measurements of infarct size. Importantly, variants of this technology will also permit studies of the metabolism of normal and diseased myocardial tissues.

A particularly noteworthy application of radionuclide imaging has been the gated radionuclide scan. In addition to displaying subtle abnormalities in regional wall motion, this technique permits a reproducible measurement of ventricular function, specifically the ejection fraction. Numerous studies of this measurement in acute myocardial infarction have shown it to be highly correlated with subsequent early and late mortality--a consideration that is discussed further in Section 9, "Heart Failure and Shock." Measurements of left ventricular function at rest and exercise by gated radionuclide scan can disclose sequelae of ischemia before detectable electrocardiographic changes are present.

Computer-assisted, cross-sectional imaging of the heart provides detailed anatomic information. Another major advance has been the development and application of digital subtraction angiography. Although motion artifacts have made the application of intravenous arteriography more difficult in coronary heart disease, improved instrumentation may eventually make this method a practical substitute for intraarterial angiography. Intravenous arteriography may be particularly helpful in following the natural history of disease and the outcome of coronary bypass grafts.

The dynamic spatial reconstructor, which is a multiple x-ray source and detector scanner based on the principle of computerized tomography, was recently designed for use as a research tool with which intraaortic injection of a contrast agent permits detailed imaging of the coronary arteries down to a diameter of approximately 1 mm. Computer-generated displays of the three-dimensional data permit accurate localization and orientation of images of oblique sections through structures of interest. In addition,

three-dimensional anatomic information can be conveyed by a perspective display.

Advances in miniaturization of catheter-tip Doppler ultrasonic flow meters have led to detailed studies of the normal and abnormal velocity patterns of coronary artery flow in patients with coronary artery disease and bypass grafts. Further evolution of pulse Doppler flow meters has led to improvements in monitoring cardiac output.

An improved small vessel prosthesis for aortocoronary bypass grafting is being developed. A recent workshop on vascular prostheses provided professional and public education about the current state of the art and the future needs for suitable large and small vessel prostheses.

The development of an implantable defibrillator may improve the future prognosis of patients with ventricular arrhythmia secondary to coronary heart disease.

Clinical evaluation of the pneumatically powered temporary ventricular assist device was initiated in patients who could not be weaned from the heart-lung machine after surgery. A majority of these patients were undergoing coronary artery surgery, and approximately 20 percent of this group went on to long-term survival. These accomplishments are discussed in greater detail in Section 12, "Circulatory Assistance."

Management of Symptomatic Coronary Heart Disease

Systematic study of patients with angina pectoris has led to the discovery that symptomatic high-grade left main coronary obstruction is an indication for coronary bypass grafting. Improvements in surgical techniques for bypass grafting--particularly, improved intraoperative myocardial preservation--have brought about a reduction in operative mortality to less than 2 percent. The incidence of postoperative myocardial infarction has also been reduced.

During the past 10 years, improvements in coronary care unit management of patients with acute myocardial infarction have occurred, including widespread application of hemodynamic monitoring and careful elucidation of the indications for, and safety and efficacy of, administering intravenous nitrates, beta-adrenergic blocking agents, and vasodilators. Safe application of cardiac catheterization for investigative purposes early in the course of acute myocardial infarction was reported from several centers. The high incidence of coronary thrombosis in patients with transmural infarction was noted.

These improvements in medical management during the acute phase of myocardial infarction have been associated with decreasing hospital mortality. The deleterious effects of prolonged bed rest were appreciated, and the safety of early ambulation and early discharge of patients with uncomplicated myocardial infarction was demonstrated. The average hospital stay for such patients has been shortened to approximately 12 days. The latter part of this period is spent preparing the patient for a post-discharge rehabilitation program that emphasizes a prescribed exercise program, modification of risk factors, and attention to psychological and social factors that permit resumption of normal or near-normal lifestyle. Submaximal exercise testing of myocardial infarction patients prior to discharge has also been applied as a method of identifying patients with demonstrable ischemia and therefore at high risk for sudden death or recurrent infarction.

During the decade, several groups of survivors of myocardial infarction were studied by 24-hour ambulatory monitoring and by radionuclide angiography in an attempt to identify reliable predictors of sudden death. Frequent high grades or complex forms of ventricular premature beats (VPB's) are recognized predictors of sudden death in patients with CHD. Although these advanced grades of VPB's occur in patients both with normal and with depressed ejection fractions, sudden out-of-hospital deaths occur most commonly in those who have both advanced grade VPB's and depressed ejection fractions--that is, in patients with extensive CHD. The relative ease with which such high risk subgroups can now be identified will facilitate focusing of future research efforts that deal with prevention of sudden death in CHD.

Clinical Intervention Studies

The DHVD implemented several studies over the past decade to improve the understanding and prevention of CHD.

A prospective randomized study comparing medical therapy with urgent coronary bypass surgery for the acute management of patients with unstable angina pectoris was begun in 1972. Between 1972 and 1976, 288 patients were randomized. Followup ended in March 1982, with a minimum followup of 5 years and a maximum followup of 9 years. The results of this Unstable Angina Study indicate that patients with unstable angina pectoris can be managed during the acute phase with intensive medical therapy, including the administration of propranolol and long-acting nitrates, with adequate control of pain and no increase in rates of early mortality or myocardial infarction. The results of this clinical trial have produced changes in clinical practice. Fewer patients now presenting with unstable angina are immediately submitted to bypass surgery.

A large-scale collaborative clinical trial--the Coronary Artery Surgery Study (CASS)--was designed to assess the effects of coronary artery bypass surgery on morbidity and mortality in patients with chronic coronary heart disease. Randomization of 780 patients to medical or surgical management began in July 1975 and was completed in May 1979. In addition, all nonrandomized patients who underwent coronary arteriography at participating centers are being followed prospectively in the CASS Registry. At the end of randomization, 24,959 patients had been entered into the Registry. All patients, both randomized and nonrandomized, will be followed for a mean followup of 6 years.

Two clinical trials employing aspirin to prevent recurrent myocardial infarction (MI) and death were conducted by the Institute during the past 10 years. The Coronary Drug Project Aspirin Study (CDPA) enrolled 1,529 subjects who had been in one of several treatment regimens of the earlier Coronary Drug Project. They were randomized to aspirin (one 324 mg tablet three times daily) or placebo for an average of 22 months. The mortality in the aspirin-treated group was 30 percent lower than that in the placebo group. This datum suggests a beneficial therapeutic effect of aspirin in the secondary prevention of coronary heart disease. The number of patients studied and the length of followup, however, were not sufficient for drawing definite conclusions.

The promising results of the CDPA stimulated the initiation of the Aspirin Myocardial Infarction Study (AMIS) by the Institute. In this clinical trial, which was completed in 1979, 4,524 men and women with at least one myocardial infarction were assigned randomly to aspirin (500 mg twice daily) or placebo, and followed at 30 clinical centers for a minimum of 3 years. Total mortality, incidence of myocardial infarction, and the percentage of definite, nonfatal myocardial infarctions in the two groups were not significantly different. Approximately twice as many patients in the aspirin-treated group experienced gastrointestinal side effects. On the basis of this study, which is the largest investigation to date of aspirin in a postinfarct population, aspirin is not recommended for routine use in patients who have survived a myocardial infarction in order to prevent subsequent infarctions. Questions that remain unanswered concern the optimal dose of aspirin to achieve an antithrombotic effect, and whether patients in the immediate postinfarct period, who were not included in the AMIS, might benefit from the use of aspirin or another platelet-active drug.

The Workshop on Use of Platelet-Active Drugs in Secondary Prevention of Cardiovascular Events was held at the Institute in 1980 to review the results of the seven clinical trials conducted during the past decade and the basic research on the usefulness of platelet-active drugs in the post-MI population. While the trials

involved varying dosages and followup periods, six out of seven trials showed a trend favoring the use of platelet-active agents. Therefore, the role of these drugs in secondary prevention requires further study. The workshop participants concluded that a further clinical trial of those drugs in the acute period immediately following an acute myocardial infarction is warranted. The size and cost of such a trial, however, are prohibitive. A Randomized Trial of Aspirin and Mortality in U.S. MD's was recently approved. This 5-year, double-blind, placebo-controlled trial among 21,900 U.S. male physicians, 50 to 75 years of age, is primarily to assess the effect on cardiovascular mortality of alternate-day consumption of 325 mg aspirin and, secondarily, to assess the effect on cancer incidence of alternate-day consumption of 30 mg beta-carotene. The trial began in 1982, and followup will be completed in 1985.

Based on results of earlier studies suggesting that long-term administration of antiarrhythmic drugs may prevent ventricular fibrillation that frequently precipitates sudden death after myocardial infarction, the Beta-Blocker Heart Attack Trial was initiated in 1978. Presumed beneficial modes of action of propranolol are its antiarrhythmic effect and its effect in lessening myocardial oxygen demand. The objective of this randomized, controlled clinical trial was to determine whether regular, long-term administration of propranolol to survivors of acute myocardial infarction would reduce mortality from all causes (primary endpoint), coronary heart disease mortality, sudden cardiac death, or incidence of subsequent infarction. A total of 3,837 patients at 31 clinical centers were enrolled within 5 to 21 days (average 13.8 days) after the onset of an acute myocardial infarction and were randomized to propranolol (either 180 mg or 240 mg per day, based on the serum levels at 120 mg per day) or to placebo. Baseline comparability between the groups was excellent. Intervention was originally scheduled to end in June 1982, but the trial was stopped early due to a statistically significant finding ($p<0.02$) of a beneficial effect on total mortality. The results were consistent across clinics and patient subgroups. A reduction of 26 percent in total mortality (9.5 percent in the placebo group compared to 7.0 percent in the propranolol group) was observed over an average followup period of almost 2 years. Approximately two-thirds of the patients in each group complied with the treatment regimen. The results of the BHAT strengthened and extended the conclusions of previous studies of beta-blockers in survivors of acute MI, notably the recently completed Swedish metoprolol study and the Norwegian timolol trial. The site of infarct appears to be immaterial in the BHAT, contrary to an earlier study of practolol that demonstrated benefit only in anterior infarctions. Also, as in the timolol study, but contrary to an alprenolol study, older patients (over 65 years) benefited from the treatment as much as younger ones.

The BHAT results indicated that the beneficial effects of propranolol appear to occur primarily in the first year after an MI. None of the completed beta-blocker trials that had been published at the time of this review addressed the issues of possible benefit from institution of therapy at a time remote from the infarction or at what point treatment can be discontinued.

A prospective randomized study--a Multicenter Investigation of the Limitation of Infarct Size (MILIS)--designed to compare the effects of pharmacological agents in limiting the size of a myocardial infarction was initiated in 1977. By July 1981, 800 patients were randomized to either propranolol, hyaluronidase, or conventional coronary care therapy. Recruitment will continue until January 1984, and it is expected to include 1,000 randomized patients.

In March 1979, the NHLBI initiated a voluntary international registry on percutaneous transluminal coronary angioplasty to expedite the evaluation of this new therapeutic technique for the treatment of symptomatic obstructive coronary artery disease. To date, 3,049 patients from 117 centers in the United States, Canada, Switzerland, West Germany, and Yugoslavia have been entered into the registry. Short-term results are promising in that the procedure has been shown to be relatively safe and effective for carefully selected patients with single-vessel disease. Long-term evaluation of this technique is not yet available.

A workshop entitled Strategies for Secondary Prevention of Coronary Heart Disease was held in March 1981 to identify interventions that might be tested by means of a clinical trial in the near future. Priority was assigned to a feasibility study of antiarrhythmic agents in patients at high risk for sudden death. In 1982, the Division responded to this charge by implementing a pilot study of antiarrhythmic agents. The proximate goal of this Cardiac Antiarrhythmic Pilot Study (CAPS) is to demonstrate the feasibility of designing the ultimate study to assess the effectiveness of an antiarrhythmic regimen in suppressing significant but not immediately life-threatening ventricular arrhythmias and thereby reduce mortality.

Prevention of Coronary Heart Disease

Demonstration and Education Research

On the premise that the optimal point for heart disease prevention is in childhood, before negative health habits have become ingrained, the Chicago Heart Health Curriculum Program was implemented in 1978. Its objective is to help 6th-grade students

in the Chicago public schools acquire knowledge about cardiovascular risk factors and develop positive attitudes toward themselves and toward healthful living. Teachers received training in a 2-day workshop on effective presentation of materials. In a second phase, parents were involved in an attempt to develop an increased capacity for judgment, responsibility, and self-realization toward a healthy lifestyle. A report on the final results of the program is scheduled for late 1982.

The NHLBI established the Preventive Cardiology Academic Awards (PCAA) Program in July 1979. The overall objectives were to improve the quality of preventive cardiology curricula in schools of medicine and osteopathy, to attract promising young investigators to a research and teaching career in preventive cardiology, and to develop a superior faculty with a commitment to preventive cardiology and with skills for teaching it. Fourteen schools of medicine have been awarded funds for this program, and additional schools have been approved for funding in 1982. The awardees meet annually to discuss progress and to share problems and successes.

In 1979, the Institute funded an American Health Foundation program entitled "Know Your Body." The objectives are to identify and follow heart risk factors in a cohort of public school children, reduce elevated risk status within a controlled intervention design, and maintain risk reduction over a period of several years. The basic methodological strategy includes screening for multiple risk factors, giving children their own results in a "Health Passport," and providing schools with health education materials focused on chronic disease control to enrich the existing curricula. In addition, specific intervention activities within study schools focus on nutrition (weight and cholesterol control) and on primary prevention of cigarette smoking.

Preventing the onset of smoking can be a major step toward prevention of CHD. In early adolescence, social pressure is clearly an important factor. Important strides have been made in preventing the onset of smoking through work with adolescents to teach them skills for resisting pressures to smoke. The Adolescent Smoking Program was a longitudinal study of the onset of smoking behavior in two matched, middle-income junior high schools in California. In one school, specially trained high school students conducted a 2-year program to help 7th-grade students resist social influences toward smoking and other drug use. Students in the control school were exposed to a course in health education but received no special training in assertiveness against inducements to smoke. The estimated linear onset rate was 8.4 percent per year in the control school but only 3.2 percent per year in the experimental school. This research, combined with that of other investigations, has provided important insight into

the efficacy of theoretically grounded innovative strategies in health promotion in adolescents.

Community Demonstration Programs

Another major focus has involved primary prevention of CHD through community intervention programs. In three large-scale ongoing programs, the effects of various educational strategies to reduce cardiovascular risk over time and to lead to a decrease in cardiovascular morbidity and mortality are being assessed.

The Stanford Heart Disease Prevention Program (SHDPP), which included the Three-Community Study, was supported by the NHLBI from 1971 to 1977 and demonstrated the potential for communitywide reduction of CHD risk factors by use of mass media. Three communities (one control and two intervention) were selected for this demonstration. The control site was isolated from the media of the other communities. The intervention communities were provided with 3 years of a mass media campaign, and in one of the experimental communities, a group of high risk individuals and their spouses was given supplemental, intensified personal instruction.

The mass media and counseling were designed to increase awareness of the causes of cardiovascular diseases and to motivate the learning of specific skills including changing eating habits (designed to lower intake of salt, sugar, saturated fats, and cholesterol) as well as discouraging smoking and cultivating good habits of exercise. The mass media and intensive counseling were both effective in reducing risk for cardiovascular disease. High-risk participants who received intensive instruction benefited more than those who did not. This program demonstrated the feasibility and efficacy of communitywide intervention in lowering risk of cardiovascular disease.

In 1977, this program was expanded to a five-community study that sought to improve knowledge and skills relevant to CHD in individuals and organizations by means of an extensive media campaign. The study was designed to evaluate the impact of the program itself on reduction of CHD and perhaps on morbidity and mortality from cardiovascular disease. In addition, the program included an attempt to link the intervention to behavioral changes through a study of change processes and to expand and increase the effectiveness of the program itself.

The Minnesota Heart Health Program (MHHP), which began in 1980, is a demonstration approach to the primary prevention of premature heart attack and stroke in six selected Minnesota communities. It is based on the importance of several cardiovascular risk factors and on evidence that they can be modified

safely. These risk factors include elevated blood pressure, cigarette smoking, elevated blood lipids, and physical inactivity. The MHHP strategy employs communitywide education in a sequential comparison of experience in three selected pairs of Minnesota communities. In each pair, one community is surveyed and observed as the control, and one is organized for a long-term, multiple-factor, multiple-strategy effort in health education. Tactics include direct "hands-on" education, professional education to enhance prevention services, organization and training of community leaders, mass communications, and enhanced community support for healthy behavior.

Processing techniques for MHHP program data have been developed, classification for surveillance of mortality and morbidity has been refined, and techniques to evaluate educational processes have been developed. Data collection is now under way.

The Pawtucket Heart Health Program, begun in 1980, is a 6-year study of over 25,000 residents designed to compare the morbidity and mortality rates from CHD and stroke in a control community and in an intervention community.

The specific intervention in this program, which makes use of educational strategies to modify CHD, is based upon social theory, social network concepts, community organization, and extensive utilization of lay volunteers to deliver programs to their own organizations. This effort will be aided by new strategies for behavioral changes at individual, small group, organizational, and community levels. The program will work with and through all major groups and organizations within the community, such as schools, government, labor, industry, service clubs, and churches. Short-term, mid-term, and long-term evaluation includes sample surveys for changes in physiological variables, such as serum cholesterol, and continuing surveillance of morbidity and mortality.

The Coordinating Committee for the Community Demonstration Studies (CCCDS) was established to provide a mechanism for NHLBI coordination of information and technology exchange between the three community demonstration programs (the Stanford Five-City Multifactor Risk Reduction Program, the Minnesota Heart Health Program, and the Pawtucket Heart Health Program). The CCCDS also provides a mechanism for the standardization of protocols of data collection whenever possible.

Much of behavioral medicine research on CHD risk factors has sought to delineate the relationship between the coronary-prone behavior pattern (CPBP) and CHD. A Forum on Coronary Prone Behavior was held in June 1977 to identify opportunities for further study. The proceedings, which were published in Circulation (June 1981), have stimulated considerable

investigator-initiated research on the development and assessment of CPBP.

The Division has released a program announcement to encourage applications that represent support for research on the influence of psychosocial stressors on smoking, smoking cessation, and the maintenance of cessation. It has been hypothesized that cigarette smoking may function as a stress-reducing or coping behavior for certain individuals. These individuals apparently increase their smoking behavior in stressful circumstances; if they stop smoking, there is a tendency toward relapse under such circumstances. The data in support of this hypothesis have been derived from several sources but lack sufficient integration to provide a comprehensive and definitive statement concerning the nature of the interaction of stress and smoking. Further research is needed to clarify this issue and to provide practical direction for smoking cessation programs.

State of Knowledge in 1982

A decline in coronary heart disease mortality in the United States was recognized initially in 1972. During the last decade, there was a 25 percent reduction in age-adjusted CHD mortality. In 1982, the decline continues seemingly unabated. Geographic variation in the decline has been observed. In other countries, variable trends during the same decade--some decreasing, some increasing--have also been observed. Although aspects of medical care such as use of coronary care units, coronary artery surgery, and diagnostic technology, and changes in diet, smoking habits, hypertension management, and exercise have been suggested as possible causes of this decline, there is currently no national data base on incidence and prevalence from which to extract the relative contributions of these factors.

The NHLBI has generated an important set of epidemiologic data showing major differences in CHD rates among social, ethnic, regional, and national groups. Studies of Japanese living in Japan, Hawaii, and California have demonstrated a rate of CHD in California three times higher than that in Japan. CHD rates in Puerto Rico are one-half the rates seen in the United States. Some states in the United States have CHD rates twice as high as those in other states. It is also known that people in low socioeconomic groups have CHD rates twice those of people in high socioeconomic groups. CHD rates for men are two to three times higher than those for women.

These differences in rates cannot be entirely explained by such recognized risk factors as diet, serum lipids, blood pressure, and cigarette smoking, nor can they be explained by

genetic factors. For example, when Japanese migrate to the United States, those who acculturate to Western lifestyles have CHD rates twice as high as those who retain traditional Japanese behaviors even after other CHD risk factors are taken into account. In another example, behavioral studies in Framingham have indicated that those individuals with type A behavior have CHD rates two to three times higher than those with type B behavior.

The decline in CHD mortality has also been paralleled by an increasing sophistication in diagnosis and treatment of coronary diseases and an increasing knowledge of the pathophysiology of ischemia. New information is available concerning the role of collateral flow in determining the severity and progression of ischemic injury, the mechanical effects of ischemia and reperfusion, the effects of ischemia upon diastolic properties of the ventricle, and the gross and histological characteristics of infarcts in relation to the anatomic vascular bed at risk.

Much new information is available about the role of vasoactive hormones, including the prostaglandins, in the circulation, and about the effects of platelet-active agents. There is a need for a better understanding of the mechanism(s) of platelet aggregation and thrombus formation in the coronary arteries, and of the mechanism responsible for increases in coronary vasomotor tone. This basic information is important in light of recent clinical advances in antithrombotic and thrombolytic therapeutics and of the increasing recognition of the clinical importance of coronary vasospasm.

New techniques that have been developed for detecting and quantifying ischemic myocardium have provided much information about the consequences of ischemia in intact animals and humans. Since most of these techniques are noninvasive, they offer an attractive approach to detection of the long-term consequences of ischemia and to its modification by protective agents.

The degree of development of the coronary collateral circulation in patients with coronary heart disease could be of great importance in determining the severity of clinical symptoms in the presence of narrowing, as well as the extent of myocardial infarction and overall survival following abrupt coronary occlusion. The NHLBI Working Group on Arteriosclerosis (1981) has emphasized that presently, in humans and subhuman primates, the functional capability of myocardial regions dependent on chronically developed collateral channels remains obscure. The factors that lead to extensive collateral development in some individuals and scanty development of such vessels in others are unknown and involve fundamental biologic processes of growth and differentiation. Reliable approaches for measuring coronary collateral flow also need further development.

In the past 10 years, several of the noninvasive techniques that make use of radiopharmaceuticals (for example, detection of necrosis with technetium-99^{m} pyrophosphate, perfusion scanning with thallium-201, and ventricular function assessment with radionuclide ventriculography) as well as echocardiography, advanced from preclinical evaluation to clinical use. Emerging techniques, such as high speed computerized axial tomographic scanning, positron emission tomography, nuclear magnetic resonance, and the dynamic spatial reconstructor (DSR) are now at a similar juncture. Possible use of these techniques for the elucidation of mechanisms at the basic level and also their application in clinical cardiology as precise diagnostic tools require assessment.

In most communities, improved techniques for cardiopulmonary resuscitation are now available. Sophisticated electrophysiologic studies that have been performed in the increasing numbers of resuscitated patients have led to a better understanding of the mechanisms by which CHD leads to sudden death. Newer anti-arrhythmic drugs, improved ambulatory monitoring, and improved pacing techniques are now available for study and also for clinical application in high risk individuals. During the next 5 years, the implantable defibrillator will be evaluated clinically.

A result of the work of the last 10 years has been a better definition of the safety, efficacy, and clinical indications for administering nitrates, beta-adrenergic blocking agents, and vasodilators in the coronary care unit. The efficacy of beta-blockade in reducing mortality in patients who have survived myocardial infarction has recently been demonstrated. The optimal duration of this therapy is not ascertainable, however, from the data of several clinical trials, and the question requires resolution.

The variant angina syndrome, its relationship to coronary vasospasm, and its favorable response to calcium antagonists is better understood now.

The natural history and prognosis of patients after acute myocardial infarction or of patients with stable ischemic heart disease have been better defined. A set of descriptors that predict reduced survival has been developed. Risk factors indicative of reduced survival include left main or multivessel disease, positive low-level exercise stress test, poor ventricular function, and high-grade ventricular ectopy.

The NHLBI PTCA Registry has demonstrated that successful dilatation of lesions is possible in 70 to 90 percent of patients with single vessel disease. There is a need, however, for long-term followup data. Additional unresolved issues are optimal

post-PTCA medical management using calcium antagonists, antiplatelet drugs, and anticoagulants, and also the feasibility of application of PTCA to patients with multivessel disease.

During the past decade, cardiac catheterization for investigative purposes early in the course of acute myocardial infarction was shown to be feasible, and it was also learned that patients with transmural infarction have a high incidence of coronary thrombosis. In addition, recent clinical studies have demonstrated that the intracoronary or intravenous administration of certain plasminogen activators in patients with acute myocardial infarction can lyse an intracoronary clot. Data involving case series and clinical trials are accumulating rapidly. These data were discussed in an NHLBI workshop that resulted in a recommendation for further clinical evaluation of this technique.

In multicenter collaborative studies in Scandinavia, Canada, and the United States during the past decade, investigations of exercise rehabilitation of patients with ischemic heart disease did not provide conclusive findings concerning the efficacy of exercise in the primary and secondary prevention of ischemic heart disease. Although some evidence for a positive effect of exercise may be inferred from these studies, inadequate sample sizes and generally poor adherence to exercise or control group assignments left the question unresolved.

Techniques for bypass grafting and for intraoperative myocardial preservation have led to a reduction in surgical mortality to less than 2 percent and to a reduction in the incidence of postoperative myocardial infarction.

Several multicenter clinical studies were initiated during the past decade to assess the efficacy of coronary artery surgery to reduce mortality and morbidity in patients with ischemic heart disease. The Veterans Administration Cooperative Randomized Trial initially reported no improvement in survival attributable to surgery in patients with three-vessel disease. However, data from the 10 centers (out of 13) that had the lowest mortality showed a substantially improved survival rate in surgically managed patients.

In a subset of patients with three-vessel disease and good ventricular function, the European Randomized Collaborative Trial reported impressive improvement in survival with surgery. The NHLBI Unstable Angina Pectoris Trial, which excluded patients with left main vessel disease or persistent unstable angina, showed no improvement in survival with surgery compared to treatment by medical management, although subsequent elective surgery may have been necessitated by chronic symptomatology. Randomization of the NHLBI Coronary Artery Surgery Study was completed in May 1979, with 780 patients randomized to medical or surgical management.

The results of this study, which will be published in 1983, will provide a more comprehensive picture of the criteria for the selection of surgical or medical management.

Program Goals 1982 to 1987

- Improve the understanding of the fundamental pathogenic mechanisms involved in CHD and its various manifestations, including sudden death.
- Develop and refine methods for use in diagnosis and in estimating prognosis in patients with asymptomatic and symptomatic CHD.
- Develop and refine medical and surgical interventions for the treatment of acute coronary events and chronic ischemic heart disease.
- Identify factors that are involved in the pathophysiology of coronary heart disease and in the transition from latent to overt CHD.
- Continue to support research on the mechanisms underlying arrhythmias in myocardial ischemia.
- Continue development of reliable methods of studying the coronary collateral circulation in humans and the factors influencing its development.
- Elucidate profiles of individuals at enhanced risk of first myocardial infarction and of postmyocardial infarction sequelae in order to develop means of risk reduction in these groups.
- Enhance methods to reduce or prevent new and recurrent myocardial infarction.
- Improve the rehabilitation of patients with CHD.
- Study the phenomenon of silent myocardial ischemia, its prevalence, and its significance.

Research Activities 1982 to 1987

- Expansion of knowledge of the mechanisms that result in coronary spasm, coronary thrombosis, myocardial ischemia, and myocardial infarction.

- Identification of cellular and molecular sequelae of ischemia with the use of new methodologies for measuring metabolic events in normal and ischemic myocardium.

- Continuation of studies that identify determinants of irreversible myocardial ischemia.

- Continuation of investigation of the pathophysiology of sudden death and of evaluation of methods of prevention.

- Development and validation of minimally invasive means of imaging coronary vessels, quantitating flow in coronary vessels and collaterals, and displaying ventricular structure and function in individuals with CHD.

- Refinements in the indications, techniques, outcome, and followup of patients undergoing coronary artery bypass grafting.

- Continuation of the evaluation of percutaneous transluminal coronary angioplasty, including indications, techniques, outcome, and understanding of the relevant pathophysiology.

- Continuation of evaluation of existing and new drugs in the treatment of the manifestations of CHD, including the clinical trial of thrombolysis in myocardial infarction (TIMI).

- Development of reliable methods of identifying high risk patient subsets, in particular the preclinical and post-infarction populations, and of treating and preventing new and recurrent events.

- Elucidation of the mechanisms of rest angina and unstable angina.

- Continuation of support of the Specialized Centers of Research in Ischemic Heart Disease.

7. Peripheral Vascular Disease

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7. Peripheral Vascular Disease

Peripheral vascular diseases involve the vessels that comprise the peripheral circulation. Several diseases affect these vessels. The most common is arteriosclerosis, which consists of irregular thickening of the vessel wall and plaque formation in the vessel lining. The plaques lead to narrowing and obstruction of the vessel. Arteriospasm (Raynaud's phenomenon) is another form of arterial abnormality. Venous damage results when veins become dilated (varicosities) or inflamed (phlebitis) or are obstructed with blood clots (thrombophlebitis). Together, these conditions comprise the bulk of peripheral vascular disease. They can cause considerable suffering and disability, including organ damage, skin ulcerations, gangrene, and, in some cases, death.

The peripheral vessels, arteries, veins, and lymphatics are subject to a variety of diseases that tend to be focal or segmental. Anastomotic channels may or may not be present. Most important among the arterial disorders are arteriosclerosis obliterans and aneurysm; most important among the venous lesions are venous thrombosis and varicosity. Disorders of larger lymphatics are rare in the United States.

State of Knowledge in 1972

It has long been the common view that atherosclerosis of the peripheral arteries is like atherosclerosis elsewhere. As vessels become more peripheral to the aorta, plaques are more fibrous, more often laminated, and less lipid-rich, but these differences have been regarded as minor. Aneurysms, although very different in natural history, have been regarded as an expression of severe focal atherosclerosis. Some, as in the popliteal artery, are commonly thought to be a result of trauma.

The risk factors for peripheral arteriosclerosis were not well characterized in 1972 but were usually held to be similar to those for coronary heart disease. In particular, diabetes mellitus was recognized as a potent risk factor for arteriosclerosis obliterans of the lower limbs. It was not well established whether the nature and distribution of vascular lesions are similar to those found in nondiabetic atherosclerosis, but differences in progress, presentation, and surgical approach lent credence to the view that differences must exist, perhaps at the

level of the microcirculation or at the level of the small distributing arteries and their anastomoses. Epidemiological data about incidence, prevalence, and risk factors were scanty both for cohorts and for international and geographic studies. Recent detailed and systematic pathological studies that addressed the nature and distribution of presymptomatic atherosclerosis were few. The question of why some lesions progressed to dilatation and aneurysm while others obliterated was unanswered. There was a need for improved noninvasive diagnosis.

Arterial occlusive disease of the extremities and the abdominal viscera was usually diagnosed through a combination of history, physical examination, and contrast arteriography. Noninvasive diagnostic techniques, including Doppler ultrasound and plethysmography, had been used in evaluating only symptomatic and asymptomatic arterial disease of the lower extremities. Patients with asymptomatic or minimally symptomatic disease were usually managed with nonsurgical measures, including an active exercise program, cessation of cigarette smoking, and treatment of diabetes, obesity, and hyperlipidemia. More severely symptomatic patients underwent endarterectomy or bypass grafting, using prostheses for larger arteries, including the aorta and iliac arteries, and autogenous saphenous veins for the femoropopliteal arteries. Vascular prostheses had not been developed that were suitable for smaller vessel bypasses, such as femorotibial bypass grafts.

By 1972, replacement of major vessels by synthetic vascular grafts was accepted surgical procedure. Aortic grafts usually remained patent for many years, although the intimal surface of the graft remained devoid of endothelial cells, save at the anastomotic line. Prior to this time, it had been recognized that porosity of the graft influenced healing and that increase in porosity improved graft performance but also resulted in risk of hemorrhage. Knitted Dacron® was the material of choice.

There were accepted diagnostic procedures and surgical treatments for peripheral ischemic disease but little descriptive pathology and little active research on its natural history, on risk factors, and on genesis of plaque. There was little research on experimental animals, and routinely useful animal models of arteriosclerosis obliterans did not exist. Acute pathophysiological studies of the control of limb circulation of animals were available as were acute metabolic studies.

There was limited understanding of venous disorders in 1972. They were known to be common, and those expressed as varicosities, particularly of the lower limb and of the anus, were--and still are--a major health burden. Venous thrombosis, especially deep venous thrombosis of the leg, was known to be life threatening. There was limited understanding, and little research, of the

pathogenesis of varicose veins. There was little or no animal investigation. Available treatment was of variable effectiveness.

Venous thrombosis was a matter of great research interest, but the research was focused on the thrombotic process per se and was often conducted in artificial systems with extrapolation of the conclusion, by analogy, to the peripheral veins. The diagnosis of deep venous thrombosis was made on clinical grounds assisted occasionally by venous angiography. Application of Doppler techniques to these clinical problems was just beginning. Risk factors for venous thrombosis were limited to circulatory stasis or to local vascular injury by trauma, tumor, or inflammation.

During the 1960's, it became apparent that microcirculatory studies of perfused organs were limited in their ability to describe peripheral vascular function. More detailed descriptions of events taking place within the organ were necessary. Techniques for measuring capillary exchange depended solely on indirect estimates of the relevant forces for the determination of permeabilities. The resistance of the peripheral vasculature was known to be distributed over several series of channels, and measurements of segmental resistance could not answer all of the questions of differential control of various portions of the vasculature. Problems had also begun to appear in defining the quantitative relations between delivery of oxygen and delivery of substrate to tissues. Finally, knowledge of the anatomy of the microcirculation had reached a point at which the heterogeneities among various types of vessels and within different types of cells of a given vessel were well known, but quantitative data for an overall analysis of vascular function were inadequate. These limitations necessitated the study of the peripheral circulation at the level of single microvessels.

In summary, limited effort was devoted in 1972 to research on peripheral vascular disease. Surgeons had developed techniques to replace large peripheral, intrathoracic, and intraabdominal artery segments with vascular or prosthetic grafts, but little attention was given to research on disorders of the veins or the medium or smaller branches of the large arteries. Very little was understood of the underlying mechanisms, other than arteriosclerosis, that might lead to peripheral vascular disease, and more information was needed to improve the diagnosis, therapy, and rehabilitation of patients.

Program Goals Through 1982

The general goals of the Institute for the peripheral vascular disease program were:

- Develop diagnostic procedures for the early detection of vascular diseases.
- Conduct clinical, laboratory, and epidemiological research into the causes, diagnosis, and treatment of diseases of the peripheral arteries and veins.
- Identify the relation of physiology and pathophysiology to clinical manifestations of disease.

In 1977, these goals were reaffirmed and more precisely focused, centering on the following proposed efforts:

- Develop more effective noninvasive methods of evaluating the severity of peripheral arterial diseases, suitable both for the assessment of symptomatic patients and for the recognition of latent arterial diseases.
- Improve the management of patients with peripheral arterial diseases, with particular attention to the long-term effects of arterial grafts and the improvement of graft techniques for smaller arterial vessels.
- Encourage greater research effort on the causes and treatment of peripheral venous diseases.

Accomplishments Through 1982

Arteriosclerosis

Peripheral arterial disease, with its frequent clinical manifestation of intermittent claudication, has been studied in the context of large epidemiologic surveys of cardiovascular disease. Certain risk factors, such as elevated blood pressure and serum cholesterol, glucose intolerance, and especially smoking, have been found to be precursors of intermittent claudication.

More recently, ABO blood types were determined in the Framingham population, and a 10-year followup study for occurrence of cardiovascular events was completed. A significant association was found between blood type and intermittent claudication, with blood group O showing the lowest frequency. Because this apparent protective factor was independent of the other known risk factors,

blood type should be considered, possibly through an effect on clotting, in the pathogenesis of intermittent claudication.

The clinical significance of intermittent claudication and its prognosis were studied in a followup investigation of newly diagnosed patients in the Framingham population. This study provided a more comprehensive view of outcome. After followup averaging 8 years, about 4 percent of the patients suffered amputation of limb or loss of toes. More striking was the observation that almost one-half developed a major cardiovascular event during this period.

Initial studies utilizing intraarterial infusion of prostaglandins E_1 and I_2 in limbs with ischemic lesions have been promising. Although further trials are required, these potent vasodilators and inhibitors of platelet aggregation may prove useful in selected patients with end-stage arterial insufficiency.

Instrumentation

Ultrasonic imaging techniques and intravenous arteriography have proved to be useful diagnostic methods for evaluating patients with peripheral arterial occlusive disease, specifically carotid artery disease. In peripheral arteries, real-time B-mode imaging has been limited to the femoral bifurcation, particularly in the detection of disease of the profunda femoris artery, which is an important collateral when the superficial femoral artery becomes occluded. Intravenous arteriography has provided a method for excellent visualization of the renal arteries and peripheral arteries, and further application of it may permit avoidance of routine contrast arteriography in patients who are candidates for arterial reconstruction of the lower extremities. These techniques are also used to define the long-term patency and integrity of vascular grafts.

Nuclear magnetic resonance studies have provided electronic systems and techniques for imaging the anatomical structure of organs and vessels and for imaging and quantifying blood flow. The techniques are especially applicable to experimental examination of the vessels of arms and legs, which can be inserted into the smaller sample regions of presently available magnet systems. Current techniques provide spatial resolutions of the order of 1 to 2 mm in measurement times of a few minutes.

The many recent advances in noninvasive diagnostic technology are discussed in more detail in Section 3, "Arteriosclerosis," pages 107-108.

Microcirculation

In keeping with the program goals expressed over the past decade, several major areas have been the focus of investigations. They include methodology, morphology, local control of blood flow, reactivity of microvessels, capillary exchange, microrheology, interactions between platelets and endothelial cells, endothelial cell growth, and pathology.

Methodology

Methodology necessary for quantitative study of microvessel function was developed during the 1970's. Techniques are now available for making almost all of the necessary measurements of pressure-flow relationships in the microcirculation. Velocity, pressure, and diameter of vessels can all be measured on-line with a reasonably high degree of precision, and relations between red cell velocity and bulk blood flow in the microvessels are known. There are also new methods for the measurement of microvessel hematocrit.

Great effort has been devoted to the development of a variety of new animal models. Preparations for the study of striated muscle and cardiac muscle as well as for in vivo microscopic examination of gut, brain, and skin have been developed. An important recent contribution has been a hamster cheek pouch chamber technique that allows tissue to be transplanted into an environment in which the transplanted tissue can be visualized with its own vascularization intact.

There has been significant progress in the development and perfection of methods for the measurement of the filtration coefficient and diffusion permeability of capillaries. The hydraulic conductivity of capillaries can now be measured with substantial accuracy by the occlusion method. Efforts to measure diffusion permeability have been less successful, although recent advances have been made with the use of densitometric measurements of dye efflux from capillaries and electrode measurements of ion exchange across the capillary endothelium.

Capillary exchange studies and studies of oxygen transport to tissue have been facilitated through the combination of in vivo microscopic techniques with a variety of specific microelectrodes. Hydrogen, sodium, potassium, calcium, and oxygen in tissues can be measured with reasonable precision under direct microscopic observation.

In vitro studies of isolated vascular segments have also made possible the investigation of the structure and function of the smaller subdivisions of the microcirculation. Techniques have

been developed for the in vitro study of transport through capillaries and morphology of capillaries isolated from the brain, and at present it is possible to isolate and cannulate single arterioles for the study of smooth muscle mechanics.

Substantial effort has also been directed toward developing mathematical models for all components of microvascular function, and new modeling techniques have advanced the capability for research on the microcirculation.

Morphology

In the study of the morphology of the microcirculation, interrelations between endothelial cells and smooth muscle cells in the resistance vessels have been defined; the formation, distribution, and turnover of micropinocytotic vesicles in the endothelium have been observed; and detailed descriptions of the pathways from capillary to tissue in a variety of tissue types have been made. The morphology of the lymphatics has been examined and related to lymph formation and edema formation.

Local Control of Blood Flow

It has been shown that local control processes can modulate both the bulk flow into the tissue, largely by arteriolar contraction and relaxation, and the distribution of flow within the tissues by recruitment or derecruitment of capillaries. An important advance in microvascular research has been the finding that flow into an organ and distribution of flow within the organ need not be regulated in the same way. More recent studies have shown that microvessel hematocrit is lower than systemic hematocrit and that the hematocrit varies in relation to metabolic needs of the tissue.

Various experimental models of local control have been developed, including models of reactive hyperemia, functional hyperemia, and autoregulation. These models have been used for study of the metabolic and myogenic components of the local regulatory process. Through the use of microvessel pressure measurements and the observation of single microvessels, it has been established that in many tissues, there is a myogenic component to regulation. This component is important in establishing the tone of the microvessels and especially in determining microvessel behavior during rapid changes. There is some suggestion that the myogenic mechanism may also be important in regulating the capillary pressure.

Metabolic mechanisms have also been examined, and tissue oxygen supply has been established as a major factor in metabolic

control. The distribution of blood flow within tissues, either between various parts of the tissue, as between epicardium and endocardium in the heart, or between various capillary channels, appears to be regulated by local control processes that may be metabolic in nature. The feedback factors responsible for regulating flow at the level of single capillaries remain to be determined. This area of peripheral vascular physiology has not yet been extensively investigated at the microvascular level.

Reactivity of Microvessels

The realization that reactivity of various segments of the microcirculation is likely to be different was an initial stimulus for microvascular studies. Over the past 10 years, clear differences at various levels in the microvascular tree have been shown for vasoactive substances such as histamine, prostaglandin, and norepinephrine. Some specificity has been shown at levels that were not detected with previous approaches to the study of the peripheral circulation.

With the use of direct microvessel observation and intravascular pressure measurement, it has been possible to begin studies of the mechanics of the microvessels and of the relation between smooth muscle function and intraluminal distending pressure. It has been shown that the relationship of force development to contractile fiber length applies at the level of the microcirculation, and beginning efforts have been made to relate microvessel reactivity to the length-tension curve of vascular smooth muscle.

Capillary Exchange

During the past 10 years, the exchange of materials at the level of single capillaries was one of the most lively areas of research on microvessels. Much work centered on the anatomy of the microvessels with regard to the exchange process, and especially the possible importance of pinocytosis in transcapillary exchange. The relation between micropinocytotic vesicles and the provision of pathways across the capillary wall remains a subject for investigation.

Research has been focused on the accurate determination of the hydraulic conductivity both of single capillaries and of organs. It has been shown with a variety of methods that single capillary hydraulic conductivity is a function of intravascular protein concentration and that the conductivity is greater than heretofore anticipated. More classical measurements of solute and water exchange combined with microscopic observations have ensured continued progress in establishing the regulatory effects on

capillary permeability of agents such as histamine, prostaglandin, and bradykinin. Data from studies of capillary water flux have been correlated with data from studies of the process of lymph formation. The forces leading to absorption of fluid from interstitium to lymphatics have been widely debated and related to lymph protein concentrations.

Capillary exchange of oxygen continues to occupy a central place in studies of tissue exchange. Microelectrode measurements of tissue oxygenation have been correlated with capillary flow patterns. It has been demonstrated that oxygen transport occurs across the walls of all of the vessels of the microcirculation, arterioles, capillaries, and venules. Hemoglobin saturation has been measured in capillaries and larger vessels in the microcirculation. These studies have strengthened the concept that a significant fraction of oxygen bypasses the microcirculation either by diffusional shunting from arteriole to venule or, perhaps, by anatomical shunting.

Microrheology

Rheologic studies in the past 10 years have been concerned largely with interactions between small vessels and red cells. The reduction in viscosity of blood in microvessels has been shown to be closely related to hemodilution in the microvessels. With the use of measurements of red cell velocity in microvessels and direct measurement of microvessel hematocrit, it has been possible to determine the velocity profile in smaller arterioles, down to 10 microns in diameter.

The dynamics of red cell flow has been studied, and models of red cell flow have been developed. The models are currently being applied to the study of pathological alterations in red cell flexibility and morphology.

Interactions between Platelets and Endothelial Cells

Important advances have been made in determining the hemostatic interactions between platelets and endothelial cells. The function of the nucleotides, prostaglandins, and prostacyclines in stabilizing platelets and in activating clotting mechanisms at the time of tissue injury has been elucidated. A new method that involves a sensitive radioimmunoassay for fibrinopeptide A, a constitutent of blood clots, has been developed for detecting small clots in veins. As an indicator of clotting, the assay is more specific and more sensitive than other available methods, and clinical diagnosis of peripheral venous thrombosis can now be made more accurately.

Endothelial Cell Growth

The growth and development of endothelial cells have been the subject of many investigations. Basic angiogenic processes have been studied in vitro and in vivo, and patterns of proliferation and growth of the cell have been established. Study has been made of normal capillary proliferative processes that occur in muscular hypertrophy and physical training, as well as in wound healing and tumor growth.

The existence of an angiogenic factor has been clearly established, although its chemical nature remains to be identified. A variety of tumor cells has been shown to induce endothelial cell proliferation and angiogenesis.

Pathology

With the use of new knowledge and methods, study has been made of the response of the microcirculation to a variety of pathological processes, including recovery processes following tissue injury induced by heat, radiation, chemotherapeutic agents, and physical trauma.

An area of substantial interest during the past 10 years has been the alterations in vascular reactivity at the microvessel level that occur during hypertension. Reactivity to a wide variety of vasoactive agents has been assessed, including catecholamines, prostaglandins, kinins, and nucleotides. All responses have been shown to be altered in various forms of hypertension. Additional changes at the microcirculatory level in hypertension include altered capillary exchanges of plasma proteins.

Recent interest has focused on the changes in the microcirculation induced by diabetes. Thickening of basement membranes as a part of the pathology of the disease has been examined. It is likely that the rheology of the red cell as well as transport of oxygen to tissues is altered in diabetes. The role of hemoglobin A_{1c} in limiting oxygen delivery has been studied. Finally, platelet aggregation secondary to altered characteristics of both plasma and platelets has been examined, and it appears to be part of peripheral vascular pathology.

Vascular Grafts

Over the past decade, there have been a number of alterations in Dacron® graft design, including the use of woven rather than knitted fabrics to decrease porosity and improve hemostasis, and the addition of velour on the outer, or both, surfaces to provide

a scaffold for cell growth and formation of a neointima. Early in the decade, expanded polytetrafluorethylene (PTFE, Teflon®) was introduced as vascular graft material. Although the early grafts of larger diameter developed aneurysms, reinforcement appears to have eliminated the problem. Improvements have been made in chemistry and design in both Dacron® and PTFE grafts; however, autologous saphenous vein remains the preferred material for grafts of small diameter vessels.

Various types of tissue grafts have been studied during the decade, including homologous and heterologous tissues. A variety of preservation techniques has been tested. Currently, no single type of tissue graft is in wide use. Some, such as the bovine artery heterograft introduced earlier, have fallen into disfavor. Others, such as the Dacron®-reinforced human umbilical vein and the negatively charged glutaraldehyde-tanned bovine carotid artery, have been quite recently introduced. Experience with biologic grafts has shown that good patency rates may be achieved but that the collagenous structure of the graft may eventually deteriorate, with resulting complications, particularly in situations with high pressure.

More recently, methods to seed endothelial cells onto synthetic grafts have been developed with the hope that the living surface will be nonthrombogenic and that the synthetic scaffolding will provide structure and strength for a long period of time. Currently, these methods are being studied in animal models.

Arteriospasm

The etiology of arteriospasm remains unclear although recent investigations have provided new information. The most important finding has been that idiopathic Raynaud's disease appears to be related to a neuroendocrine dysfunction. A variety of neuroendocrine and psychophysiologic data was collected during an objective cold stress test in subjects both with and without identifiable autoimmune abnormalities. Both of these groups of patients appeared to show identical heightened vasomotor tone in response to cold. The neuroendocrine data revealed that patients who did not have an autoimmune abnormality showed exaggerated adrenocortical activity and suppressed noradrenergic response to cold. The subjects with an autoimmune disorder, whose arteriospasm was probably related to a compromised vasculature, showed neuroendocrine responses similar to those of normal controls. Thus, two different pathological processes that cause similar symptoms can be seen. This bimodal occurrence suggests reassessment of the biobehavioral approach to arteriospasm.

Another finding has been that exposure to changing ambient temperature provides a controlled, repeatable method for assessing

noradrenergic activity. Unlike other psychological stresses, exposure to cold can be graduated slowly and can be made temporally compatible with changing noradrenergic function. It was also shown that individual differences in mentation and reaction time remained the same when subjects were affected by the stress. This approach may be ideal for the study of other diseases with presumed neuroendocrine involvement.

State of Knowledge in 1982

Arterial Disease

In 1982, there is a greater recognition that marked arterial regional peculiarities as well as similarities exist in atherogenesis. The observation of distinct but not unique local features is based on incomplete clinical, pathological, and epidemiological data. Detailed studies of the natural history of regional disease were not made during the past decade, and little basic research was done on the fundamental processes of atherogenesis of the various peripheral arteries comparable to basic research on the aorta or coronary arteries. During the decade, data has been strengthened on risk factor associations, particularly with regard to diabetes and cigarette smoking. In addition, diagnostic methods have been appreciably improved. Digital subtraction angiography may permit useful visualization of long segments of arteries.

During the past decade, it was found that, in general, the surgical treatment of peripheral vascular disease improves the quality of life of patients but that long-term mortality rates are relatively unaffected since the patients are likely to be claimed in their time by coronary heart disease or stroke. Whether reconstructive vascular surgery or amputation offers a patient a better quality of life remains an individual decision. In the United States, vascular reconstruction to avoid amputation has been favored. An estimated 147,000 peripheral vascular procedures were performed in 1979. In 1972, a number of new synthetic grafts were available, and over the past decade, a number of new products, which are very successful in larger caliber, high-flow circulations, have been developed. In low-flow systems, however, they commonly undergo thrombosis and are inferior to vein grafts in such situations (for example, femoropopliteal or coronary bypass surgery). Failure of the graft is of two main types. Thrombotic failure affects chiefly the synthetic graft. Such grafts apparently fail to endothelialize, and they do not develop a luminal surface that is fully neutral with respect to clotting. The use of polytetrafluoroethylene (PTFE) has allowed femorotibial bypass procedures to the level of the foot in situations of

unavailability of autogenous saphenous vein. The rigidity of this prosthesis and the resultant compliance mismatch of the prosthesis with the artery, however, have led to frequent development of neointimal hyperplasia at the distal anastomosis. To develop a substitute with qualities similar to the autogenous saphenous vein, further refinements in small vessel prostheses are needed. At present, vein grafts fare better although they are subject to intimal smooth muscle hyperplasia that may cause severe stenosis. Also, attention to intraluminal dilatation of stenotic vessels is increasing, but the procedure has not yet been evaluated sufficiently.

In 1982, noninvasive diagnosis of peripheral vascular disease is available in most medical centers throughout the country. Although relatively simple techniques employing pulse wave contour and plethysmography are still used for first level assessment of symptomatic patients, real-time B-mode scanning and pulse wave contour arteriography have greatly increased the ability to visualize arterial lesions noninvasively. However, the linear extent of peripheral atherosclerosis in symptomatic patients requires methods of imaging to which ultrasound techniques cannot be easily adapted. Digital subtraction radiography with intravenous injections may eventually replace the use of more risky intra-arterial procedures in patients with symptomatic peripheral arterial occlusive disease. For many cases, the resolution of current instruments in digital subtraction radiography is sufficient to provide adequate images to allow decisions about surgery. Further refinements in digital subtraction radiography should eventually eliminate in most cases the need for intra-arterial studies. In addition, refinements in digital subtraction technique for intra-arterial studies may permit use of much smaller volumes of contrast material and thus reduce the risks associated with arteriography in these patients, particularly the risk of renal failure.

Venous Disease

During the past decade, there was little basic or applied research in diseases of the veins. During this same period, however, there were major increments in understanding the basic pathophysiology of platelets and prostaglandin metabolism and function. As a result, the understanding of the fundamental processes of thrombosis has greatly improved. The contribution of smoking and of the use of oral contraceptives to the incidence of venous thrombosis has also been documented in cohort and case control studies.

Concepts of the pathophysiology of thrombophlebitis and pulmonary embolism were well developed by 1972. The underlying causes of varicose vein disorders, however, were not understood,

and the situation remains unchanged today. An estimated 66,000 procedures were performed in 1979 for the treatment of varicose veins. Progress has been made in the prevention of pulmonary embolus by pharmacological and physical means. Pharmacologic thrombolysis applied to pulmonary emboli, which was proved effective at the beginning of the decade, is now under consideration in the treatment of the postphlebitic limb. Noninvasive diagnostic procedures for detecting peripheral venous thrombosis have also been improved.

Lymphatic Disease

Possibly because the infectious causes of lymphedema are uncommon in the United States, there has been little interest in research on lymphatic disease. Nevertheless, research on lymphatics would have great importance for understanding the circulation, lymphatic metastases of neoplastic and bacterial origin, and postoperative or congenital lymphedema.

Microcirculation

Many issues that are of concern to the understanding of basic physiology of the microcirculation have been raised by past investigations. These require continuing study. Quantitative studies of physiological processes, using new techniques, are needed. Descriptors for the heterogeneity of the microcirculation are necessary, as are rapid methods of measuring pertinent microvascular variables such as vessel length and tortuosity.

The control of microcirculatory function is of importance to pathological states and to normal tissue function. The focus of studies of local control mechanisms is shifting toward mechanistic investigations. The role of neural mechanisms in the control of the microcirculation has received limited attention. Emphasis on a neural component to the pathogenesis of hypertension and perhaps to other vascular diseases is leading to research on the neural control of the microcirculation. Similar opportunities exist for research on the role of a class of vessels that is commonly not studied at either the macrocirculatory or microcirculatory level--that is, vessels between 500 and 50 micrometers in diameter. Measurements show that substantial pressure drops occur across these vessels. This observation suggests that such vessels may have some role in regulation of blood flow.

Capillary exchange studies have focused on the sites of exchange of various molecules and on the determinants of capillary permeability. New emphasis is developing on the study of factors such as protein molecules that may modulate capillary permeability directly.

A very useful new technique is the use of fluorescent labels, especially in conjunction with antibodies that confer specificity on the labeling process. They are being used at present for tracing microvascular pathways, and it is anticipated that this work will be expanded, utilizing cell biology techniques, to the labeling of specific cells, either in the microvessels themselves or in blood, for assessing development of capillaries and flow pathways for red cells.

In the recent past, the active component of the microcirculation has been perceived to be the vascular smooth muscle cell. Recent evidence suggests that endothelial cell contractility may also be important in the control of a variety of microvessel functions, including flow control and capillary exchange. The factors controlling endothelial cell growth and migration are just now beginning to be studied with the newest methods and techniques. In particular, the use of combinations of microvessel methodologies with the methodologies of organ and tissue culture should allow rapid expansion of knowledge regarding factors determining angiogenesis in normal tissues and in tumors.

Program Goals 1982 to 1987

- Promote fundamental research on the nature, etiology, and pathogenesis of disorders of the peripheral arteries, veins, and lymphatics in order to enhance diagnosis, treatment, and prevention.

- Continue to develop and refine methods to diagnose peripheral vascular disease.

Research Activities 1982 to 1987

- Expansion of investigation of the pathophysiology of the peripheral vessels including circulatory dynamics, neural control, capillary exchange phenomena, and properties of the microcirculation in health and disease.

- Increase in knowledge of the relationship of thrombotic phenomena occurring in peripheral arteries and veins to vascular sclerosis and occlusion.

- Increase in knowledge of the risk factor associations for peripheral arterial and venous disease.

- Further refinement of minimally invasive techniques for detection and quantification of developing and regressing arterial plaques in the peripheral vessels.

- Further development and refinement of small vessel prostheses.

8. Arrhythmias

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8. Arrhythmias

A cardiac arrhythmia is an abnormality of the rate or rhythm of the heart. "Extra beats" (premature beats or extrasystoles) are instances of cardiac excitation occurring prematurely. They are caused by electrical activity outside the intrinsic cardiac pacemaker that briefly (one beat) or for a more prolonged interval usurps control of the heart rate and rhythm. Many of the cardiac arrhythmias are tachyarrhythmias, in which the heart rate is above the normal range of 60 to 100. Such arrhythmias are classified as supraventricular when the site of origin is above the ventricle and as ventricular when the site of origin is the ventricle. The bradyarrhythmias are the arrythmias in which the heart rate is less than 60. They can be due to a very slow rate of impulse formation in the sinus node, which is the normal cardiac pacemaker, or to delayed or blocked conduction of the impulse to the atrium and/or ventricle. Cessation of impulse formation is referred to as asystole.

There are many factors that singly or in concert can cause cardiac arrhythmias. Some arrhythmias are associated with underlying heart disease and may place the patient at risk of sudden cardiac death. Other disturbances of cardiac rhythm can be symptomatic by virtue of their ability to impair cardiac pump function and result in weakness, fatigue, or fainting. Such disturbances can also lead to the sensation of abnormal heart rhythm (palpitations). Most arrhythmias, however, are asymptomatic, and many arrhythmias are not associated with underlying heart disease.

State of Knowledge in 1972

In 1972, lethal arrhythmias were believed to be the cause of 50 percent of deaths from heart attacks (myocardial infarction). It was known, for example, that during the course of a heart attack, ventricular extrasystoles were often observed prior to the development of ventricular fibrillation and death. The importance of ventricular fibrillation in out-of-hospital sudden cardiac death was suspected but not known. The mechanism of action of lethal arrhythmias was incompletely understood, and additional knowledge was needed in several areas. The means of assessing risk factors and identifying populations at risk were of limited effectiveness and availability, and the technology for continuous

electrocardiographic recording and rapid interpretation of the cardiac rhythm was in its early stage of development. The effectiveness of long-term preventive therapy for ventricular arrhythmias was poorly documented, and the therapies themselves were based largely upon empirical methods with often inadequate means of assessing efficacy and safety. The effectiveness of standard pharmacologic agents in reducing the incidence of arrhythmic events was limited, and their effectiveness in reducing mortality was unknown; furthermore, most agents had serious and undesirable side effects. Implantable cardiac pacemakers had been available for a number of years, but these devices continued to present major problems, including frequent pacemaker failure or breakage of lead systems, limited electronic versatility of power generators, and the relatively short life of the battery pack.

A better understanding of the fundamental characteristics of arrhythmias associated with ischemic myocardium (heart muscle deprived of an adequate blood flow) was needed. Clinical studies that incorporate analysis of recorded electrocardiographic data were needed to assess the possible efficacy of therapeutic regimens. Research on fundamental arrhythmic mechanisms unrelated to myocardial ischemia and other causes of sudden death was also needed.

Program Goals Through 1982

In accordance with the recommendations of the National Heart and Lung Advisory Council and the Heart and Blood Vessel Disease Panel, the National Heart and Lung Institute in 1972 emphasized the need for research to improve the understanding and prevention of nonlethal and lethal arrhythmias. Needed research on arrhythmias ranged from a better understanding of the fundamental mechanisms to the facilitation of clinical investigation.

The goals of the Institute identified in 1972 and 1977 were to:

- Encourage research on the overall problem of sudden cardiac death.
- Encourage research on the fundamental mechanisms of arrhythmias, particularly those associated with ischemic heart disease.
- Expand clinical studies of various populations, designed to develop more effective descriptors of those at increased risk of sudden cardiac death.

- Encourage research on the significance and prognosis of conduction disturbances.

- Develop Specialized Centers of Research in Ischemic Heart Disease to provide a multidisciplinary clinical and basic research environment for studying various aspects of heart disease including sudden cardiac death and rhythm disturbances.

- Develop methods of long-term prophylactic therapy, using pharmacological agents, to prevent sudden cardiac death.

- Sponsor workshops on the prevention of sudden cardiac death emphasizing clinical trials of potential approaches to arrhythmia prophylaxis.

- Assess the significance of artificial pacemakers in the management of various conduction disturbances, and define the indications for their use.

- Achieve a better understanding of the significance of rhythm disturbances commonly found in long-term, ambulatory monitoring of cardiac rhythm to permit better clinical management.

- Develop more effective methods for the recognition of those at heightened risk of sudden cardiac death.

Accomplishments Through 1982

Cardiac Electrophysiology

There has been a considerable increase in the understanding of cardiac electrophysiology. Much of this information has been acquired through recent advances in the voltage clamp technique. It is now known that cardiac electrical activation is due to various ionic currents through ion-specific channels in the cardiac cell membrane. Changes in cardiac cell membrane permeability to various chemical species such as Na^+, K^+, Ca^{2+}, which exist both intracellularly and in the interstitial fluids surrounding the cell, have been carefully described.

A most dramatic advance in electrophysiology is knowledge of the slow inward current--that is, the movement of Ca^{2+} into the cell during the plateau phase of the cardiac action potential. In certain cells in the heart, notably the nodal cells, this current is responsible for the upstroke of the action potential. In ischemic myocardial cells and in specialized conducting (Purkinje)

fibers, the fast Na^+ current, which is the normal current, may be inactivated. In such regions, the "slow-response" type of action potential may supervene, especially in the presence of high catecholamine concentrations. The velocity of conduction of such slow-response action potentials is very low. This type of action potential can lead to reentrant arrhythmias, which may be life-threatening. The calcium-channel blocking agents, which have only recently been used in the treatment of cardiac disorders, act on this slow inward current and hence tend to interrupt the reentrant circuits. Thus, an understanding of basic cardiac electrophysiology and changes observed with ischemia have generated a hypothesis that is being tested in patients with cardiac disease. The hypothesis is that calcium channel blockers modify the conditions leading to ventricular fibrillation.

Another important advance in cardiac electrophysiology has been the recognition of oscillatory after-potentials, or "triggered activity." Arrhythmias involving disorders of impulse generation have traditionally been ascribed either to enhanced automaticity of ectopic pacemaker sites or to reentrant circuits. The distinction was usually based on the nature of the coupling of the abnormal beat or sequence of beats to the preceding normal beat. Tight coupling was usually interpreted as reentry. During the past decade, electrophysiological studies have shown that certain experimental conditions, such as rapid, repetitive excitation, and certain drugs, notably digitalis glycosides, induce oscillatory after-depolarizations. Such after-depolarizations may reach threshold, and thereby evoke a propagated action potential. This triggered excitation is tightly coupled to the preceding beat, and thus possesses one important characteristic of a reentrant depolarization. Furthermore, a triggered excitation is often followed by an oscillatory after-depolarization. If this after-depolarization also reaches threshold, a second triggered excitation follows the first. This pattern could continue to a series of triggered excitations that would have all of the characteristics of a paroxysmal tachycardia.

Advances in electronics, computer technology, and other fields of engineering have fostered concomitant advances in pacemakers, defibrillators, and monitors. Advances in cardiac monitoring and in telemetering of the electrocardiogram and in computer analysis of the cardiac rhythms have led to better supervision and treatment of patients in coronary care units. Advances in long-term recording of the electrocardiogram (ECG) in ambulatory patients and the computer analysis of such protracted recordings have permitted timely, less costly, and more precise detection of arrhythmias in patients with disorders of the sinoatrial (S-A) node, atrioventricular (A-V) junction, and the ventricular specialized conduction system. Computer-based analysis of the rhythm in these continuous recordings has facilitated clinical studies of arrhythmias and also critical

assessments of pharmacologic interventions for the prevention or termination of disorders. The latter development is of particular significance.

Prior to the 1970's, cardiologists succeeded in recording the His bundle electrogram by pervenous insertion of an electrode catheter into the region of the A-V junction. His bundle electrocardiography led to a greater understanding of various types of A-V block and of paroxysmal tachycardias. It permitted more precise diagnoses and better informed therapy. These advances have continued during the past decade. Signal averaging techniques have allowed the recording of the His bundle electrogram from the surface ECG. Other electrodes, some sewn to the right atrial surface and some threaded into the right atrium on a catheter, have permitted the registration of sinus node electrical activity. As a consequence, there is a much better comprehension of the behavior of the numerous clusters of pacemaker cells that comprise the S-A node, which is the normal cardiac pacemaker.

Electrical mapping of the heart by catheter electrodes inserted into the heart through a peripheral vein or at the time of surgery has aided in the identification of abnormal pathways (bypass tracts) and has guided the surgeon in ablating the accessory bundles or in removing ventricular muscle that serves as a site of reentry rhythms. This technology allows the surgical management of arrhythmias not controllable by other forms of therapy. Patients with these severe forms of preexcitation syndromes heretofore had suffered from symptomatic tachyarrhythmias. Many died of their arrhythmias.

The development of programmed electrical stimulation to intentionally induce reentrant arrhythmias in humans has been explored. This technique may serve to identify those patients at risk of dying suddenly and may permit identification of the proper and effective course of therapy to prevent sudden coronary death.

Pacemaker research has incorporated the latest innovations in electronic circuits and technology. It is now possible to diagnose many aspects of pacemaker performance by telephone between the patient and a pacemaker diagnostic clinic. Improvements in batteries and pacemaker electrodes significantly prolong operation. Developments in electronics have led to pacemakers that are less susceptible to interference from outside electrical and magnetic sources.

New knowledge from research on defibrillators has resulted in optimization of defibrillator waveforms so as to permit defibrillation to be performed at lower power levels. Implantable defibrillator devices have performed well in animals. Their clinical usefulness in patients at high risk of ventricular fibrillation is currently being investigated.

Considerable information has been acquired over the past decade relative to the importance of the autonomic nervous system in the genesis of arrhythmias. Stimulation of certain areas of the brain evokes arrhythmias. Increased sympathetic nervous activity has been shown to lower the ventricular fibrillation threshold and to increase the incidence of extrasystoles and other arrhythmias in ischemic hearts. This increased activity appears to be more deleterious when the distribution of that neural activity to the heart is heterogeneous. Augmented parasympathetic activity tends to counteract the deleterious effects of the increased sympathetic activity. The beneficial effect of beta-adrenoreceptor blocking agents in survivors of myocardial infarction probably counters the deleterious effect of high levels of sympathetic nervous activity on a scarred myocardium.

Treatment

New or improved analytical methods have been developed for measuring the plasma concentration of many of the currently used antiarrhythmic drugs. This technology has resulted in new approaches to the frequency of administration and dosage of drugs that may improve control of cardiac rhythm disorders and decrease the frequency and severity of undesirable side effects. The ability to detect metabolites has led to the recognition that not all patients metabolize drugs in a similar manner and that genetic differences among patients can determine the degree to which a drug may be tolerated. Furthermore, the ability to follow plasma concentrations of drugs accurately has led to the recognition of a potentially unfavorable interaction between two commonly used agents--digoxin and quinidine--and has provided conclusive evidence to explain heretofore unexplained occurrences of toxicity when these agents were used in a combined therapeutic regimen.

Over the past 10 years, major advances in the treatment of cardiac arrhythmias have resulted from fundamental physiological and pharmacological studies of the most prevalent form of arrhythmia, the tachyarrhythmias. The most striking advances have been made with three classes of drugs: local anesthetics, calcium blockers, and beta-adrenergic receptor blockers.

Fundamental research found that local anesthetics produce many of their pain-relieving effects by the prevention of conduction along the nerve fibers that are responsible for transmission of painful sensations to the brain. Many of these agents prevent the passage of sodium ions through the nerve membrane. Prevention of this movement stops the electrical activity that is necessary if neural transmission is to take place. Since the passage of sodium ions is the basis for electrical activity in certain heart muscle cells, as well as nerve cells, experiments with various local anesthetics were undertaken on the heart in order to test

whether they can be used to suppress abnormal electrical activity. One such local anesthetic, lidocaine, was found to be particularly effective in the myocardial cells of the ventricles. Lidocaine has been found to be particularly useful in suppression of arrhythmias that occur after myocardial infarction. These arrhythmias are frequently life-threatening. The use of lidocaine in coronary care units has controlled these dangerous rhythm disorders in many instances, and it is contributing to increased survival of heart attack patients.

The recent introduction (1970's) of a new class of anti-arrhythmic agents--the calcium channel blocking drugs--has added a new approach to the management of patients with supraventricular arrhythmias. In certain heart muscle cells, especially those concerned with initiation and conduction of the heart's excitation in the region above the ventricles, the electrical activity is much more dependent on entry of calcium than entry of sodium, which is important in the ventricles. Over the past 10 years, a group of drugs has been developed that specifically blocks this entry of calcium. They are very effective in altering the electrical activity of these specialized cells. The supraventricular focus or foci are the site of the most commonly occurring cardiac arrhythmias--the so-called "supraventricular tachycardias" (rapid arrhythmia arising above the ventricles). The calcium-blocking drug that was first approved for use in the United States was verapamil. It is effective in the treatment of many arrhythmias that arise in the atria. In addition, it has a minimum of undesirable side effects. This group of drugs represents a major advance in the treatment of disordered rhythms of the heart.

The third group of agents, though not used as frequently for arrhythmias as those just discussed, contains the beta-adrenergic receptor blocking drugs. The catecholamines, which are epinephrine ("adrenalin") and norepinephrine, and the adrenalin-like drugs exert their effects in various organs throughout the body by interacting with specific receptors on cells called "alpha" and "beta" receptors. In the heart, stimulation of the beta-receptors by adrenalin or by related pharmacologic agents can produce marked increases in heart rate (tachycardia) and arrhythmias. Receptors can be blocked with agents that prevent the interaction of the catecholamines or adrenalin-like substances with the receptors and thus block their stimulating effects and terminate the associated arrhythmias. The beta blockers are currently used as adjunctive treatment for certain arrhythmias in which modification of catecholamine activity is desirable. Large scale clinical application of one of these agents, propranolol, was tested in the Beta-Blocker Heart Attack Trial and demonstrated reduced mortality in survivors of acute myocardial infarction. Timolol and metoprolol, two other beta blockers, have also been found effective in decreasing total mortality in survivors of myocardial infarction.

Bretylium is another drug investigated over the past decade. It is known to be particularly effective in treating certain of the life-threatening ventricular arrhythmias that are resistant to other agents. The mechanism of action of this drug is still under investigation, but since it is probably different from lidocaine or the beta blockers, it is an important addition to the inventory of agents for the treatment of ventricular arrhythmias.

Newer antiarrhythmic agents are becoming available for clinical investigation and offer considerable promise of being effective against disturbances of ventricular rhythm. The wide range of clinical problems encountered in patients at high risk for sudden cardiac death suggests that no single therapeutic approach will apply to all individuals requiring treatment. Since the final common pathway in the vast majority of patients with sudden cardiac death is ventricular fibrillation, considerable interest has arisen concerning the development and evaluation of drugs designed to raise the fibrillation threshold, especially in the ischemic heart. Several new agents are in the early stages of evaluation for their potential to protect against the development of ventricular fibrillation. The wide variety of new antiarrhythmic agents has resulted in the development of sophisticated clinical testing procedures involving multicenter trials employing double-blind, crossover techniques with ambulatory monitoring of the electrocardiogram and detailed studies of the pharmacokinetics of drug distribution, metabolism, and elimination.

Major advances have occurred in the introduction of new techniques of emergency care into emergency medical systems, including the recognition of, and emergency therapy for, high-risk arrhythmias. Electrocardiographic tracings of a patient's heart rhythm can be immediately transmitted telephonically or telemetrically to the cardiologist, who in another location can recommend appropriate therapeutic measures. The recognition that sudden cardiac death due to ventricular fibrillation is a reversible electrical derangement of cardiac rhythm has resulted in widespread community involvement in learning techniques of cardiopulmonary resuscitation. It has also resulted in the establishment of emergency medical teams to assist victims of sudden cardiac death, many of whom are resuscitated.

Biobehavioral Investigations

Increasing attention is being directed to the role of biobehavioral factors related to sudden cardiac death. Recent research findings have implicated the central and peripheral nervous system in the precipitation of arrhythmias, conduction disturbances, and hemodynamic impairment resulting in some cases of sudden cardiac death. It is now recognized that sudden cardiac death usually occurs in the presence of preexisting coronary

artery disease rather than in normal hearts, and results from ventricular fibrillation rather than asystole. Basic biobehavioral research has been refocused on defining the influence of neural and biobehavioral factors on ventricular electrical stability.

In studies addressing the biobehavioral contributions to this problem, several diverse factors are being explored that may bear on the development and maintenance of potentially lethal cardiac arrhythmias. For example, research continues on the behavioral factors and physiologic mechanisms involved in the voluntary self-regulation of heart rate and on clinical applications of this biofeedback technique. In other areas of investigation, the contribution of psychologic stressors in identifying or aggravating physical aspects of cardiac disease is being assessed. Inherent in these investigations is the development of requisite methodology that permits recording of the pharmacologic, neurophysiologic, and psychologic indices of the reaction(s). An important goal of current biobehavioral studies is to determine whether psychological stress alone can produce lethal consequences in animals with a predisposition to arrhythmias.

State of Knowledge in 1982

Sudden cardiac death, which claims over 350,000 lives annually in the United States, continues to be a major health problem. The gravity of this problem is underscored by estimates that approximately 100,000 of these fatalities occur in persons younger than 65. It is now clearly established that in the United States and in other Western countries, there is an overwhelming association of coronary atherosclerotic heart disease with sudden cardiac death.

In these countries, between 80 and 90 percent of sudden coronary deaths are associated with severe stenosis of one or more of the coronary arteries. Although it is known that ventricular fibrillation is the proximate cause of sudden coronary death, the fundamental problem that awaits resolution is the mechanism by which coronary heart disease leads to this terminal event. The general belief presently is that myocardial ischemia is central to this lethal process.

It is clear that therapy is not necessary for the patient who has asymptomatic, simple ventricular arrhythmias and no detectable evidence of heart disease, but the proper course of action for the patient with recognized heart disease and arrhythmias, particularly patients who have been successfully resuscitated, remains less clear. Various interventions, including antiarrhythmic

agents, vasodilators, aortocoronary bypass surgery, implantable defibrillators, and left ventricular aneurysm resections, are being used in treating these patients. The prospect of being able to modify the probability of sudden cardiac death, however, is uncertain, and at the present time, there is no consensus concerning the optimal program of management for those at high risk.

In an attempt to control ventricular arrhythmias, a wide variety of antiarrhythmic drugs is used in the management of patients who are at risk for sudden death. Several drugs such as lidocaine and procainamide have been reported to prevent ventricular fibrillation in patients hospitalized in a coronary care unit. For clinical effectiveness in an outpatient setting, however, lidocaine cannot be used, and procainamide must be administered frequently and in large doses, with a resultant increase in the incidence of side effects that often require discontinuation of the drug. Assessment continues of other new antiarrhythmic drugs that may have more specific antiarrhythmic activity and greater efficacy in the control of arrhythmias. The wide range of clinical problems in patients at high risk for sudden death suggests that no single therapeutic approach is applicable to all individuals requiring treatment.

Several groups are presently evaluating the role of surgical intervention in patients with recurrent ventricular arrhythmias. In these studies, a variety of approaches is being used to eliminate the presumed reentry pathway, including removal of ventricular aneurysm, extension or excision of ventricular scars, removal of endocardium, and undercutting in the subendocardium. Although the initial reports concerning these procedures have been favorable, experience is limited and long-term followup data are not yet available.

Research is also continuing at the fundamental level. As better understanding of the mechanisms of arrhythmias is gained, new gaps in understanding are identified that are critical for the development of effective prevention and therapy. Investigations are in progress to determine the relationship of metabolism at the cellular level (including changes in ion exchange) to the cause and the sequellae of arrhythmias. Research concerning ion fluxes across cardiac cell membrane is underway, and the possible association of the "slow" calcium current with certain rhythm disturbances is under study. The roles of both the autonomic nervous system and the central nervous system in the genesis of arrhythmias have also become the subject of increased research effort.

Several large clinical trials have demonstrated a reduction in mortality in survivors of myocardial infarction given beta-blocking agents as compared to controls given placebo. These

trials were randomized and conducted in a double-blind fashion. Further studies of the relationship between central and autonomic neural activity and ischemic myocardium are needed.

The management of arrhythmias in the coronary care unit in the acute phase of myocardial infarction has reduced hospital mortality. A variety of management strategies has evolved, which ranges from prophylactic antiarrhythmic administration to no drug therapy combined with application of electrical defibrillation when warranted. Development of new drugs, which are more easily administered and have fewer side effects, for use both in the hospital and after discharge remains a high research priority.

As techniques of diagnosis have improved over the past 20 years, the attention of pediatric cardiologists has been drawn to an increasing number of children with conduction abnormalities. Insufficient data exist on the nature, incidence, and natural history of arrhythmias and conduction abnormalities in the fetus, the newborn, and the child. In the diagnosis and the understanding of the causes and effects of such arrhythmias, there is a need for substantial improvement of the techniques of automated data acquisition and processing and of the noninvasive diagnostic methods available for young patients. In addition, it is recognized now that large numbers of individuals who undergo cardiac surgery for repair of congenital heart lesions will later suffer various kinds of arrhythmias. The combination of these congenital and acquired conduction abnormalities has a bearing on the risk of sudden death in the infant, adolescent, and young adult populations.

The proper use, in children and adults, of invasive electrophysiologic testing, of ambulatory ECG monitoring, and of exercise testing in revealing latent arrhythmia is not yet delineated. The latter two techniques, which are noninvasive, yield similar but not identical diagnostic and prognostic information. All techniques are used in tailoring antiarrhythmic therapy to individual patients, but it remains to be determined whether antiarrhythmic drugs are antifibrillatory.

Program Goals 1982 to 1987

- Continue to identify the fundamental electrophysiologic mechanisms of normal and ischemic myocardium and their relationship to arrhythmias and sudden death.

- Develop and refine methods useful in identifying individuals in all age groups at risk of arrhythmias and sudden death.

- Improve the understanding of the role of the nervous system in the pathogenesis of cardiac rhythm abnormalities.

- Develop and refine medical and surgical interventions to reduce or prevent sudden death in high risk populations.

- Encourage multidisciplinary studies of cardiac rhythm in both the normal and diseased heart.

Research Activities 1982 to 1987

- Continuation of exploration of the metabolic, membrane, and ionic events associated with normal and ischemic myocardium and their relationship to arrhythmias.

- Expansion of studies of the role of the autonomic and central nervous systems in the genesis of arrhythmias and sudden death.

- Continuation of the study of the independent contribution of arrhythmias in the identification of individuals at high risk of sudden death.

- Continuation of the search for and evaluation of a variety of antiarrhythmic and antifibrillatory pharmacologic agents.

- Long-term assessment of indications for and effectiveness of surgical interruption of intracardiac conducting pathways in the treatment of symptomatic, medically intractable arrhythmias.

- Development of improved techniques for monitoring cardiac electrical activity.

- Continued assessment of implanted, automatic monitoring and therapeutic electrical devices as a means of detecting and reversing lethal arrhythmias.

- Investigation of the effect of reperfusion on the generation of arrhythmias.

- Exploration of biobehavioral influences upon cardiac rhythm and its disturbances.

9. Heart Failure and Shock

Contents

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Heart failure is a pathophysiologic state in which an abnormality of cardiac function leads to failure of the heart to pump blood at a rate commensurate with the requirements of the metabolizing tissues. Heart failure is a most common cardiac disorder, affecting at least 2 million Americans. The term "cardiogenic shock," when discussed in the context of heart failure, refers to a situation of rapidly developing failure of the heart to pump an adequate amount of blood into the circulatory system. This occurs when a large segment of heart muscle undergoes ischemic necrosis during acute myocardial infarction. Cardiogenic shock accounts for a large proportion of deaths in patients after acute myocardial infarction. Over the past decade, investigators increasingly recognized the need to focus on this important problem. Many other syndrome(s) of circulatory failure referred to clinically as "shock," such as failure of the circulation due to loss of blood or plasma volume, sepsis, and anaphylaxis, are not addressed in this discussion.

State of Knowledge in 1972

The presence and severity of heart failure and shock are related to the amount of heart muscle that is damaged in the course of a heart attack. Irreversibly damaged muscle rapidly loses contractility and ultimately forms a scar. Whenever more than 40 percent of the heart muscle is necrotic or scarred, death usually ensues. In 1972, it was postulated that the amount of heart muscle that would go on to irreversible damage in the course of a heart attack was generally not fixed at the onset of the attack. It was believed that significant areas of heart muscle were deprived of adequate blood flow and were in jeopardy, but had not undergone irreversible damage. An important research need at that time was to test this hypothesis and develop a means for minimizing damage to the jeopardized heart muscle. As a corollary, it was necessary to develop methods for quantifying accurately the extent of heart muscle that had undergone irreversible damage, and for identifying and treating the area that was potentially salvageable.

The diagnostic evaluation of heart failure and shock generally involved assessment of clinical manifestations such as pulmonary congestion and edema, and measurements of hemodynamic

parameters such as systemic blood pressure and central venous pressure. Cardiac catheterization was necessary for hemodynamic assessment of ventricular function. Echocardiography had just begun to be applied to the measurement of chamber size and function. Evaluation of cardiac function using radionuclide techniques was in the experimental stage.

Many of the biochemical derangements at the subcellular and systemic levels associated with heart failure and shock were recognized. Pharmacological methods were sometimes effective in raising the blood pressure during cardiogenic shock, but rarely effective in saving life. Prevention of chronic heart failure was dependent upon early treatment of some forms of heart disease, or better yet, upon prevention of heart disease itself.

In 1972, the National Heart and Lung Advisory Council, in recognition of the magnitude of this problem, recommended that studies of heart failure and shock receive high priority.

Program Goals Through 1982

In 1972, the following goals were set by the Institute:

- Minimize heart failure associated with, and following, heart attack by enhancing the survival of damaged heart muscle.

- Develop and apply a variety of therapeutically effective, safe, and reliable cardiac assist and total replacement devices together with the supporting diagnostic and monitoring information.

- Elucidate the fundamental biochemical and cellular mechanisms involved in myocardiogenic ischemia and gain a better understanding of the systemic effects of cardiogenic shock.

- Develop methods for protecting ischemic myocardium and for preventing the conversion of reversibly ischemic tissue to irreversibly infarcted and scarred myocardium.

- Develop methods for quantifying the extent of ischemic myocardium to aid the assessment of therapeutic efficacy and patient management.

Accomplishments Through 1982

The goals listed above relate largely to the acute and chronic stages of heart failure resulting from ischemic heart disease. Myocardial ischemia and infarction are a major cause of both acute and chronic cardiac decompensation; however, hypertensive heart disease, cardiomyopathy, and valvular heart disease are also important causes. Several important advances have been made in these areas in terms of fundamental research, instrumentation, pharmacology, and other diagnostic and therapeutic approaches.

Fundamental research on ischemic heart muscle has improved the understanding of basic mechanisms and biochemical processes. The most important of these advances is an ability to estimate the time interval beyond which the ischemic heart muscle undergoes irreversible change. (Other accomplishments are discussed in Section 6: "Coronary Heart Disease.") Further refinements in this area, however, are still needed. Many other striking milestones were reached in the effort to elucidate the fundamental mechanics and energy metabolism of cardiac muscle cells. (These are reviewed in Section 11, "Cardiomyopathies and Infections of the Heart.")

For clinical assessment, invasive and noninvasive techniques have been refined and developed. These techniques have been useful in determining the anatomical and functional state of the myocardium. In addition to their increasing resolution, the chief attractive features of most of these new techniques are their noninvasive nature and their adaptability to rapid measurements of changing hemodynamics in the critically ill patient. Examples of these developments are:

- Sequential mapping of electrical signals from the heart at various sites over the chest to determine the size and area of infarction.

- Measurement of the time course of release of enzymes from damaged heart muscle and correlation of these sequential enzyme levels with the actual size of infarction.

- Injection of radioisotope tracers that have preferential avidity for necrotic myocardium or normal myocardium. These scans provide a reasonably good idea of the location, size, and overall geometry of an infarct or area of ischemia.

- Another radioisotope technique, the gated radionuclide ventriculogram, with which clinicians can measure the extent and timing of the movement of various segments of the heart chamber and also can infer the "ejection

fraction," which is the ventricular blood volume that is ejected with each heart beat. This measurement correlates highly with survival.

- Equally impressive advances in the application of improved ultrasonic techniques. Real-time ultrasonic imaging and computer-controlled, two-dimensional echocardiography have greatly improved the assessment of cardiac function and anatomy.

- The dynamic spatial reconstructor, which is an innovation based on the principle of computerized tomography, permits three-dimensional analysis of cardiac function in health and disease. Intra-aortic injection of a contrast agent permits detailed imaging of the coronary arteries down to approximately 1 mm diameter. Computer-generated displays of the three-dimensional data permit accurate localization and orientation of oblique section images taken through structures of interest.

The steady, rapid evolution of these sophisticated diagnostic techniques has led to a better understanding of the temporal aspects of ischemia and resulted in more precise measurement of the results of pharmacologic and mechanical interventions that are designed to reduce the extent of damaged myocardium and prevent or reduce heart failure and shock.

Pharmacological advances in the treatment of heart failure have involved drugs that reduce the preload or afterload of the damaged heart or attempt to increase the inotropic function of the heart. Use of these drugs represents attempts to increase the effectiveness of myocardial contraction and more closely tailor peripheral vascular resistance to circulatory needs.

One of the great advances of the past decade has been the use of vasodilator therapy in the management of the patient with chronic congestive heart failure. Peripheral vasodilators, such as hydralazine, prazosin, nitroprusside, and nitrates, reduce preload and afterload of the heart by inducing dilatation of capacitance and resistance vessels.

While many new vasodilator agents and new methods of administering these drugs have appeared during the past decade, the number of new, inotropic agents has been relatively minimal. Digitalis, a time-honored, mild inotrope, has been one of the mainstays of treatment of heart failure. Drugs of the dobutamine class and other drugs, which act directly or indirectly by stimulating or enhancing the adenylcyclase system, have been developed for use in treating heart failure. The most recent introduction in this area has been amrinone and several related drugs that appear to function as inotropic agents. These drugs are

nonglycosidic and appear to evoke contractility above that evoked by full doses of digitalis.

Advances have been made in other diagnostic and therapeutic approaches. Studies using the Swan-Ganz catheter have led to a better understanding of the hemodynamic variants underlying heart failure and shock. This development has permitted more precise identification and therapeutically useful classification of individual cases of heart failure and shock. Intra-aortic balloon counterpulsation has been developed to mechanically support the failing heart. It has also permitted further diagnostic study to determine the need for more definitive therapy.

After extensive bench and animal testing, the pneumatically powered left ventricular assist device has been evaluated clinically. Twenty percent long-term survival has been achieved by the use of this device for less than 2 weeks in a group of postsurgical patients who could not be weaned from the heart-lung machine despite extensive pharmacologic intervention and use of the intra-aortic balloon pump. In 1980, clinical evaluation of the LVAD was extended to patients in shock secondary to myocardial infarction and to patients with reversible cardiomyopathy.

Surgical approaches have been applied when the inexorable course of myocardial failure has rendered pharmacological and mechanical assistance futile. The development of cardiac surgery was once limited by the problems associated with cardiopulmonary bypass and the technical aspects of the surgical procedure. Other major advances in diagnostic techniques, anesthetic management, and intraoperative protection of the heart have improved the ultimate outlook for the patient undergoing cardiopulmonary bypass. Coincident with these advances has been improvement in the prosthetic or bioprosthetic valve devices and improved pharmacologic means of providing relative freedom from the complications of thromboembolism. Valve replacement has resulted in significant clinical and hemodynamic improvement in patients with severe valvular stenosis or incompetence.

Coronary artery bypass surgery has recently been applied to patients in the early hours of myocardial infarction to minimize necrosis and prevent failure. The single or combined reperfusion modalities represented by percutaneous transluminal coronary angioplasty or intracoronary infusion of thrombolytic agents are experimental approaches under intensive evaluation for this same purpose.

There has been renewed interest in the chronic phase of congestive heart failure--an interest that has included such elements as prognosis, circulatory adjustments that occur both in the myocardium and in the periphery, and the application of new therapies. Increasing survival is being reported from some centers

that are using a combination of pharmacologic and mechanical approaches. The entire concept of end-stage or advanced heart failure is undergoing reexamination, especially with reference to differences that may be related to varying etiologies.

A radical approach to the problem of refractory heart failure in selected patients is cardiac transplantation. Improvements have been made in the techniques of preservation of the donor heart and in the operative procedure, and there have been remarkable improvements in immune suppression. A number of centers in the United States are engaged in cardiac transplantation. Actuarial survival rates of 73 percent at 12 and 24 months have recently been reported. At one center, 90 percent of the patients who survived 1 year appear to be fully rehabilitated. One of the centers has performed combined heart and lung transplantation. During this period, better prediction of acute rejection and better techniques of detection and treatment of acute and chronic rejection have evolved. The standard immunosuppressive regimen of prednisone, azathioprine, and antithymocyte globulin carries the risk of infection and chronic steroid toxicity. The use of Cyclosporin A represents a major advance in treating the rejection process. Much progress has been made in overcoming the problems of early rejection, which abate considerably by the end of the first year. What remains to be resolved is the chronic rejection reaction (20 to 30 percent), which is manifested, quickly and without warning, by atherosclerosis in the donor coronary arteries. Future progress of cardiac transplantation appears to be dependent upon the development of improved and more selective immunosuppressive therapy and upon methods to prevent the development of accelerated atherosclerosis.

In April 1981, the Division of Heart and Vascular Diseases sponsored a Workshop on Advanced Congestive Failure that summarized the accomplishments and state of knowledge in the basic and applied science areas. The participants recommended that the NHLBI expand its existing program of basic multidisciplinary and corroborative research in structure, function, and biochemistry, with emphasis on the genetic and molecular studies of heart failure, the epidemiology of heart failure in the 1980's, and the development of techniques for early diagnosis of heart failure.

State of Knowledge in 1982

Since 1972, research on heart failure and shock has contributed significant therapeutic benefits and has developed the knowledge base for current and future research activity. Many of the therapeutic benefits derive from a new understanding, through human and animal studies, of basic mechanisms and the pathophysiology of congestive failure. These studies include

observations of alterations of contractile proteins; demonstration of altered diastolic properties of the heart in certain forms of heart disease, and of the contributing role of the pericardium; assessment of the peripheral effects of elevated systemic vascular resistance in congestive failure, including the importance of altered regional blood flow, autonomic tone and reflexes, and circulating vasoactive hormones; and clarification of the relationship between cardiac mass, volume, and load in defining the onset of congestive heart failure.

Greater sophistication in assessing the status of left ventricular performance, using both invasive and noninvasive techniques, has made serial assessment over long periods of time possible and also allows testing during exercise.

As diagnostic techniques have improved, there has been a greater recognition of the growing importance of cardiomyopathy as a cause of chronic congestive failure. Safe techniques for serial myocardial biopsy have been useful in the diagnosis of the cardiomyopathies and have been very helpful in detecting cardiac transplant rejection.

Intensive hemodynamic monitoring has improved the management of acute cardiac decompensation, including shock and pulmonary edema, and has permitted optimizing preload, afterload, and cardiac output. Some mechanical applications of basic physiologic discoveries during the past decade include intubation, positive end expiratory pressure (PEEP) ventilation, and hemofiltration.

Clinical management of heart failure has also been aided by the development of new agents and methods such as vasodilators, inotropic agents, the newer selective beta agonists, and more effective diuretic agents. Management of bradyarrhythmias and tachyarrhythmias using physiologic pacing or new antiarrhythmic drugs has also contributed to the management of difficult cases of congestive failure. Refinements of methods for assay of serum digitalis levels and application of this methodology to clarify digitalis-related toxic arrhythmias, the importance of renal function in digoxin clearance, and the digitalis-quinidine interaction have further refined the management of complex instances of heart failure. Newer studies showing discrepancies between plasma levels and myocardial accumulation of antiarrhythmic agents suggest a need for further evaluation of currently accepted dosage regimens.

Achievements that have improved the outcome of cardiac surgery include intraoperative protection of the myocardium, development of better xenograft and artificial cardiac valves, resection of ventricular aneurysm, and adoption of an aggressive surgical approach to ruptured papillary muscle and perforated interventricular septum. Some progress has been made in

determining optimal timing of replacement of the aortic valve in aortic regurgitation or stenosis, and of the mitral valve in mitral regurgitation. This is an area, however, where further refinements are needed. In the last 10 years, steady progress has been made in prolonging survival after cardiac transplantation, with improved management of rejections and infections.

Despite these advances, better understanding of the mechanisms of heart failure and its treatment is needed. Because available methods of intervention in cardiogenic shock have reduced mortality only slightly, high priority should be given to further fundamental and applied research in this disorder, which remains a formidable challenge to the physician.

Program Goals 1982 to 1987

- Improve the understanding of the basic mechanisms and the natural history of heart failure and shock.

- Improve techniques for the clinical detection, treatment, and prevention of heart failure and shock.

Research Activities 1982 to 1987

- Continuation of investigations into the basic pathogenetic mechanisms operative in heart failure and cardiogenic shock.

- Improvement of current clinical capabilities of recognition, quantitation, and management of shock complicating myocardial infarction.

- Prevention or mitigation of cardiogenic shock by continued testing of methods of protection of ischemic myocardium. This activity includes the recently inaugurated clinical trial of the efficacy of thrombolytic therapy in acute myocardial infarction.

- Institution of basic studies of cardiac hypertrophy and dilatation, the progression to heart failure, and several other underlying mechanisms of heart failure in animals and humans.

- Elucidation of the role played by the autonomic nervous system and neurohumoral mechanisms in maintaining circulatory function and in contributing to physiologic derangements of heart failure.

- Improvements in noninvasive technologies that permit reliable serial measurements of cardiac performance reflecting natural history, progression of disease, and response to therapy.

- Continued development and testing of inotropic agents, diuretics, vasodilators, and other safe pharmacologic interventions for heart failure.

- Definition of optimal timing of valve replacement and further improvement in prosthetic heart valve design and function.

- Continuation of multidisciplinary studies in the field of heart and heart-lung transplantation with efforts toward increased long-term survival and reduction in complications of transplantation, rejection, and infarction.

- Continuation of studies of mechanical circulatory support devices.

- Continuation of the program studying physiologic adaptations that occur in response to the use of circulatory assist devices in the management of intractable heart failure.

10. Congenital and Rheumatic Heart Disease

Contents

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Congenital and rheumatic heart diseases are serious illnesses that impair the quality of life from childhood through adolescence to adulthood, and are often the cause of premature death.

Congenital heart disease occurs when the heart or major blood vessels fail to develop normally during gestation. Examples include defects or "holes" in the partitions separating the cardiac chambers, malformed heart valves, persistence of fetal short-circuit vessels between major arteries, and combinations of these defects. The causes of these various malformations are largely unknown although several factors appear to be associated with their development. Among them are the mother's use of drugs such as thalidomide during pregnancy, maternal diabetes, genetic predisposition to heart malformations, rubella or other viral infections in the first 3 months of pregnancy, and certain genetic diseases, such as Down syndrome.

Rheumatic fever is an acute, generalized inflammatory process that follows a streptococcal infection of the upper respiratory tract and has one or more of the following: fever, swollen joints, rash, inflammation of heart muscle and heart valves, and involuntary muscle twitching. It is generally a disease of childhood. Rheumatic heart disease is the term applied to the scarring and deformity of heart valves that follow one or more attacks of acute rheumatic fever. Progression of this process leads to heart failure, usually during the prime of life. The scarred valves are susceptible to bacterial infection that leads to further destruction of the valves.

State of Knowledge in 1972

In 1972, the development of diagnostic and surgical techniques applicable to the newborn was increasing the success rate of the surgical correction or palliation of congenital heart disease in children. M-mode echocardiography was just beginning to gain prominence as a noninvasive means of determining heart defects in newborns. Cardiac catheterization and angiographic technology applied to infants and neonates, and cardiac catheterization laboratories designed specifically for the problems of the young, were just being developed. Open heart surgery, already in use for adults and older children, was being applied to the

correction of heart malformations in infants and newborns, and was proving successful for most of the more common defects. Surgical techniques for repair of more complicated defects were still largely inadequate, although a few centers were beginning to report success at complex repairs.

In order to improve the indications for surgical repair, there was a recognized need to establish for the various defects functional status categories of severity that incorporated hemodynamic and clinical criteria. Artificial heart valves, which usually consisted of a ball or disc in a cage, were used extensively in 1972, but there were problems associated with them, such as significant hemodynamic pressure gradients and cardiac decompensation, particularly with the smaller size prostheses. In addition, the artificial valves required anticoagulation and were associated with a significant incidence of thromboembolic complications. Homograft cardiac valves had been employed to overcome some of these limitations, but late failures of such biologic valves were increasingly reported.

In 1972, the etiology of rheumatic fever and rheumatic heart disease was known, and penicillin had been in use for over 20 years for treatment of its known precursors. A dramatic decrease in rheumatic fever occurred after the 1930's, but even in the 1960's, the incidence in several American cities was still 25 to 50 cases per 100,000 children between 5 and 14 years of age.

Program Goals Through 1982

The general goals developed by the Institute in 1972 for the congenital and rheumatic heart disease programs, and augmented in subsequent years, were to:

- Achieve a better understanding of the basic causes of congenital heart disease, the ultimate objective being the prevention of defects of the heart and vascular system in the developing fetus.

- Improve noninvasive diagnostic techniques and surgical repair of patients with congenital heart defects, with increased focus on the newborn and young infant.

- Facilitate the long-term followup of patients who have undergone surgical repair for specific defects.

- Determine the efficacy of pharmacologic agents for the management of consequences of congenital heart disease, such as congestive heart failure and arrhythmias.

- Emphasize studies of the immunological properties of the streptococcus associated with rheumatic fever and the specific immune responses of individuals at risk.

- Educate practicing physicians and the public in the diagnosis and treatment of throat infections, particularly those of streptococcal origin.

Accomplishments Through 1982

Congenital Heart Disease

Although notable advances in prevention of predisposing maternal illnesses have been made in the past 10 years, there has been no noticeable decrease in the total number of infants born with critical congenital heart disease. Due to improved case findings associated with the New England Regional Cardiac Program, the incidence per 1,000 live births between 1969 and 1979 increased marginally, from 2.07 to 2.29. With the 25 percent decrease in the birth rate during that 10-year period and the slight increase of case findings, the actual number of infants treated within the program has stayed approximately the same. Nevertheless, the development of an effective rubella vaccine has reduced the number of infants born with rubella-caused congenital heart disease. There also has been decreased incidence of congenital heart disease associated with Down syndrome. This decline can be attributed to two factors: older women are having a smaller proportion of all babies, and the technique of amniocentesis permits earlier diagnosis of some forms of congenital heart disease associated with chromosomal abnormalities. It has been discovered that alcohol, anticonvulsants such as trimethadione, and certain drugs such as lithium can cause congenital heart disease, and that some forms of congenital heart disease have a pure (single gene) genetic origin.

Improvements in the use of echocardiography have proven beneficial in noninvasive diagnosis in older children and have shown special merit in the early diagnosis and management of congenital lesions in newborn and young infants. With devices such as the real-time multiple-crystal ultrasound scanner, sometimes combined with Doppler arteriography, the spatial locations of the chambers of the heart and the major heart valves can be visualized. Moreover, it is often possible to determine how the heart valves are functioning, which chambers of an infant's heart are enlarged, and how the enlargement responds to medical treatment. Congenital cardiac malformations can now be identified through ultrasound examination of the fetus after the 20th week of gestation. Two-dimensional echocardiography has been particularly

helpful in delineating with great accuracy, comparable to that of good cineangiograms, the morphologic structure of even the more complex malformations. M-mode echocardiography continues to remain a sensitive tool for measuring the various parameters of myocardial function. Refinements in fetal electrocardiography and monitoring have provided new tools for obstetric care.

The Joint Study on the Natural History of Congenital Heart Defects was completed in 1973. This study provided clinical criteria for evaluating severity of disease and also assessed the clinical course of patients treated medically and surgically for several types of congenital heart defects. Guidelines keyed to the functional status of the patient's condition clarified indications for surgery.

In recent years, new and refined surgical techniques that permit surgical intervention in the very young infant with complicated heart defects have led to steadily decreasing mortality. The application of the deep hypothermia technique, applied almost exclusively to infants within the first postnatal year, has reduced the overall hospital mortality rate to slightly more than 10 percent in a large group of critically ill infants. First-stage primary repair within the first postnatal year has become the preferred management of even complex congenital cardiac malformations and has replaced the practice of initial palliative surgery.

Research interest in prosthetic heart valves has included the development of a tri-leaflet aortic valve prosthesis and leaflet valves for ventricular assist devices, and studies of the fluid dynamics and mechanics of heart valve prostheses. After a number of years of use, the leaflets of implanted xenograft valves often calcify. This calcification has been recognized as an important mechanism of failure. Some of the biochemical components of this process have now been identified. Improvements in vascular grafts and prostheses have led to the development of valved conduits for the repair of complex congenital heart lesions.

Basic physiologic research on developmental abnormalities of the ductus arteriosus has provided new concepts in basic physiology and has led to a major advance in the management of critically ill infants. In the cardiac anomaly known as patent ductus arteriosus, the fetal vessel connecting the pulmonary artery to the aorta fails to close once the infant becomes free-living. In earlier NIH studies, a class of drugs developed for adult arthritic conditions was found to have the property of inhibiting endogenous production of prostaglandins--naturally occurring substances that mediate inflammation and dilate blood vessels. Inhibiting the vessel-dilating property of prostaglandins was the premise for the first stage of investigations of the use of indomethacin (one of the prostaglandin inhibitors) in

small premature infants with patent ductus arteriosus and the respiratory distress syndrome. Success at this stage (that is, closure of the patent ductus) led to a more extensive trial, which is discussed below. An equally exciting, converse aspect of the medical manipulation of patent ductus arteriosus is the use of prostaglandins to maintain ductal patency in neonates with atresia of one or the other semilunar valves, so that adequate cardiac output can be maintained via the ductus arteriosus. This expedient allows the infant to reach a relatively good hemodynamic state that permits a surgical procedure.

The initial success with the ability of indomethacin to close a patent ductus in premature infants led to a clinical trial comparing surgical closure to medical therapy for patent ductus arteriosus. The Management of Patent Ductus in Premature Infants trial enrolled 400 infants with patent ductus and randomized them to early indomethacin, delayed indomethacin, or usual medical therapy backed up by surgery. Mortality and morbidity in the three groups were very similar. In only 30 percent of the two groups that received indomethacin was surgery necessary to close the ductus compared to 70 percent of the cases that did not receive indomethacin. These results suggest that the use of indomethacin makes surgery unnecessary in 40 percent of the infants with this condition.

Prerequisite for optimal management of many forms of heart disease in infants, children, and adults is a thorough understanding of the way the heart develops during embryonic and fetal stages. Research on the causes and effects of cardiovascular defects in the fetus has led to continued efforts to develop animal models with a high incidence of congenital heart lesions. Strains of dogs and mice with a variety of defects, such as pulmonic, aortic and subaortic stenosis, patent ductus arteriosus, relational abnormalities of the great arteries, and septal defects, are becoming increasingly available for study. The genetic and mechanistic contributions to these lesions are being analyzed in physiologic, embryologic, histopathologic, biochemical, and statistical studies. The goal of such studies is the establishment of better criteria for the definition and diagnosis of these defects and the development of an information base that will facilitate their prevention.

The majority of developing embryos have the genetic potential for normal cardiac development that can be overridden by environmental influences. Alcohol, anticonvulsants, drugs used to treat mental illness, and infections, however, can result in abnormalities of cardiovascular development. There is evidence that suggests that some embryos have unique backgrounds that make them more susceptible to subtle or multiple environmental factors. The full spectrum of genetic and environmental factors resulting in

congenital cardiac defects needs further study. This field offers great potential for preventive efforts.

Rheumatic Heart Disease

The etiology of rheumatic fever and rheumatic heart disease is known, and effective preventive regimens have been available for several decades. The correct diagnosis and prompt treatment of streptococcal throat infections have been recognized as vital for reducing the incidence of rheumatic fever and preventing rheumatic heart disease. Nonetheless, these diseases have not been eradicated in the United States. It was reported in 1972 that rheumatic heart disease affected approximately 100,000 children and 1.7 million adults in America and was the cause of 15,000 deaths annually. By 1979, this number had decreased to 7,500. Although valvular damage may have occurred during an attack of rheumatic fever, its consequences may go undetected until years later.

Studies of the cell capsule, cell wall, and cytoplasmic membrane of the streptococcus have provided useful data. For example, the antigen that is responsible for the immunological responses associated with rheumatic fever appears to be located in the streptococcal cytoplasmic membrane. In other studies, because of similarities in physicochemical properties and amino acid composition, group A streptococcal M proteins were seen to resemble mammalian alpha fibrous proteins, particularly tropomyosin. This is the first direct evidence, on the molecular level, of a structural similarity between a streptococcal protein and a mammalian muscle component. Further work here may provide insights into the recognized cross-reactions between streptococcal membrane or cell wall proteins and smooth tissues of cardiac or skeletal origin.

State of Knowledge in 1982

In spite of the significant advances that have been made in prevention over the last decade, an estimated 25,000 infants are born each year with heart and vascular defects. Although accurate data are lacking, the true incidence of congenital heart disease is probably considerably higher if one includes lesions such as bicuspid aortic valves, which usually do not produce symptoms and are not diagnosed in childhood but may be the basis for infective endocarditis and aortic stenosis in adulthood. In addition, arrhythmias, cardiomyopathies, endocardial fibroelastosis, and prolapse of the mitral valve may occur on a congenital basis. With this extended definition of congenital heart disease, the estimated incidence of such defects may be as high as 40 to 50 of

every 1,000 live births. The incidence of congenital heart disease among abortuses and stillbirths may be even higher.

Expansion of the understanding of the developmental biology of the cardiovascular system during the fetal period and in early infancy is needed. It is believed that most developmental anomalies of the cardiovascular system arise from an interaction between genetic and environmental factors. Some anomalies are due primarily to genetic factors. For example, trisomy 21 involves gross chromosomal aberrations that result in multisystem involvement including the cardiovascular system. In other anomalies, the cause is primarily environmental, fetal rubella being the best known example. Most congenital cardiovascular anomalies are multifactorial and appear to be the result of environmental factors, such as drugs, radiation, or viruses, acting on a genetically predisposed fetus at a specific period in fetal development. Some drugs have been implicated (for example, thalidomide), and others have been suspected (for example, lithium chloride and progesterones), and a seasonal and geographic clustering of lesions has been described. The basic mechanisms of abnormal organogenesis require delineation, and the identification of other environmental factors should continue.

Advances have occurred in surgical techniques for correction of congenital heart disease, but knowledge concerning the early and particularly the late results of surgical intervention requires further definition. These gaps in knowledge are handicaps to making decisions about the most appropriate time and technique for surgical intervention. Although the natural history of subjects with large atrial or ventricular septal defects and of severe pulmonic stenosis is understood, little is known about the course of the more frequent but less severe lesions. A reliable method for identifying those infants with a large ventricular septal defect who will need early surgical closure as distinct from those who will improve spontaneously needs to be identified.

The bicuspid aortic valve is the most common congenital cardiovascular anomaly, and is a very important one. Some reports indicate that this lesion may occur in as many as 2 percent of all live births and that perhaps one-half of these may result in aortic stenosis or incompetence later in life. Data concerning the incidence and natural history of this lesion are limited.

Congenital cardiovascular lesions do not remain static; changes occur with the passage of time. Many children now require multiple cardiac catheterizations in order to establish the diagnosis and to note sequential changes that determine the appropriate timing of surgical intervention. Accordingly, there is a need to devise and improve noninvasive tests that will be inexpensive, painless, and risk-free. The most promising recent

advance in noninvasive instrumentation has been in echocardiography, particularly the development of two-dimensional real-time systems. The latter technique provides direct information about wall thickness, but resolution is not optimal for the right ventricular wall in infants, and improved methods to define the diameters of the cardiac chambers and to measure stroke volumes and ejection fractions are desirable. Other noninvasive technologies, such as nuclear magnetic resonance, are in the developing stages.

Although there has been a dramatic decline in the incidence of acute rheumatic fever in the United States, the disease has not disappeared. New cases of rheumatic fever continue to occur, particularly in crowded urban settings. The importance of rheumatic fever lies in its tendency to produce valvular disease later in life. A number of questions still must be resolved before substantial additional progress can be made toward eradication of the disease. How streptococcal infections lead to rheumatic fever remains uncertain. The most popular hypothesis is that the tissue damage is due to an immune response that consists of antibodies to streptococcal antigens that cross-react with myocardial antigens. Current methods for preventing streptococcal infections and rheumatic fever do not approach the level of effectiveness of vaccines available for many communicable diseases, and it is unlikely that rheumatic fever can be completely eradicated by the use of antimicrobial agents. Until a major advance in the understanding of the pathogenesis of rheumatic fever occurs, future progress in its eradication lies primarily in the development of a safe and broadly protective vaccine. Purification of the group A streptococcal M protein is being accomplished, and limited clinical testing is under way. However, the short duration of demonstrable immunity, the multiplicity of antigenically distinct streptococcal types, and the possibility that new M types of streptococci might evolve are challenges to be confronted.

The medical and surgical management of valvular heart disease has progressed dramatically since the development of cardiopulmonary bypass devices in the mid-1950's. The indications and techniques for valve replacement are still influenced by considerations inherent in valve prostheses. The risks of infection, hemolysis, thrombosis, and stenosis apply in varying degrees to all replacement devices. The search for improved valve designs and materials will continue. The timing of valve replacement in patients with volume overload lesions such as mitral and aortic insufficiency is a matter of concern because delay can sometimes result in intractable myocardial failure and poor survival, whereas early replacement exposes the patient for a longer period to the side effects of the valvular prosthesis. The etiology of nonrheumatic valvular disease, congenital or otherwise, requires further investigation.

Program Goals 1982 to 1987

- Improve the understanding of the genetic and environmental factors involved in the pathogenesis of various congenital cardiac malformations.
- Develop and refine methods for accurate diagnosis and curative or palliative therapy for patients with congenital heart disease.
- Explore the fundamental etiology and pathophysiology of valvular heart disease.
- Develop and refine medical and surgical interventions for valvular heart disease.

Research Activities 1982 to 1987

- Further monitoring of environmental factors associated with congenital cardiac diseases.
- Further investigation of the mechanisms involved in formation of cardiac septa and valves.
- Refinement of various minimally invasive means of imaging cardiovascular anatomy and function in infants and children.
- Further investigation of pharmacologic means of closure of the ductus arteriosus.
- Improvements of methods of surgical correction of complex cardiac malformations.
- Examination of the long-term incidence and significance of arrhythmias in patients surviving corrective cardiac surgery.
- Systematic approach to the study of the optimal timing of surgical correction of selected congenital cardiovascular malformations.
- Further development of strategies to reduce the occurrence and recurrence of rheumatic fever and to reduce the incidence of endocarditis.
- Development and validation of treatment strategies that will provide reliable guidance for optimal timing of valve replacement.

11. Cardiomyopathies and Infections of the Heart

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The term cardiomyopathy was introduced into clinical medicine in 1954 by Brigden. He defined cardiomyopathies as a form of generally fatal, primary cardiac diseases in which there was enlargement of the heart accompanied by severe congestive heart failure. The diagnosis of these diseases required that the patient be free of known causes of cardiac enlargement and failure such as ischemic heart disease, valvular abnormalities, and hypertension. The clinicopathologic work that has taken place in the past 25 years has made it clear that this diagnosis includes a variety of serious, often fatal myocardial diseases.

It has been recently proposed by the Task Force on Cardiomyopathies of the World Health Organization and by the Scientific Council on Cardiomyopathies of the International Society and Federation of Cardiology that the nomenclature for these disease entities be made more specific and less ambiguous. According to the new classification, the term cardiomyopathy should be used to describe the group previously known as "primary cardiomyopathy" or "heart muscle disease of unknown cause" and that "secondary cardiomyopathy" should be replaced by the term specific heart muscle disease. For example, a disease entity in which a viral agent is the proposed etiologic factor should be referred to as "viral heart muscle disease" and not "viral cardiomyopathy."

Infections of the heart of current clinical concern are most often due to bacteria. Involvement of the myocardium by viruses (myocarditis) is being increasingly recognized. In the past, attention focused upon bacterial infection of the endocardium and heart valves (bacterial endocarditis) because of its frequency and its potentially preventable morbidity and mortality. This infection, with its accompanying destruction of valves, is a cause of serious morbidity and mortality. The morbidity expresses itself most often in terms of heart failure and embolic events, chiefly involving the brain.

State of Knowledge in 1972

In 1972, cardiomyopathies were beginning to be recognized with increasing frequency. It was not clear whether the increase was due to the availability of better diagnostic methods or whether some forms were appearing more often. In addition, there

was little firm information on the actual incidence, prevalence, or geographic distribution of these diseases.

Bacterial endocarditis, almost uniformly fatal before the advent of antibiotics, was being seen less frequently. A substantial majority of those afflicted were surviving, though often with significant heart and peripheral organ damage.

New forms of infection, often due to unusual organisms, were becoming prevalent in patients who did not have underlying heart disease. Among those patients were cancer and transplantation patients receiving certain types of chemotherapeutic agents known to suppress immunological mechanisms.

The diagnosis of these conditions usually required cardiac catheterization and angiocardiography. Echocardiography was just being applied.

Program Goals Through 1982

In 1972, the Institute saw the need for further investigation on the nature of cardiomyopathies and infections of the heart and set the following broad goal:

- Improve the diagnosis of cardiomyopathies and increase understanding of the etiology of the various cardiomyopathies and infections of the heart.

In 1977, the following additional goals were set:

- Clarify further the cause of cardiomyopathies.
- Develop more effective methods for diagnosis and treatment.

To achieve these goals, research activities were planned to:

- Develop techniques for the recognition and management and prognostic assessment of cardiomyopathies.
- Elucidate the causative factors and mechanisms in cardiomyopathies.
- Develop improved methods for the recognition, treatment, and future assessment of myocarditis of various forms.
- Continue research on the basic phenomena of muscle contraction and relaxation and also on the genesis of muscle hypertrophy.

Accomplishments Through 1982

Cardiomyopathies

During the past decade, considerable advances have been made in understanding the basic structure and function of cardiac and skeletal muscle and the processes of biosynthesis of the cellular structures involved in contractility and regulation, in noninvasive procedures for monitoring cellular metabolism, and in other diagnostic techniques. A better understanding of developmental processes at the cellular and molecular level has clarified some problems relating to developmental anomalies of the heart and also some of the pathological processes that depend on the unfolding of the intrinsic genetic program as a function of age. Toward the end of the decade, a significant achievement was the development and application of modern molecular genetics to the problem of cardiomyopathies. The newer fields of molecular biology and immunochemistry are being applied to questions formerly addressed only by more classical approaches such as biochemistry and biophysics.

The decade was marked by many advances in fundamental research and technological developments. Nuclear magnetic resonance technology, for example, was refined for application in monitoring metabolic processes of the heart and, as an adjunct to other methodologies such as x-ray, radioisotope, and ultrasound techniques, in the delineation of internal organs including the heart.

Several modalities of new diagnostic techniques applicable to the heart in situ have been developed. These include echocardiography, in which ultrasound is used to visualize details of cardiac structure, and utilization of radioactive elements, including positron emission tomography systems. The development of real-time B-mode ultrasonic scanning and duplex (B-mode and Doppler) ultrasonic imagers has led to refinements in ability to diagnose cardiomyopathies. Improved resolution of echocardiographs has led to increased ability to detect vegetations on heart valves associated with endocarditis.

Improvements in noninvasive diagnostic instrumentation, especially echocardiography, were applied in the Framingham Study, which for the first time allowed documentation of the prevalence and characteristics of hypertrophic and congestive cardiomyopathies in a free-living population. These two broad categories of cardiomyopathy were each found in 1 to 2 percent of the Framingham Cohort and in 0.1 to 0.3 percent of their offspring. Prior to echocardiographic study, cardiomyopathy had not been detected or suspected in most of these subjects. In addition, a familial predisposition to some forms of cardiomyopathy has been identified

in numerous families in the general population. These findings are significant since recent data suggest that there are sizeable subgroups of subjects with cardiomyopathy at high risk of sudden death.

Developments in the field of membrane biology, the transport of ions across membranes, and the relation between ion transport and electrical phenomena have led to important results, which have found clinical applicability in the control of cardiac function. The recognition of the existence of distinct molecular entities performing the same function (for example, isoenzymes of myosin) laid the foundation for recognizing the specific forms of proteins that exist in different stages of development, in different portions of the heart, and in forms that possibly may have direct relation to various disease processes.

Animal models have played an important role in studying conditions that may be analogous to those existing in human cardiomyopathies. Among these are strains of cardiomyopathic hamsters, alcohol-induced cardiomyopathy in mongrel dogs and in isolated perfused rat hearts, and viral infections, chiefly in mice infected with coxsackie B or herpes simplex viruses and in swine infected with encephalomyocarditis viruses.

Progress has been made in learning how alcohol interferes with normal myocardial structure, function, and biochemistry. Research findings have shown that alcohol (and acetaldehyde) may inhibit the (Na^+,K^+)-activated ATPase of the plasma membrane and the binding and uptake of Ca^{2+} by myocardial microsomes. In addition, alcohol and its metabolite(s) may have deleterious effects on myocardial contractile proteins. Such alterations in myocardial structure and function at the cellular level may play a role in reducing contractile performance and may be of importance in the pathogenesis of alcoholic heart muscle disease.

The drug adriamycin, used in cancer chemotherapy, has been frequently found to produce heart failure due to heart muscle disease in humans when the total dose administered exceeds an average of 450 mg per m^2. Intensive biochemical, histological, and clinical studies of the mechanisms of damage have been conducted. Clinical techniques with strong potential for use in the clinical diagnosis and management of this disease have been developed, and include endomyocardial biopsy and noninvasive radionuclide methods.

The diabetic patient appears to be at substantial risk for developing cardiomyopathy. Recent basic studies have demonstrated alterations in the mechanical behavior of the heart and subcellular alterations in the calcium binding and uptake by the cardiac sarcoplasmic reticulum. In addition, protein synthesis in the diabetic heart is reduced by as much as 30 percent. These

biochemical changes are associated with a reduction in the functional capacity of the myocardium.

The identification of additional causes of cardiomyopathies (for example, cobalt ingestion, selenium-deficient diets, carnitine deficiency, and fetal alcohol syndrome) plus improved diagnostic procedures (such as echocardiography and myocardial biopsy) have led to better classification of cardiomyopathies and, in some instances, specific treatments.

Better understanding of how radiation treatment can damage myocardial tissue has led to improved radiation regimens and prevention of some radiation-induced heart muscle diseases.

Behavioral researchers have assessed the effects of selected psychological variables (stress predictability, availability of coping responses, and conflict) on myocardial pathology. Rat models of behaviorally induced focal myocardial necrosis are being developed and studied.

Since relatively little was known a decade ago about cardiomyopathies and specific heart muscle diseases, and since what information that was available was widely scattered in the literature in the form of case reports and experimental studies, a workshop on cardiomyopathies was conducted by the National Heart, Lung, and Blood Institute on July 11-12, 1978. The experts gathered for this workshop were selected to describe what is known about three specific heart muscle diseases: alcoholic heart muscle disease, viral heart muscle diseases, and adriamycin-induced heart muscle disease. Both clinical and experimental work was presented.

At this workshop, it was disclosed that much less was known about specific heart muscle diseases than was believed to be the case at the time the recommendation was made to hold the workshop. It was concluded that there is an important need to stimulate additional basic research on these conditions. Previous laboratory investigations of the pathophysiology of cardiomyopathies had resulted in an improved understanding of contractile mechanisms, cardiac hypertrophy, organelle turnover, atrophy, repair, and toxic cell injury. While these investigations led to an improved understanding of cardiomyopathies and specific heart muscle diseases, these topics needed to be considered in terms of the diseases themselves. This meant that good animal models of some representative specific heart muscle diseases were needed in order to study the pathogenesis of these disorders and to apply this knowledge to humans. The Institute issued a request for applications in 1980 to accomplish this goal. In 1981, seven grants were awarded to conduct research involving the use of animal models of alcoholic, viral, and adriamycin-induced heart muscle

diseases with the goal of learning more concerning the pathogenesis of these conditions. Recent progress in this program includes the establishment of a rat model of cardiac dilatation and failure induced by chronic alcohol ingestion, lesions in rabbits typical of those seen in chronic adriamycin cardiotoxicity in man, and improved understanding of coxsackievirus-induced myocarditis in inbred mice pointing to an autoimmune mechanism, a genetic susceptibility, or both.

Infections (Endocarditis)

During the past decade, improvements have been made in the ability to identify causative agents of bacterial endocarditis. Refinements in B-mode ultrasound have led to increased accuracy in detection of vegetations of heart valves in patients with endocarditis. This advance permits identification of patients at high risk for early mortality. These advances, coupled with a better selection of antimicrobial agents, have reduced the reinfection rate and have allowed successful treatment of some types of infective endocarditis that were previously incurable. Progress in other areas of instrumentation has facilitated earlier physiologic measurements of rapidly deteriorating pump function. This accomplishment permits clinicians to identify those patients in whom early surgical intervention to replace a severely damaged heart valve reverses the course of rapidly progressive, fatal heart failure.

Improvements in preoperative diagnosis, surgical techniques, and myocardial preservation during cardioplegia have decreased the risk of surgery of valve replacement to less than 4 percent.

Valve designs in 1972 included caged ball, caged disk, and tilting disk. Various types of hinged and leaflet valves had been developed but abandoned. Results with mechanical valves, however, were generally more encouraging than results with various types of tissue grafts, which tended to calcify soon after implantation. During the 1970's, emphasis in valve development was on improvements in design and on materials to improve hemodynamics and reduce thromboembolism and wear of valve components. Prior to this time, the concept of covering valve components with fabric to encourage growth of a nonthrombogenic cell layer had been tested. The development of a sewing ring led to the observation that a fabric surface develops cellular ingrowth and less thrombogenic neointimal surface. As a logical extension of this observation, valve struts were covered with fabric to encourage cell growth and reduce incidence of thromboembolism.

In an attempt to decrease thromboembolism and wear, a number of materials have been used in valve designs, including metal alloys, polymers, and carbon coating. These materials have been

used to construct or coat struts or cages as well as the occluders. Wear of valve components has been markedly reduced over the decade, primarily due to selection and development of materials.

Development of tissue preservation techniques has led to the use of heterograft tissue valves. These valves were introduced in the early 1970's, and more than 60,000 have been implanted. Tissue valves have proven acceptable hemodynamically, can be safely used in many patients, and preclude the need for anti-coagulants. These valves have a greater longevity than earlier tissue valves, but they are still subject to calcification, albeit at a relatively slower rate than the early homografts and heterografts. Current research focuses on identification of the mechanism of calcification and development of preservation methods that might reduce the tendency to calcify.

Muscle Mechanics and Metabolism

During the past decade, important developments have occurred in understanding the basic phenomena of muscle contraction and relaxation in skeletal, cardiac, and smooth muscle. Detailed studies have characterized the mechanical behavior of the muscle during contraction and relaxation and have related the mechanical events to ultrastructural and biochemical aspects. It should be emphasized that, apart from differences noted below, which are specific for smooth muscle, the basic mechanism of muscle contraction is identical and generally thought of in terms of the sliding of two sets of protein filaments, thick and thin (containing chiefly myosin and actin, respectively), relative to each other. At the risk of oversimplifying, one can discern three key questions in the area of muscle contraction: the mechanism by which molecular interaction of the filaments is expressed as a mechanical event; the mechanism of energy transduction, namely, how the free energy of adenosine triphosphate (ATP) hydrolysis is converted into mechanical work; and the mechanism by which periods of rest and activity alternate under the control of Ca^{2+}.

Great progress has been made in the technology available for the study of contraction of single fibers under conditions in which rapid changes in length or load can be imposed. Particularly useful for these studies are fibers devoid of their outer membrane (skinned fibers); this technique permits adding ATP as an energy source and Ca^{2+} as a trigger of contraction. A more recent approach uses an inactive form of ATP (caged ATP) that can be activated by a light pulse, which makes extremely high temporal resolution possible.

In connecting mechanical studies with molecular events, x-ray diffraction studies of muscle have played an important role.

Synchrotron radiation has made it possible to expose fibers to x-rays for very short periods of time, which preserves the integrity of the fiber and provides clues, on a millisecond time scale, to the molecular events underlying tension development and contraction. Efforts have been initiated to establish a precise correlation between the molecular state, which is inferable from x-ray and mechanized studies, and conclusions resulting from analysis of the ATPase system, which provides the biochemical basis of contraction.

Membrane Systems

Membrane systems containing lipids and proteins play crucial roles in the control of muscle contraction. Such membranes are involved in the electrical events associated with muscle contraction, and they contain various channels for ion transport across the membrane. The plasma membrane surrounding the muscle cell contains the (Na^+,K^+)-activated ATPase that appears to be the binding site of the digitalis glycosides. Another membrane system, located intracellularly, is involved in sequestering calcium ions at rest and releasing them on activation. Studies of the interaction among constituents of the membrane and various ions have utilized sophisticated techniques including rapid kinetic methodology, which permits the resolution of events over a time scale of milliseconds. In the study of the interaction between the lipids and proteins in membranes, considerable progress has been made in the area of naturally occurring membranes, in vesicles reconstituted from natural membranes, and in model membranes reconstituted from various lipid components and purified enzymes.

Changes in membrane structure that accompany the excitation process can be monitored by probes attached to either the lipid or the protein moiety. These probes can possess suitable optical (fluorescent) properties or can contain paramagnetic centers, the latter making it possible to conduct electron spin resonance studies. Nuclear magnetic resonance spectroscopy has also been an important tool for the study of membrane structure and function. The structure of the membranes has been investigated at high spatial resolution by means of x-ray diffraction, and important conclusions have been obtained about the distribution of proteins in the architecture of the membrane.

During the past decade, the role of phosphorylation has been established as a key control step in various biological systems. The role of phosphorylation as a modulator of membrane function, which in turn controls intracellular calcium, has been shown in cardiac muscle. Phosphorylation processes involve enzymes that contain calmodulin--a subunit that appears to have a wide distribution in various tissues. This protein is closely related to the

calcium binding protein--troponin C--attached to the thin filament of muscle. Both calmodulin and troponin belong to a large family of calcium-binding proteins that is characterized by extensive homologies of evolutionary origin. The protein that regulates calcium uptake in sarcoplasmic reticulum has been named "phospholamban." Its phosphorylation is regulated in various ways, one of which depends on cyclic adenosine 3',5'-monophosphate (cyclic AMP), which is a "messenger" involved in many biological processes.

Molecular Basis of Contraction and Its Regulation

During the past decade, great progress was made in the elucidation of the structure of the proteins that constitute the contractile and regulatory machinery of muscle. The contractile process is well established as being due to the interaction of myosin and actin. These two proteins are located in the thick and thin filaments, respectively. The thick filaments contain some additional proteins such as the C protein and M protein, the precise roles of which remain to be elucidated. In striated muscle, which includes cardiac muscle, the actin filaments contain tropomyosin and a three-subunit protein complex, troponin. The stoichiometry of actin, tropomyosin, and troponin is 7:1:1. For actin, the troponin subunits, and tropomyosin, the precise sequence of the amino acids constituting the polypeptide chains has been established. Not only troponin but also tropomyosin and myosin are multisubunit proteins, and the subunits constituting these proteins differ from one type of muscle to another.

Myosin, which is the most complex of these proteins, consists of two heavy chains and four light chains falling into two classes. The sequence of the light chains is known. Although much work needs to be done to describe the full sequence of myosin, progress has been made in obtaining various fragments of myosin that contain functionally important groups, and partial sequences are rapidly emerging. Considerable progress is to be expected from the application of new techniques of DNA cloning and DNA sequencing, which will permit the full determination of the corresponding genes from which the amino acid sequence can be derived. Parallel progress has occurred in the study of the synthesis of muscle proteins. Various proteins can be made in cell-free systems with a view to elucidating the complex process of gene transcription and translation.

Isozymes and Isoproteins

Much progress has been made possible by the widespread use of gel electrophoretic techniques. Gel electrophoresis under denaturing conditions in the presence of sodium dodecylsulfate has

made it possible to detect, among homologous proteins in different types of muscles, differences based on slight differences in molecular weight. This knowledge has led to the establishment of the existence of various isozymic or isoprotein forms of contractile proteins. Thus, myosin in skeletal (fast and slow), cardiac, and smooth muscle has been characterized in terms of the light chains contained in it, and one of the light chains so far identified is recognized as being capable of undergoing phosphorylation. The phosphorylatible light chain plays a regulatory role in smooth muscle, but the functional importance of phosphorylation in striated muscle, including cardiac muscle, has yet to be established.

A recently developed technique of electrophoresis, which makes it possible to separate proteins under nondissociating conditions (in the presence of pyrophosphate), has led to the recognition of a variety of cardiac isozymes, some of which may play a role in the transformation of cardiac muscle in connection with pathological processes, during physiological adaptation, and in response to hormones such as thyroxin.

Antibodies

Antibodies specific for certain types of proteins (for example, myosins occurring in fast or slow skeletal muscle and in cardiac muscle, or myosins occurring during various stages of development) have played an important role in research and will continue to do so. This is particularly true for monoclonal antibodies directed against specific regions within a given molecule. These antibodies have been used to detect changes in the complement of contractile or regulatory proteins in muscles that undergo changes as a result of imposed stimulation and in cardiac muscle undergoing hypertrophy.

Calcium Regulation

The final pathway of the calcium-coupled regulation in cardiac and skeletal muscle appears to be identical in that the binding of calcium released from the sarcoplasmic reticulum to the calcium binding subunit of troponin induces a change in the thin filament, presumably involving a change in the position of tropomyosin that allows the interaction of actin and myosin. The details of this process on the ultrastructural level are now being worked out with the use of x-ray diffraction techniques and optical diffraction of electron micrographs. The regulation process in smooth muscle, although involving calcium, appears to follow a different pathway. Calcium, as already indicated, is involved in the calmodulin-dependent activation of a phosphorylating enzyme,

which in turn transfers the phosphate of ATP to one of the myosin subunits.

Thus, in smooth and cardiac muscle, activation of the contractile apparatus occurs upon phosphorylation, and calcium participates indirectly in the process. An important regulatory component in smooth muscle is the dephosphorylating enzyme of myosin, which returns smooth muscle to rest. Cyclic AMP participation is not directly involved in activation, but phosphorylation of the phosphorylating enzyme in a cyclic AMP-dependent process provides an important point of attack for various neuropharmacological agents that may regulate the contraction and relaxation of smooth muscle.

Submolecular and Supramolecular Motion of Muscle Proteins

It is a generally accepted view that the sliding of the two kinds of filaments in muscle is actuated by a movement of that portion of myosin that attaches to actin, the so-called crossbridge. To understand the behavior of these crossbridges in vivo, considerable effort has been made on the molecular level to study the motion of myosin molecules in relation to actin and to study the flexibility within the myosin molecule. These studies involve probes--that is, molecules attached to the proteins at specific sites. The probes either are suitable for optical spectroscopy, including fluorescence, or have magnetic properties that make them suitable for electron spin resonance and nuclear magnetic resonance studies. In connection with fluorescence studies, a powerful technique, which is applicable to muscle proteins, has emerged that involves energy transfer between groups that is detectable by changes in fluorescence. This technique permits the determination of distances between various groups as well as changes in these distances that can be correlated with changes in the physiological state of muscle. Important developments are to be expected from the use of these optical and magnetic techniques when the probes, attached to the proteins in muscle fibers, permit the observations of changes under conditions in which mechanical measurements can also be made. Such studies have recently been initiated in various laboratories.

Relation of Ultrastructure to Metabolic Function

The relation between anoxia and glucose transport is being described in studies of perfused hearts, and in recent applications, nuclear magnetic resonance studies have provided a noninvasive tool for distinguishing in the heart various phosphorylated compounds, the levels of which can be monitored in normal and pathologic states. These phosphorylated compounds reflect the energy stores available for contraction. Mitochondria

contain the enzymes necessary for the synthesis of ATP, and various ultrastructural studies have provided correlative information to the biochemical investigations. In electron microprobe studies based on the analysis of the energy spectrum of x-rays induced by impinging electrons, it has been possible to localize ultrastructurally various elemental components such as phosphorus, potassium, Ca, and Cl_2 with a precision previously impossible.

State of Knowledge in 1982

Since 1972, advances have been made in achieving the Institute's goal of a better understanding of the underlying causes of cardiomyopathies and infections of the heart. Although the causes of most cardiomyopathies still remain obscure, a number of factors have been identified as causative agents, and their specific roles have been clarified. Identification of etiologic agents has made it possible to prevent certain kinds of cardiomyopathies; most, however, remain of unknown etiology and are not yet preventable. Alcohol has been identified as a possible etiologic agent and its effect on heart muscle function and structure is better understood, the role of certain viral diseases in some forms of myocarditis has been made clearer, a hereditary predisposition to some cardiomypathies has been demonstrated through clinical and animal studies, and heart muscle function of the diabetic patient is receiving more attention. Although there has been an increase in knowledge regarding some types of cardiomyopathies, the basic underlying mechanism of cellular damage remains unknown.

Improvements in noninvasive diagnostic instrumentation have led to increased frequency of recognition of certain cardiomyopathies. In 1982, real-time ultrasonic scanning and images are being increasingly employed to detect abnormal heart wall motion associated with all types of cardiomyopathy. Refinements in B-mode ultrasound have led to increased accuracy and detection of vegetations on the heart valves of patients with endocarditis.

Even in the cardiomyopathies for which an etiology can be identified, therapy to reverse the damage, once it has occurred, has a low order of efficacy. Cardiac transplantation, though still an investigative procedure, has extended the lives of selected patients with cardiomyopathies and other cardiac disorders. Efforts to develop a chronically implanted ventricular assist device and cardiac replacement devices are continuing, and they may be of benefit to these patients in the future.

The ability to diagnose, prevent, and treat myocarditis, endocarditis, and other infections and inflammatory processes of

the heart is a significant current need. However, many types of bacterial infections are now susceptible to treatment as a result of improved antibiotics and, in some instances, of surgical intervention. Yet, there is a population at risk for infection with unusual bacteria that are currently resistant to treatment. In addition, transplantation patients, due to their impaired immunological defenses, are at risk for systemic infections with these bacteria.

Program Goal 1982 to 1987

- Develop and refine methods for diagnosis, treatment, and prevention of cardiomyopathies and infections of the heart.

Research Activities 1982 to 1987

- Continuation of fundamental studies of the etiology and pathogenesis of cardiomyopathies and heart muscle diseases.
- Continuation of investigation of the natural history of cardiomyopathies and means of prevention.
- Development of new and improved approaches to the medical and surgical interventions for cardiomyopathies.
- Improvement of noninvasive procedures for evaluating myocardial function and metabolism, and their application to the problems of cardiomyopathies.
- Further development and evaluation of improved techniques for diagnosis, including endomyocardial biopsy.
- Continued support of research relevant to various aspects of cardiac transplantation.
- Assessment of the effectiveness and reliability of implantable circulatory assist devices, as these become available, for the treatment of complications of cardiomyopathies.
- Continuation of studies of infective endocarditis and of strategies that will reduce and prevent its occurrence, particularly in individuals predisposed to valve infection.

12. Circulatory Assistance

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Circulatory assistance is the use of mechanical systems to augment or replace the pumping function of the heart. Such mechanical assistance can take the form of blood pumps to replace the natural heart or to bypass a diseased ventricle. The Institute's circulatory assistance program was initiated as a focused effort to reduce death and disability from circulatory and respiratory diseases through development of materials, instrumentation, and devices for prevention, diagnosis, evaluation, and treatment of such diseases. The program became a part of the 1972 National Program with specific goals to investigate and assess emergency, temporary, and short-term circulatory assist devices (hours to weeks), intermediate ventricular assist devices (months), long-term ventricular assist devices (years), and total cardiac replacement devices. The program has supported research, development, and evaluation of biomaterials; development of implantable devices to assist or replace the failing heart; development of devices to assist or replace the failing lung; development of diagnostic, monitoring, and bioinstrumentation systems; and the establishment of test and evaluation centers. The program specifically included research on blood pumps, power sources, energy transmission, energy storage, special testing, fabrication programs, and biomaterials. Investigations of respiratory devices and membrane oxygenators, begun in the early 1970's, were transferred to the NHLBI Division of Lung Diseases, which was established in 1973.

State of Knowledge in 1972

Several technologic concepts for circulatory assistance were under development in 1972. Several blood pump designs were under consideration, including diaphragmatic, centrifugal, and the pneumatically driven sac-type and axisymmetric pumps. It had already been demonstrated during short-term testing in animals that such devices could assume most of the pressure and volume load of the natural heart. Several assist devices had also been developed by then, including the intra-aortic balloon augmentation procedure and the so-called "dynamic aortic patch." Studies were being conducted to assess the clinical safety and usefulness of the intra-aortic balloon pump. A diaphragmatic ventricular assist pump had been implanted in some human patients a few years earlier, and the axisymmetric pumps had been implanted in calves

for up to 7 months. These devices employed textured surfaces on which a pseudoneointima was formed. The science was in its descriptive and empirical stage.

Mechanical assistance of the heart for months or years requires that energy be storable for use in brief operations of the device when the recipient is not supported by direct connection to a power source. These conditions underlie the use of electric and thermal engines together with rechargeable electric and thermal batteries to power implantable devices whether intended for long-term use as a ventricular assist device or as a total cardiac replacement device. In 1972, two basic types of energy systems to actuate and control ventricular assist systems were under development. The types included electromechanical and thermal engine concepts. The electromechanical systems were being considered for the 2-year-life ventricular assist systems, and the thermal engines were being developed for the 5- to 10-year systems. At that time, feasibility studies were being performed for two DC electric motor converters, a solenoid actuator, and a piezoelectrically driven converter. The best of the electromechanical devices had achieved an efficiency of approximately 18 percent at this time. Also, four thermal engine converters were under investigation. Two Stirling cycle engines, a Rankine cycle engine, and a unique vapor cycle engine were under development.

The thermal engines in 1972 weighed approximately 4.5 kg (about 10 lbs) and occupied a volume of 5 liters. Although such engines were much too bulky for humans, their feasibility as power sources was demonstrated when prototypes were implanted in calves for up to a week. These engines used a radioisotope capsule to generate the heat necessary to power the engine. Studies had demonstrated that any excess heat generated by a radioisotope source could be tolerated by the host. Results in experimental animals demonstrated the ability to tolerate 24-watt sources of plutonium-238 for a period of 2 years. Other animal studies demonstrated that 50 watts of heat could be safely dissipated in animals. Technical questions regarding radioisotope energy sources (vented fuel capsules and production of adequate amounts of isotope), nontechnical issues, and societal concerns remained to be answered. Thermal engines, which in bench tests had a demonstrated life of up to 5,000 hours, were 8 percent efficient. It was apparent that there was a need for further reduction in weight and volume of such engines, for refinement of the control systems, and for demonstration of reliability.

Pneumatic actuator systems were being developed to actuate and control temporary assist devices such as the intra-aortic balloon. While waiting for energy converter development to reach implantable weight and volume, researchers employed pneumatic activator systems in studies of blood pump feasibility to permit

orderly development of other components. Electrical energy converters were in the "breadboard" stage at this time, and implantable electrical energy devices were not available.

Prior to 1972, as part of the development of an electrically powered device, the Institute had supported feasibility programs in battery development, fuel cells, and energy transmission across the skin. It was realized that there was a need for power on the order of 20 to 50 watts for energizing an implantable heart assist device. No satisfactory methods were available for transferring that level of electrical power across or through the skin. Although solutions to these problems were needed, the limited knowledge base and limited resources necessitated a program that focused on the primary problems of blood pump design and energy system development.

Other tasks foreseen at that time were: reduction in size and weight of components for implantable systems, integration of the blood pump with an implantable energy converter for long-term assistance in humans, and demonstration of in vitro and in vivo reliability for use in humans. Long-term blood compatibility and physiological effectiveness remained to be demonstrated; control systems capable of meeting instantaneous energy demands and physiological needs were yet to be developed; and high quality, reproducible techniques for fabrication of blood pumps, valves, and conduits as well as new synthetic materials with improved properties also remained to be developed.

In 1972, the quantity of any polymer that could be produced in many research laboratories was frequently limited, and reproducible polymer bulk chemistry was not always readily achieved. Methods of fabrication often dictated that device configurations include seams. The numerous concepts regarding surface chemistry that were under consideration compounded the variables to be tested. Many in vivo, ex vivo, and in vitro test methods had been devised to evaluate blood-material interactions, but correlations of test results with clinical performance had not been established.

Major efforts were also directed in 1972 to the development of devices for cardiac replacement. Concepts of cardiac replacement device design included four chambers and four valves that replicate a natural heart. The devices were bulky and compromised the lung and large blood vessels. Other problems included thrombosis, hemolysis, and limited flex life of the pumping chambers. Calves supported by such artificial hearts lived only for several days.

In 1972, the term "biomaterial" was more a concept than a realization. Engineers had long been accustomed to addressing the limitations of materials that are factors of design. In the

emerging field of blood-handling devices, however, it was soon recognized that physical properties such as resilience, flex life, and permeability were not as immediately limiting as compatibility with blood or other tissues. Because of the biological interactions inherent in such devices as artificial valves, vascular grafts, or pacemaker electrodes and casings, a new set of constraints had to be considered. The concept of "biocompatibility" was soon introduced, and the term "biomaterial" came into use to designate materials that could be successfully incorporated in a clinical environment for use in devices of medical interest. Only a handful of polymers, such as silicone rubber, Dacron®, Teflon®, and polyvinylchloride, was in clinical use or had been studied in animals. Among these, only silicone rubber was "medical grade." A novel heparin coating (GBH) had been developed, but it was suitable only on rigid substrates. Modified processes for coating heparin on flexible supports had been developed and were being investigated. The cardiovascular devices or implants in clinical use included catheters, pacemakers, heart valves (mainly the ball-in-socket type), large-diameter arterial grafts, blood oxygenators, and dialyzers.

Many investigators in 1972 operated on the belief that the identification of a biomaterial for a specific device was just a matter of screening the almost endless catalog of compounds developed for other purposes and identifying the most appropriate candidate. In vitro tests of materials were relatively crude, but they had evolved from open test-tube clotting tests to a variety of flow cells that avoided the parallel concerns of the air interface and stagnant or undefined fluid flow patterns. In vivo tests involved only one major animal model, the mongrel dog. After disappointing results with various shapes of test materials inserted in the heart to evaluate the blood-material interaction, the vena cava ring test evolved as a major in vivo test. The renal embolus ring test had been developed to clarify and possibly separate the concurrent processes of thrombosis and embolization. One "chronic" ex vivo shunt system was under development, and different test cells were designed to assay thrombus formation on different materials.

The science of biomaterials was largely descriptive and empirical. A common belief was that if a material exhibited appropriate physicochemical properties, some type of surface treatment would render it "antithrombogenic" and allow it to function in contact with blood for an indefinite period. Theories on achieving blood-compatible materials involved the following concepts: critical surface tension; electrically (negatively) charged surfaces; heparinized surfaces (the activity of covalently bonded heparin remained to be established); prevention of adsorption of coagulation factor XII or fibrinogen; prevention of platelet adhesion and aggregation; and appropriate fluid dynamic design to avoid secondary or separated flow effects.

Program Goals Through 1982

- Develop and assess therapeutically effective, safe, and reliable cardiac assist and total replacement cardiac devices for supporting or taking over the workload of the heart.

- Develop and test, in priority order, short-term, intermediate, and long-term circulatory assist devices for clinical use.

- Identify and develop materials that display the requisite blood compatibility and mechanical properties to make them suitable for circulatory assist and other cardiovascular device applications.

Accomplishments Through 1982

During this past decade, wider applications for short-term left heart assist devices were developed. After extensive animal testing, clinical evaluation of these devices confirmed their safety and efficacy in short-term use in humans. Long-term effectiveness, however, requires implantable cardiac assist devices. During the decade, there was sustained progress in the development of the individual components of the implantable ventricular blood pump, the electrical energy converter, and their integration. Needed progress has also been made in biomaterials development.

Intra-aortic Balloon

After demonstration of the feasibility of an intra-aortic counterpulsation balloon that augments diastolic blood pressure while reducing cardiac work, the device was successfully applied in humans. In the early 1970's, the first patients in whom the device proved successful were cases of postcardiotomy shock. This intervention was applied to bypass patients who could not otherwise be "weaned" from cardiopulmonary bypass or who, later in the postoperative phase, developed cardiogenic shock. In the mid-1970's, the indications for the device were extended to patients with cardiogenic shock complicating myocardial infarction. The device was applied not only in specialized intensive care units but also during transportation to such units. The device proved lifesaving, and it has become part of the armamentarium of clinical care for such patients. The synergistic combination of the intra-aortic balloon with certain drug regimens has proven to increase survival of a number of patients.

Short-Term Left Ventricular Assist Devices

After extensive testing, the pneumatically powered axisymmetric short-term ventricular assist device was approved in 1975 for clinical evaluation of safety and benefit in postcardiotomy patients who could not be weaned from cardiopulmonary bypass by conventional procedures. By use of this ventricular assist device for less than 2 weeks in a group of such patients, 20 percent long-term survival was achieved. This initial program demonstrated that ventricular assist devices can be safely used in postcardiotomy patients and that a significant number of these patients recover myocardial function within several days.

The feasibility studies and guidelines for clinical studies of the left ventricular assist devices were discussed extensively in 1975. Since that time and on several other occasions, advisory panels have reviewed the direction of the program. In 1977, a working group of the Cardiology Advisory Committee recommended that the Institute emphasize development of integrated components for implantable ventricular assist devices and continue its support of cardiac replacement devices, since the latter could readily utilize much of the technology needed to achieve the former. In 1980 and again in 1981, two working groups reviewed the program and developed guidelines for utilization of mechanical support devices.

Implantable Ventricular Assist Devices

By the mid-1970's, interest had shifted to implantable ventricular assist devices, and emphasis was placed on the development of the diaphragmatic, pusher-plate type of blood pump. This type of pump can be integrated with miniaturized energy converters that are actuated by electrical energy or by coupling with thermal engine systems. A variety of pump designs utilizing smooth or integrally flocked surfaces evolved. The implantable volume and weight of the blood pumps were reduced by 50 percent (currently about 250 cc and 400 g respectively). As a result of the development of refined flow visualization techniques, current pumps have flow patterns that are significantly reduced. The efficiency of a typical blood pump is now over 80 percent, compared to approximately 40 percent in 1972. A standardized mock circulatory loop has been developed for accurate evaluation of these devices. Pump bladders routinely achieve over 2 years of bench life. Partly as a result of rigorously defined pump fabrication techniques and techniques of quality control, some experimental pump bladders have operated on the bench at accelerated beat rates for over 5 years. Potentially useful tri-leaflet valves have also been developed that show characteristics of physiological flow and long life on accelerated bench testing.

Because a bolus of blood is ejected with each stroke of an implanted system, volume compensation must be provided. Several concepts are being studied. A stiff chamber with a smooth flexing diaphragm connected to the system by a tube can perform this function. After implantation, however, the chamber and diaphragm can become surrounded by dense tissue, which limits operation. Promising approaches that are under way are directed to a solution of these problems of compliance. Compensation for changes in altitude to allow patients to travel also needs to be addressed.

Early empirical efforts to fabricate pump chambers for ventricular assist devices have progressed to industrial production of standardized reliable devices. The interaction of rheologic and design factors with characteristics of biomaterials has been recognized. The evaluation of blood-material interactions in actual devices has progressed from acute observations limited to a few hours or days of operation to a recognition of the problems encountered after several months of exposure to flowing blood. Techniques of fabrication have been standardized for microscopically smooth surfaces that discourage cell attachment under the fluid dynamic conditions prevailing in a ventricular assist device and also for integrally flocked surfaces that favor blood component deposition and cell attachment to the material. Clinically satisfactory results have been obtained with both smooth and textured surfaces.

Energy Sources for Ventricular Assist Devices

The electrical energy converter program received particular emphasis during the mid-1970's, and improved design of several converters has provided better efficiency, decreased weight and volume, and better reliability. The efficiency of electrical energy systems has been increased from less than 20 percent in 1972 to well over 40 percent in 1982. Significant weight and volume reductions have also been achieved. Current electrical energy converters now weigh 300 to 600 g and occupy a volume of 160 to 300 cc. Several converters have achieved over 2 years of bench life and 3 to 7 months of life in animals. These energy converters are now being integrated with the diaphragmatic pumps and are being implanted in animals to characterize performance in vivo.

Thermal engines that convert heat into mechanical energy had been developed in prototype form before 1972 as candidates for powering cardiac assist devices. During the past decade, work on a vapor cycle engine and a Rankine cycle steam engine was discontinued in favor of more efficient systems such as the modified Stirling cycle engines, which utilize gas (helium) as a working medium. One current thermal engine can be smaller than a deck of cards and weigh no more than the heaviest electric engine of

ventricular assist devices. Implanted thermal engines can be powered by internal, ultra-reliable thermal batteries of lithium salts that are rechargeable by electrical heaters, and can provide power for up to 24 hours of operation between charges. Thermal engines have achieved efficiencies ranging from 18 percent to 20 percent and a bench life of up to 4 years.

In 1977, the Division of Heart and Vascular Diseases began supporting study of methods to transmit energy through or across the skin to power electrical or thermal engines that utilize electrical energy to reheat thermal salts. For the electrical engines, intracorporeal nickel-cadmium storage batteries provide energy for operation for emergency periods of about 30 minutes, whereas energy stored in an external belt containing larger batteries can permit untethered operation for about 10 hours. One method of transmission utilizes an electrical conductor sheathed in synthetic materials that promote a strong mechanical bond with the skin to prevent extrusion of the device by the natural, foreign-body response of the skin. Another approach transfers electrical energy across the intact skin by transformer action from an external belt containing a primary coil to a secondary coil buried beneath the skin. Both approaches have performed satisfactorily in animals for up to 1 year.

In 1980, the efforts that had been focused on the development of individual components proceeded toward the development of integrated ventricular assist systems capable of functioning for 2 years. Five types of implantable, integrated, electrically powered heart assist systems are now being developed, refined, and evaluated. They consist of a single housing that conforms to anatomical space and contains the pump and electrical energy converter together with the necessary control apparatus and a short-term battery for temporary, tether-free support. Primary power is supplied by externally worn electrochemical batteries. The electric energy converter is connected to the pump either through mechanical or hydraulic linkage. The lightest of these systems employs electric motors that operate at high speed, with some likelihood of wear, whereas the heaviest employs low-speed motors with a low potential for wear. These factors of engineering are under current investigation in bench and animal studies. One system has already achieved over 7 months of in vivo operation in a calf. These systems (energy system and blood pump) currently have an implantable volume of 400 to 500 cc and a weight of 700 to 800 g.

Total Cardiac Replacement

Significant progress has also been made in total cardiac replacement research. Several studies have repeatedly achieved 3 to 6 months of operation in calves. Calves have been supported

by a pneumatically driven heart for up to 10 months. The animals with such hearts had normal growth, organ function, hemodynamics, and hematology, and they performed well during exercise testing. Calcification and pannus formation in the inflow cannulae remain important research issues.

A key limitation in circulatory support and total cardiac replacement research has been the animal model. The calf, which is the most popular model, is a growing animal that quickly outgrows the mechanical device. Also, heart failure models with the calf have not achieved the stability desired. Some researchers hypothesize that use of calves as a model accelerates and accentuates the problems of bladder and valve calcification seen in components of the cardiac replacement device. There is need for an alternate adult animal model and a stable heart failure model to evaluate prototype devices more extensively.

Biomaterials and Blood-Material Interactions

Hemolysis, thrombocytopenia, thromboembolic phenomena, and intractable bleeding were commonly observed in the animal evaluation of ventricular assist devices in the early 1970's and were thought to be due to the biomaterials used. These consequences necessitated a major effort to design materials that would be more compatible with blood. Because of advances in polymer chemistry, surface characterization, fabrication techniques, system design, surgical techniques, blood-handling procedures, and pharmacologic intervention, these hematologic problems no longer limit the evaluation of ventricular assist devices in animals or their short-term clinical use in humans. Theories and test methods have been developed to predict mechanical properties from the knowledge of polymer composition and structure, and similar progress can be expected in relation to device surface properties.

The effect of biological environments on the properties of materials limits the performance of implanted devices. The phenomenon of calcification, first identified in modified biological valves implanted in children, has been recognized as a general phenomenon affecting a variety of synthetic materials in a number of different applications. Utility of an implant is impaired when the host cannot fully integrate or accept foreign materials. Researchers are attempting to elucidate further the mechanism by which human endothelial cells might colonize a foreign surface and render it nonthrombogenic.

Whereas in 1972, blood-material interactions were viewed primarily from the viewpoint of the coagulation cascade and the factors involved in it, the scientific community has developed an increasing appreciation of the contribution of other components, such as the formed elements of blood (particularly platelets and

white cells) and noncoagulant proteins, to processes that lead to hematologic damage or device failure.

The methods for evaluating blood-material interactions have become more sensitive and more sophisticated. The use of radiolabeled proteins (not only major plasma species but also minor ones) has improved the understanding of the role of numerous blood components in regulating protein adsorption. The influence of the kinetics, flow rate, and role of preadsorbed proteins upon adsorption of a particular species of protein is now recognized. The use of gentle methods to radiolabel platelets has improved the ability to quantify platelet adhesion, detect alterations in platelet survival, and image platelet deposition in vivo. An increased understanding of platelet physiology and the biochemistry of the platelet release reaction has led to the use of sensitive radioimmunoassay methods to detect platelet damage in vivo. Improvements in such methods have also led to improved methods for detection of coagulation. The development of tissue culture methods for initial toxicity screening of new materials has expedited the development of such materials.

The number of animal models for studies of blood-material interactions has increased, and it includes minipigs, sheep, goats, and primates. While each model presents certain advantages, certain cardiovascular or hematologic aspects of each one limit the applicability of data to humans. Investigators, however, have an ever increasing appreciation of the need to understand the hematologic and vascular biology of their test species. By studying a variety of new test configurations, these investigators are striving to identify the ideal test system that will predict long-term performance of the material in a device in humans.

Since 1972, a better understanding of the role of platelets in the development of thrombi and in device failure has led to methods to retard platelet adhesion. New antithrombogenic agents are being investigated. The development of calcified areas on flexing surfaces of certain devices is presumed to be related to a reaction between the material and blood components. This phenomenon is receiving sustained scrutiny by the NHLBI and the biomedical community. Related problems have been noted as a result of increasing long-term experience with vascular grafts, particularly with grafts that are used in the peripheral circulation. Graft failure can occur through early thrombosis and also, later on, as a result of intimal hyperproliferation leading to reduced flow and delayed thrombosis. The mechanism for the proliferative process is unknown, and it remains one of the challenges to be met before a small vessel prosthesis can be truly successful (less than 5 mm internal diameter). In 1982, the Division released a program announcement underscoring its concern

with mechanisms of failure of these prostheses and with the need for appropriate means of prevention of such failures.

The need to develop a unifying hypothesis for the basic mechanisms of blood-material interactions was recognized after the difficulty of correlating experimental test results with clinical performance became apparent. It was also difficult to assess nominally similar materials in different laboratories with different test methods. The need for common methods to characterize physicochemical properties and for assay techniques for blood-material interactions led to a program through which expert panels published two monographs, Guidelines for Physicochemical Characterization of Biomaterials and Guidelines for Blood-Material Interactions. The publications have been widely disseminated in the Federal, scientific, and industrial communities, and they are now the accepted reference in the field, in both the United States and abroad. The program also provides primary reference materials to assure a common experimental baseline among research and development laboratories.

As a result of flow visualization techniques in model systems and of studies of retrieved implants, device design was improved to eliminate seams and minimize areas of stagnation or turbulence. The contribution of rheologic factors to hemolysis and thrombosis was more clearly defined by research on the basic mechanisms of rheologic damage to erythrocytes, leukocytes, and platelets, and by recognition of thrombus formation at areas of discontinuity or surface defects, such as gel inclusions, bubbles or voids, and particulate contaminants (including dust and fibers). The pitfalls of contamination of biomaterials in the process of device fabrication and implantation have been recognized. Knowledge of the importance of "clean room" techniques and of possible alterations in the course of storage and sterilization have led to a much higher degree of reliability in the evaluation of circulatory assist devices.

Advances have been made in the synthesis and characterization of materials, and surface modification techniques are available. Some methods can be utilized to alter surface chemistry, such as radiation grafting, immobilization of special molecules (especially pharmacologic agents), plasma treatment, protein coatings, and cell seeding; other techniques, such as integral flocking, texturing, and ion beam bombardment, alter surface morphology. New techniques of modifying polymer chemistry have been applied to the synthesis of polymers having a range of surface charge, hydrophobicity or hydrophilicity, and mechanical properties. The development of sophisticated instrumentation has allowed more sensitive and specific characterization of the molecular structure and morphology of polymers of the blood-contacting surface monolayer.

The mechanical properties of polymers were usually determined by life-testing on a mock circulatory loop. The flex life of elastomers used to fabricate the moving surfaces of ventricular assist devices severely limited the life expectancy of such devices in continuous operation. As a result of such mock loop studies, some polymers were identified that have a flex life required for implantable flexing devices. As device design improved, it became apparent that the materials with acceptable flex life in vitro could also function satisfactorily in vivo. In 1977, a physical testing program was initiated to identify mechanisms of failure of candidate polymers subjected to uniaxial and biaxial stresses and to identify accelerated test methods that would predict the long-term flex life of a given polymer when used as a cardiovascular implant.

The fundamental characteristics that define the blood compatibility of materials are being elucidated with the use of increasingly specific laboratory tests in the evaluation of previously existing as well as newly synthesized polymers. Some components of circulatory assist systems, however, have presented problems of compatibility between synthetic materials and tissues other than blood. Investigations have broadened the scope of biomaterials research beyond the initial focus of blood-material interactions. These new areas have attracted the attention of pathologists and cell biologists and have provided new research tools for other areas of science.

Progress in polymer synthesis and characterization now allows the fabrication of reliable pumping chambers with a performance life of at least 2 years. Specific cell systems such as endothelial cells and fibroblasts have also been recognized as essential factors of blood-material interactions in long-term implants.

Although oriented to circulatory assist devices, biomaterials research programs have led to significant advances in other fields of medicine and surgery such as the use of composite sheets of silicone elastomer and collagen in artificial skin in the treatment of burns and the application of new polymer formulations in the search for reliable small vessel grafts. The NHLBI is now recognized as the lead agency in biomaterials studies.

State of Knowledge in 1982

Several circulatory assist projects initiated by the Institute have been completed including development, evaluation, and clinical application of emergency and temporary ventricular assist devices, pneumatic consoles for actuation and control of mechanical circulatory support devices, membrane oxygenators for

assisting pulmonary function, and an implantable transducer for continuous measurement of blood pressure. The NHLBI has focused efforts on the clinical evaluation of short-term ventricular assist devices, development of long-term ventricular assist devices, and continued research on biventricular support devices such as the totally implantable assist device.

Mechanical assistance of the circulation with the heart-lung machine and with the intra-aortic balloon pump is an accepted short-term clinical procedure to improve patient hemodynamics. Successful initial clinical use of the pneumatically powered short-term ventricular assist device represents the culmination of years of bench and animal testing. When a ventricular assist device is briefly substituted for the failed heart in a patient who cannot be weaned off the heart-lung machine, there is often recovery of cardiac performance, and in some patients, there is long-term survival.

The program for development of implantable ventricular assist devices has emphasized improvement of blood pump design and miniaturization of engines and associated apparatus to provide eventually a device capable of ambulatory patient continuous support. Each component has been tested extensively at each design stage, and integration of electrical engines with the blood pumps has begun. The thermal engines that are being developed offer the advantages of power storage inside the body (10 hours) and infinite recharging capacity for long-life systems. Thermal engines, however, have only recently reached the implantable stage of development, and integration of these engines with the blood pumps is just being initiated. The blood pumps using pneumatic actuation have functioned satisfactorily in animal tests for periods of up to 1 year. Some engines and blood pumps have been bench-tested for periods of 2 years. Five different integrated electrical devices and two thermal engines are currently being tested in animals and on the bench for performance and durability. The reliability of these integrated systems for 2-year operation in humans is yet to be determined.

Electrical power will be required for both the thermal and electric engines as now envisioned, and a means must be found for transferring the electricity into the body. The electric engines will require this power to run the engine and recharge internal chemical batteries. The implantable chemical batteries will be capable of powering this system for only 30 minutes and would therefore be used only intermittently or in an emergency situation. For the thermal engines, electric power is needed to reheat the lithium salts of the thermal battery. Under study are devices for the safe percutaneous and transcutaneous transmission of electrical energy. Animal testing has demonstrated biologic integrity of such devices for a period of at least 1 year.

The control apparatus for pneumatically actuated ventricular assist devices has been incorporated into bedside consoles that require human supervision and adjustment. More sophisticated control systems are required for the unattended operation of implanted ventricular assist systems. Prototype solid state electrical and mechanical control elements for electric and thermal systems have been miniaturized.

Pneumatically actuated totally implantable devices have been implanted in calves for periods of up to 9 months, but their further use is limited, by growth of the animal, when the animal exceeds the capability of the replacement device. These observations have suggested the use of smaller adult animals such as goats or sheep.

Most clinically acceptable devices currently rely on materials that were not originally designed for biomedical use. Attention to stability and purity of materials in the fabrication of devices, however, has contributed to the success of thousands of implants used in everyday surgical practice. No more than a few dozen chemical compounds, among the vast number of potential candidates, have been found useful in the biological environment. Another realization has been that some functional implants place demands on intrinsic material properties that are far closer to the limits of current technology than most other engineering applications: for example, the flexlife expected of a polymer to be used in a lifelong implantable heart.

During the past decade, significant advances have occurred in design and fabrication of devices such as pump-oxygenators, pacemakers, vascular grafts, prosthetic valves, and ventricular assist and replacement devices. At this point, progress in design is no longer contingent upon the synthesis of new biomaterials. Rather, it seems that the service-life of implantable devices impinges on limits that are associated with the deterioration of initially acceptable materials after prolonged contact with body tissues, or are associated with the long-term reaction of body tissues to the presence of prosthetic devices. An appropriate research environment during the next decade would allow for closer interactions between biomaterials science and basic biological sciences such as molecular and cellular pathology, immunology, and hematology. Because significant progress has been made in the conceptual organization of the biomedical sciences, major progress with cardiovascular devices will be dependent not solely upon breakthroughs in design or synthesis of new classes of materials but also upon application, to biomaterials research, of anticipated advances in the biological sciences.

It is generally agreed that all biomaterials induce a "foreign body" reaction when introduced into a biological environment: they either are walled-off by a reorganization of

surrounding tissues or are coated with biological materials derived from these tissues. Most often the outcome is characterized as an inflammatory response in the extravascular space and as thrombosis in the cardiovascular system. Each of these responses is an extremely complex biological process, involving the interactions of many different biomolecules and cells at the foreign interface. Although these processes are not fully understood, they seem to proceed in two phases: an acute phase, which is characterized by considerable protein and cellular activity; and a chronic phase, in which the dynamic changes level off, leaving what is called a passivated surface. There prevails now a more widespread and deep appreciation by materials scientists, engineers, and physicians of the complexity of these processes than was the case 10 years ago. There have been significant efforts to purify and standardize biomaterials and to apply more sophisticated physicochemical and biological test methods for characterizing these interactions. Increased knowledge and improved assays have paralleled the development of new clinical devices and implants. There is now little doubt that surface properties such as polymer configuration, charge, topography, and outermost chemical arrays can, under many circumstances, dominate the biological responses. Correlations have been proposed that link surface properties and biological responses, but there is no more general agreement here than there is on which "animal model" or "test system" is best. Rheology can also influence and, in some cases, dominate the biological responses, again depending upon the test system.

Program Goal 1982 to 1987

- Continue to develop effective, safe, and reliable cardiac assist and total cardiac replacement devices for partial or total assumption of heart function.

Research Activities 1982 to 1987

- Continuation of the clinical program on temporary ventricular assist devices (VAD's).
- Continuation of investigations of the mechanisms of calcification of certain components of circulatory assist devices.
- Investigation of a variety of means of solving problems that impair the effectiveness of the compliance chambers of blood pump actuators in VAD's.

- Further testing and integration of energy storage devices for VAD's.
- Further development and testing of methods of energy transfer across the skin in VAD's.
- Extension of animal testing of components of implantable VAD systems.
- Further animal testing and evaluation of the totally implantable heart.
- Elucidation of physicochemical characteristics of materials to be employed in cardiovascular devices.
- Systematic collection of data on the long-term aspects of blood-material interactions.

13. Prevention Research

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13. Prevention Research

Despite the decline of reported deaths in the past decade in the United States, cardiovascular disease remains the country's largest single cause of death and also of premature death during a person's productive years. The need for a preventive approach in 1982 arises from this large burden, and it is related also to the insidious nature of the disease, which develops slowly over decades, is often manifest suddenly, and, when first manifest, is already associated with extensive damage of the blood vessels and the organs they supply. This need is also shown by the fact that many victims die suddenly, having never reached medical care, that those who survive an attack may become functionally impaired, and that such survivors may also remain at an excessively high risk for subsequent mortality.

The feasibility of prevention is inferred from the observed differences, between cultures, in the frequency of atherosclerosis and hypertensive disease. Some countries are relatively free of these diseases, whereas others have a high incidence. Moreover, within a high-incidence population, individuals have different degrees of risk. The differences in population risk and personal risk are partially explained by the presence of single and combined risk factors, including high blood pressure, high blood cholesterol, and cigarette smoking. These three risk characteristics are in turn modifiable. In addition, the population rates for these diseases are dynamic--that is, they are rising in some countries and declining in others. Such trends strongly indicate the potential for preventive action.

The issue of prevention is not the exclusive purview of a particular National Program area or investigative discipline, and the research implications vary for different populations. Approaches to each population group necessarily involve different strategies and tactics. At least four populations should be considered: (1) individuals with clinical cardiovascular disease, for whom research on the prevention of recurrence and progression of the disease is needed (these individuals may account for about 5 percent of the adult population); (2) individuals without manifestations of disease but who are at especially high risk because of configurations of hereditary and culturally determined risk characteristics and who are, therefore, in special need of prevention of development of clinical disease; (3) total populations in North American and other countries that have relatively greater risk than populations elsewhere (the cultural,

behavioral, and physical characteristics that lead to this excess risk involve the bulk of the population, not just those who are at especially high risk or who are already ill); and (4) population segments, primarily youth and young adults, who do not yet possess elevated risk factors for the major adult cardiovascular diseases.

State of Knowledge in 1982

Prevention of Recurrence and Progression

Remarkable advances have been made in recognition of symptoms and signs of coronary heart disease, in the provision of responsive emergency systems in the community, in the availability of intensive coronary care, and in long-term supportive care in the medical delivery system. Preventing recurrent episodes and halting the progression of this disease, however, remain a challenge. A comprehensive preventive strategy should be directed toward persons with clinically manifest disease. They are numerous, and they account for a substantial proportion of the total deaths. The design of a functional overall strategy requires an identification of the contribution of traditional medical care and a determination of the contributions that might be made by newer preventive approaches, including patient education and changes in lifestyles. Surveillance of the frequency and the change in frequency of the manifestations of coronary heart disease and hypertension is essential to a rational approach to their prevention. A feasibility study of such a survey system is under way in several settings in the United States.

Research should be focused on at least two components of the population with manifest disease: those who are symptomatic with angina pectoris or who have survived an infarction, and those who are defined through newer diagnostic techniques as having inadequate arterial supply or organ function but who are not yet symptomatic. The rate of recurrence and progression of the disease is measured by survival, by rates of sudden death and recurrent nonfatal infarction, or by change in symptoms, signs, or evidence of altered blood supply and organ function. For comparisons of preventive approaches, new technologies may permit more sensitive measurement of progression and shorten surveillance.

Primary Prevention in High-Risk Populations

The segment of populations with a high incidence of atherosclerotic and hypertensive disease, which contributes disproportionately to the total cases in the population, presents a special challenge to preventive cardiology. Particular attention

should be directed to ongoing and systematic approaches to improve the identification of individuals and groups at special risk and to tailor appropriate risk reduction efforts in traditional and nontraditional health care environments.

Presently, the definition of high-risk populations is based primarily on single and combined risk-factor levels. High risk is the term used to refer to individuals in the upper 20 percent of the distribution of multivariate or combined risk factors or to individuals in the upper 5 percent of the distribution for single-risk characteristics. This high-risk segment of the population has come to be recognized through descriptive population studies. Risk profiles are available to the practitioner for patient assessment, education, and motivation. The NHLBI Hypertension Detection and Followup Program, the Multiple Risk Factor Intervention Trial, and the Oslo diet and smoking trial have significantly advanced current knowledge about the feasibility, effectiveness, and safety of modification of physiologic and behavioral risk characteristics. Further research, however, is needed. Additional new risk factors remain to be discovered, and the measurement and interpretation of conventional risk factors can be refined. For the high-risk individual, the conventional medical system is likely to play the major role in risk reduction. To facilitate the effective and efficient application of new knowledge and skills, health providers and health systems have to be provided with current, useful information on prevention. More research is needed on how to transfer current knowledge cost-effectively and appropriately to the settings in which high-risk individuals and groups live, work, and receive treatment.

Health Education and Health Promotion

As the potential for prevention has been recognized and public awareness has been raised, prevention and health promotion strategies have received increasing attention. Professional and public education to create demand and to provide methods of changing health-related behaviors are crucial to the preventive strategy for cardiovascular diseases, and campaigns of voluntary agencies and federal programs emphasize health promotion and disease prevention as major priorities of national health and social policy.

Health education can be delivered most effectively through educational institutions, health organizations, health care facilities, media organizations, and work settings. Each setting has distinctive organizational structure, addresses a unique population, has different organizational resources, and has specific research needs. In addition, each setting has characteristics that enable it to respond to the need to better understand the behavior of individuals in their peer groups and families and to

formulate more effective strategies that help persons achieve desired changes. Thus, the following are identified separately for research needs: schools, the family, health professionals, the worksite, and the elderly.

High Blood Pressure

Research of the last four decades has provided considerable knowledge about the pathophysiology of essential hypertension, although the pathogenesis remains unknown. Thus, essential hypertension remains the term used for the great majority (probably greater than 95 percent) of patients with high blood pressure of undetermined cause.

From a clinical and preventive perspective, the most useful current knowledge is derived from several clinical trials that have demonstrated the feasibility, safety, and efficacy of lowering elevated blood pressure. These trials primarily used pharmacologic interventions in persons with diastolic blood pressure of 95 mm Hg or greater on two screening visits, as in the Australian Trial, or with 95 mm Hg or greater at the initial home screen, and 90 mm Hg or greater at the secondary clinic screen, as in the HDFP.

Estimates of the number of hypertensive adults in the United States range from 23 million to as many as 60 million persons, depending on the criteria used for defining hypertension and whether all age groups are included in the estimates. Through the major efforts of the National High Blood Pressure Education Program and other programs, the public awareness of high blood pressure as a medical problem has increased and the proportion of treated and controlled patients has improved since the early 1970's. The recent decline in the death rate from coronary heart disease and stroke at a time when effective treatment of hypertension has become considerably more widespread suggests that hypertension treatment may be a contributing factor.

Lipids and Lipoproteins

Higher levels of total cholesterol and low density lipoprotein and lower levels of high density lipoprotein are independently related to the risk of vascular disease among individuals in high incidence populations. Clinical trials of the 1960's demonstrated the feasibility and safety of blood lipid and lipoprotein lowering by dietary modification. Prevention trials of the 1970's have further shown the feasibility and apparent safety of lowering blood lipid levels alone and in combination with the modification of other risk characteristics. The Oslo

study reported the efficacy in high-risk men of combined cholesterol lowering by dietary means and smoking cessation. Other important primary prevention trials in high-risk populations (Lipid Research Clinics and Multiple Risk Factor Intervention Trial) are to be published in the near future.

A great variety of attractive diet patterns exists that reduce the blood cholesterol level; these diets are safe, economical, and nutritionally adequate. Preventive care in high-risk populations is generally provided under the direction of a physician-nutritionist team, although dramatic changes in eating patterns are occurring spontaneously in the United States.

The feasibility of individual and group education in knowledge and skills training has been demonstrated. There remains, however, a need for well-evaluated demonstrations in specific skills training to change eating habits, increase adherence to diet, and improve selection and preparation of food.

Exercise and Physical Activity. Regular physical activity and vigorous conditioning exercise in high-risk individuals are important to energy balance and weight control, to work performance, and to cardiovascular efficiency, and also to the control of primary risk characteristics. Current information suggests many potential benefits to this approach to prevention, but there remain issues of appropriateness and effectiveness, safety and cost, and the optimal combinations of frequency, duration, and intensity of exercise. Though a direct causal relationship between increased physical activity or physical fitness and lower CHD occurrence has not been established, habitual physical activity may be important in the reduction and prevention of risk factors in high-incidence populations.

Smoking. It is assumed that the change toward social unacceptability of cigarette smoking and greater awareness of the adverse health effects of smoking are directly responsible for the remarkable decrease in smoking rates over the last two decades. Nonetheless, millions of adult smokers who try to quit each year fail, with smoking rates among women declining less rapidly than among men and with variable changes, including increases in some groups, occurring in adolescents. More research is needed on smoking cessation so that the positive changes of the past two decades may be maintained, accelerated, and extended to the adolescent. In addition, techniques to decrease the rate of onset of the cigarette-smoking habit need to be developed and tested, especially in the youth and adolescent.

Primary Prevention in Whole Populations

Because of the widespread genetic susceptibility of human populations to atherosclerosis and hypertension, and because of the apparently ubiquitous and powerful sociocultural influences that act on this genetic susceptibility, a population-wide public health strategy of preventive cardiology is needed. Whole populations, such as in North America, are at relatively high CHD risk compared to other populations. The majority of CHD cases in high-incidence countries comes from the bulk of the distribution of risk characteristics in the population rather than from the segment of the distribution labeled high risk. Attention, therefore, only to CHD patients or to any defined high-risk segment of the whole population can never deal effectively and preventively with the majority of existing or anticipated adult cases. Nor does that approach address youth and its early adoption of health behaviors that lead to increased cardiovascular disease risk in adulthood.

Significant progress has been shown in community approaches to the modification of population CHD risk characteristics through strategies of education and environmental change. The success of this kind of approach has already been shown for targeted groups, including school and other "captive populations," and for whole communities. Integrated, multiple educational strategies are being applied in general populations through community research and demonstration programs, such as the ones in North Karelia, Finland, the Stanford studies, the Minnesota Heart Health Program, and the Pawtucket Heart Health Program. The earliest two of these community-based programs, by showing changes in knowledge, behavior, and risk factors in relation to the exposure to health education, have demonstrated that such projects are feasible. All of these studies have shown that community organizations and leaders can be mobilized, that facilities for prevention can be enhanced, that the media play an important role in credibility and awareness, that school programs are desired, and that direct education of much of the adult and youthful population is achievable. The impact of such outcomes on behavior, on risk-factor distributions, and on disease rates is the subject of current trials.

Because some of the scientific community remain skeptical about the public health approach to risk factor modification, there is confusion among the public, and the adoption of certain recommendations is less than complete. Real uncertainties remain about the contribution of some risk factors to the CHD problem and about interactions among risk factors. Also, configurations of known primary risk factors (for example, blood lipoprotein levels, blood pressure, and cigarette smoking) still account for relatively little of the variation in individual CHD risk and perhaps for about one-half of the difference in population rates. Thus, a

research strategy for preventive cardiology requires continued search for unknown factors and for more information about known risk factors and their interactions over time.

Primary Modification of Risk Factors in the Young

Distributions of cardiovascular risk characteristics in school age populations often already reflect variations found in the adult population risk-factor distributions that are so strongly associated with overall CHD incidence. Within populations, the correlation between individual risk factor values in youth (or rank in the distribution) is significant but less strong. Nonetheless, most behaviors that affect adult levels of cardiovascular risk factors--eating habits, amount of physical activity, and smoking pattern--are acquired predominantly in youth or young adulthood. Therefore, descriptive and experimental research in preventive cardiology needs to focus on determinants of, and the prevention of, elevated risk characteristics and their associated behaviors across the whole population, with an emphasis on youth. In addition to the youthful populations now within high-incidence cultures, cultural subgroups in the United States and entire populations in low-risk countries exist that will experience greater future risk of mass cardiovascular disease as their lifestyles change with economic development. Prevention of elevated risk in the first place becomes, then, an essential ingredient in the primary prevention of cardiovascular disease.

Program Goals 1982 to 1987

- Continue to conduct population studies and demonstration and education strategies for the prevention of the development and the progression of heart and vascular disease.

- Improve the diagnosis, treatment, and cure of existing heart and vascular disease in order to prevent its recurrence and progression.

- Improve the characterization of risk-factor distributions and their changes over time, the understanding of health behaviors, especially in youth, and the approaches to foster healthy habits.

- Continue research on the most effective means, consistent with achieving the goals of health promotion, of translating and disseminating research findings to health professionals and the public.

- In subpopulations identified as being at especially high risk for heart and vascular diseases, improve the detection of individuals at such risk, the understanding of the host-environmental interactions responsible for the increased risk, and the efforts to modify health behaviors.

Research Activities 1982 to 1987

- Continuation of existing studies of the effectiveness of educational strategies and of environmental modifications on communitywide changes in cardiovascular risk-factor behavior.

- Further development and testing of materials useful in self-help smoking cessation, supplemented by studies of the effectiveness of larger scale antismoking programs in schools, at the worksite, and in mass media community campaigns.

- Further evaluation of health education and behavioral approaches to compliance with pharmacologic and nonpharmacologic blood pressure interventions.

- Further evaluation of school health programs to identify those strategies most appropriate for various behaviors and risk factor levels.

- Additional clinical trials of multiple risk factor modification in such groups as survivors of myocardial infarction, coronary artery bypass surgery, and percutaneous transluminal coronary angioplasty to evaluate the effectiveness of such modification on preventing further morbidity, on increasing work capacity, and on improving the quality of life.

- Investigations of the role of nutrition in the prevention of cardiovascular disease, including the influence of socioeconomic status, age composition of populations, employment status, and changes of these factors on food patterns and nutrient intake.

- A review of the state of knowledge of the relationship of physical activity to CHD and to known CHD risk factors with identification of future research opportunities in this area.

- Application of latest methods of blood pressure and electrolyte measurement to studies of the influence of

diet, including sodium and potassium intake, and weight change on blood pressure trends in youth and young adulthood.

- Examination of the interaction of heredity and environment in obesity and of the mechanisms by which obesity influences blood pressure and blood lipids.

- Investigations that explore newly identified physiological and behavioral risk characteristics in subsegments of the U.S. population and in other, different populations.

- Promotion of research leading to development of test instruments to measure awareness, attitudes, and behavior related to cardiovascular risk factors in youth.

- Trials of the effectiveness of various nonpharmacologic strategies applied before and during step-up pharmacological control and in step-down tests of drug therapy.

- Support of further studies of the contribution of behavioral and physiologic components to heart and vascular disease and of the modification of coronary-prone behavior and other prognostic psychosocial factors.

14. Research Training and Development

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14. Research Training and Development

The major accomplishments of programs in the United States for improved understanding, detection, treatment, rehabilitation, and prevention of cardiovascular disease have depended and will depend upon the availability of trained investigators. The training of new investigators is an essential aspect of progress in the conquest of such disease. The influence of such training is exemplified by the undergraduate training grants of 1948 to 1972, which introduced cardiovascular curricula into medical schools and which established heart stations. This program was largely responsible for the international stature achieved by cardiovascular scientists and clinicians in the United States today. The recruitment and training of capable research scientists are essential elements of the country's future health. Continuity and stability of training programs are also essential. Goals for future research in heart and vascular diseases are stated throughout this report. General maintenance of and selective increases in scientific personnel are prerequisites to appropriate progress toward these goals.

In this discussion, the distinction between the numbers of individuals being trained and the numbers of training awards should be kept in mind. Some training grant programs provide full- or part-time direct support to specific individuals; others provide a specified level of support to a particular institution where it is distributed among a number of full- and part-time traineeships. Thus, the total numbers of training awards, the total numbers of individuals trained, and the total numbers of full-time equivalents (FTE's) are three different measures of the total research training activity in any given year.

State of Research Training in 1972

In 1972, the responsibility to develop specialized personnel to conduct research in heart and vascular diseases and to monitor National needs for cardiovascular health specialists was met primarily by the mechanism of institutional training grants (T01), of which 242 supported 248 predoctoral trainees and 765 postdoctoral fellows. In addition, support continued for 98 individual fellowships (F02, F03) until the training moratorium in December of 1972. Thus, 1,111 individual trainees were being

supported in 1972. About three-quarters of the postdoctoral trainees held professional degrees.

The National Heart, Blood Vessel, Lung, and Blood Act (P.L. 92-423) of 1972 provided for a comprehensive range of cardiovascular research. The importance of prevention was recognized in the act, which provided for disease prevention and control programs. The same year was marked by the inception of the Institute's major commitment to clinical trials. These expanded programs signaled an increasing demand for personnel trained in different, highly specialized disciplines.

The year 1972 was also marked by the implementation of changes in the administration of national policy regarding biomedical research training, which resulted in a decline in the number of trainees supported. The original institutional grants (T01), which had been a mainstay of the establishment of graduate training programs throughout the country, were phased out. This mode of support had been quite successful in providing continuity in academic personnel. In 1969, a survey of the outcome of extramural training programs showed that approximately 40 percent of trainees supported by postdoctoral fellowships had entered academic positions. Even at that time, it was evident that the trainees supplied by these programs would be insufficient to meet future needs. A survey of U.S. medical schools in 1973 revealed that even current needs were not being met; unfilled faculty positions amounted to 144 in cardiovascular medicine, 25 in pediatric cardiology, and 84 in cardiovascular surgery. Projections of future requirements by 96 medical centers recognized a need for 500 additional positions in cardiovascular medicine, 175 in pediatric cardiology, and 425 in cardiovascular surgery. A study of the training manpower requirements for the specialist in adult cardiovascular disease conducted by the American College of Cardiology from 1971 to 1973 and supported by the then National Heart and Lung Institute found that, of the 329 clinical cardiovascular training programs that existed in the United States, 29 percent had an average of 2 unfilled staff positions. These numbers represented a shortage of 175 to 200 academic cardiologists.

Program Goals Through 1982

The National Heart, Blood Vessel, Lung, and Blood Act of 1972 also called for a National Program that would eliminate heart and blood vessel diseases as significant causes of disability and death. In compliance with this provision, the Institute defined the nation's problems in heart and blood vessel diseases, assessed the state of the science, defined national needs, and developed recommendations. The ten major areas in heart and blood vessel

diseases, which are discussed in this volume, were identified: arteriosclerosis, hypertension, cerebrovascular disease, coronary heart disease, peripheral vascular disease, arrhythmias, heart failure and shock, congenital and rheumatic heart disease, cardiomyopathy and infections of the heart, and circulatory assistance. Program goals, opportunities and needs, and research activities were identified for each of the National Program areas.

It was recognized that skilled investigators were an essential part of the planned national effort and that an expanding pool would be required to conduct the needed research and to replace skilled specialists lost through attrition. To this end, the recruitment and training of talented young scientists in the numbers needed in specific disciplines were accepted as key goals. Continued assessment of the number and distribution of investigators, as well as of projected needs, was considered essential in the pursuit of these goals.

Ongoing monitoring of grant applications and reviews yielded evidence of specific personnel shortages and needs relative to current and planned activities in research, prevention, and control. Needs for behavioral scientists with expertise in learning, motivation, and compliance were identified in connection with the Specialized Centers of Research in Arteriosclerosis and in Hypertension, the Myocardial Infarction Research Units, and many collaborative clinical trials. Ongoing and planned research in circulatory pathophysiology was found to suffer from a shortage of experts in the microcirculation. Specialized Centers of Research in Arteriosclerosis also suffered from a shortage of biomedical engineers familiar with cardiovascular pathophysiology and of cardiologists with a background in engineering to work jointly in these disciplines--for example, to improve noninvasive diagnostic instrumentation. Progress in population studies of lipid metabolism, hypertension, and congenital heart disease in children and adults was hampered by a lack of experts in population genetics. Other identified needs included biophysicists, immunologists, endocrinologists, nutritionists, and experts in blood coagulation and thrombosis. The training of an additional 322 individuals in these fields was declared a goal in 1974. At that time, an urgent need for additional clinical investigators was also recognized as well as a need for academic cardiologists with responsibilities to train academicians, practicing cardiologists, internists, generalists, pediatricians, and surgeons.

A critical shortage of epidemiologists and biostatisticians became evident in connection with several of the newer Institute-supported programs such as the Specialized Centers of Research, the Lipid Research Clinics, and other clinical trials. In 1971, a shortage of 72 epidemiologists and 40 biostatisticians was estimated in the cardiovascular area.

The phasing out of the original training grants (T01), which was begun in 1973, was completed in 1978. A nadir of 565 postdoctoral trainees supported in 1973 resulted (down from 765 in 1972). The dependency of the Institute's programs upon the availability of well-trained research scientists and academic clinicians became evident and eventually led to the establishment of two new training programs, the institutional research fellowship programs (T32) and the individual research fellowships (F22, later F32). In contrast to earlier mechanisms, these programs were for areas of documented or anticipated needs, especially for epidemiologists, biostatisticians, nutritionists, behavioral scientists, geneticists, and pathologists.

Accomplishments Through 1982

To the extent permitted by authorization and appropriations, the Division has planned and implemented programs of development and maintenance of skilled research personnel in specific categories addressed by the National Program. Ongoing estimates of training needs have been based upon:

- The number of research investigators needed for the maintenance of selected, critical research activities.
- The number of trained investigators needed to fill budgeted faculty vacancies directly related to the mission of the Division.
- The particular talents, disciplines, or areas that require additional scientists to implement the National Program.

The decade was initially beset by interruptions to orderly planning and implementation of training. In January 1973, the administration announced a phaseout of NIH research training programs. In November 1973, a new postdoctoral program of individual fellowships (F22--100 awards) was announced, only to be replaced in July 1974 by the National Research Service Award Act (NRSA T32 and F32). The uncertainties inherent in such major changes contributed to disincentives among potential biomedical research scientists.

Research training awards (F22 and T22), with emphasis on specific areas of need, were reintroduced in fiscal year 1974. They were replaced by national research service awards (NRSA), which were designed to support individual postdoctoral fellows (F32) in specific areas of biomedical and behavioral research in which a documented need for trained personnel existed. From fiscal year 1975 through fiscal year 1981, 909 such awards were made through the Division. At the same time, national research

service awards for institutional research training (NRSA institutional or T32) were established for eligible institutions to develop or enhance research training opportunities for individuals interested in specific areas of biomedical and behavioral research. From fiscal year 1975 through fiscal year 1981, the Division supported 1,117 predoctoral and 2,715 postdoctoral positions in this program.

A minority hypertension research development summer program (T35S) was initiated in 1977. This program enables minority school faculty members and graduate students to develop research skills in areas related to hypertension at institutions that have demonstrated excellence in that field. The goals of the program are to encourage the recruitment and development of individuals in hypertension research, prevention, control, and education. To date, 241 individuals have been supported in this program.

More recently, in 1980, a new program--the national research service awards for short-term training: students in health professional schools (T35)--was made available. This program addresses the disturbing decline in the number of students in health professional schools who are interested in biomedical and behavioral research careers. Seventeen of these multidisciplinary awards have been made to institutions, permitting 4 to 32 students per year in each institution to be selected for a research experience of up to 3 months.

Other training and development programs have been pursued in relation to the Division mission. These programs were planned and tailored to specific research requirements and opportunities. As a result, career development programs are considered as research activities rather than training programs and are, accordingly, supported by research funds. Such programs include the following:

- The research career development awards (RCDA) program (K04), an NIH-wide program begun in 1963, supports individuals with outstanding research potential who require additional training and experience in a productive scientific environment in preparation for a career of independent research. From fiscal year 1972 through fiscal year 1981, the Division funded 144 scientists with 5-year awards through this mechanism.

- A young investigator research grant program in heart and vascular disease areas was established in 1976 to encourage research in basic science and clinical disciplines, to enable young scientists and physicians to explore their developing research interests, and to provide young investigators with modest support for a project of their own design. Since then, 184 young investigators have been supported under this program by the Division. The program

has been incorporated within the NIH new investigator research awards program (R23).

- A clinical investigator award (K08) was made available in 1980 to encourage newly trained clinicians to develop basic and clinical research interests and skills in the areas of cardiovascular, pulmonary, and blood diseases and blood resources, and to increase the pool of physician investigators in these areas. These awards provide the opportunity for clinicians with a commitment to research to develop into independent biomedical research investigators. Twenty-five such awards of 5 years' duration have been made in the area of cardiovascular diseases.

- Under the minority biomedical research support program (S06), which is managed by the NIH Division of Research Resources, 297 individuals have been supported in the area of heart and vascular diseases since the Institute began its participation in 1976.

- In 1978, the NHLBI and the then National Institute of Arthritis, Metabolism, and Digestive Diseases (NIAMD) jointly established a special emphasis research career award (SERCA or K01) in diabetes mellitus (cardiovascular, metabolic, and endocrinologic aspects). This award provides the opportunity for a young clinician with developing research interests to acquire experience and skills in the broad fundamental and clinical scientific disciplines essential for a multidisciplinary approach to the study of the metabolic, endocrinologic, and cardiovascular aspects of diabetes mellitus. The SERCA emphasizes in-depth experience in several fundamental and clinical scientific disciplines that are not dependent upon a single laboratory or institution. The Division has supported 8 of the 15 individuals receiving such awards.

- The latest innovation--the preventive cardiology academic award (K07)--was established in July 1978 to support a specialized faculty member in a school of medicine or osteopathy. This award is intended to:

  - Encourage the development of high-quality preventive cardiology curricula that will attract outstanding students to research and practice in the field of preventive cardiology.

  - Develop superior faculty who have a major commitment to and possess skills for teaching, research, and practice of preventive cardiology.

- Develop institutional ability to strengthen continuously the improved cardiology curriculum with local funds subsequent to the award.

To date, 14 individuals have received this award.

State of Research Training and Development in 1982

The progress in cardiovascular research over the past decade is impressive. More and more scientific disciplines are being involved in this pursuit, and many research programs have become interdisciplinary. Scientists trained in fields such as molecular biology, genetics, immunology, physics, engineering, computer sciences, nuclear medicine, biostatistics, epidemiology, and behavioral sciences have become primary investigators, collaborators, and consultants in cardiovascular research. This development, along with increasing technological developments in the fields more traditionally identified with cardiovascular research, has been associated with an increasing participation of PhD's in cardiovascular research. This increase has been offset by a concurrent significant and progressive decrease in the number of physicians engaged in cardiovascular research. (Pertinent data on the distribution of heart and vascular disease research trainees, by type, over the past decade are displayed in figures 17 through 20). For the academic year 1980-1981, the Division awarded 358 postdoctoral traineeships and fellowships to holders of the PhD degree and 291 awards to holders of the MD degree or of both the MD and PhD degrees. In comparison, the figures for 1972-1973 were 212 and 630 awards, respectively. This development represents not only a 23 percent decrease in total awards but also a disproportionate decrease of 54 percent in professional trainee awards.

In the 1978 National Research Council Report of the Commission on Human Resources, the Committee on a Study of National Needs for Biomedical and Behavioral Research Personnel identified, among the underlying factors partially responsible for this decline in MD trainees, limited opportunities and funds for research experience in the medical curriculum and during residency training, financial and other career disincentives, negative feedback from accumulated educational debts and prospect of further indebtedness, and uncertain availability of research funds. To these factors must be added the demand for institutionally based cardiologists to deal with increasingly complex diagnostic and therapeutic modalities--that is, positions that offer competitive intellectual, social, and financial rewards.

Of concern also is the decrease from 842 (fiscal year 1972) to 649 (fiscal year 1979) in the postdoctoral fellows and trainees

supported by the Division. The greatest decreases were in clinical cardiology (410 to 173), cardiovascular bioengineering (51 to 13), and cardiovascular pathology (49 to 15). These personnel needs remain unfilled.

The following paragraphs summarize the state of research training in several areas of interest to the Division, including arteriosclerosis and lipid metabolism, hypertension, cardiovascular epidemiology and biostatistics, cardiovascular surgery, behavioral medicine and preventive cardiology, cardiovascular disease in the young, cardiovascular biomedical engineering, cardiovascular physiology and pharmacology, and cardiovascular imaging.

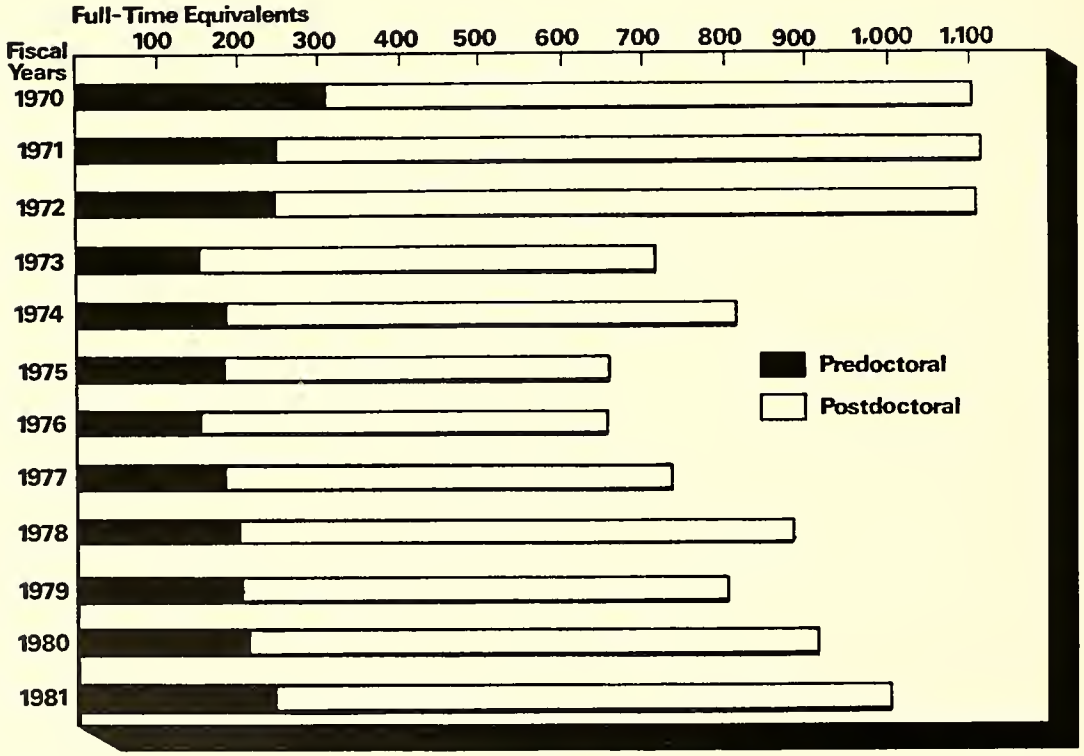


Figure 17. Number of Full-Time Training Positions Supported by the DHVD

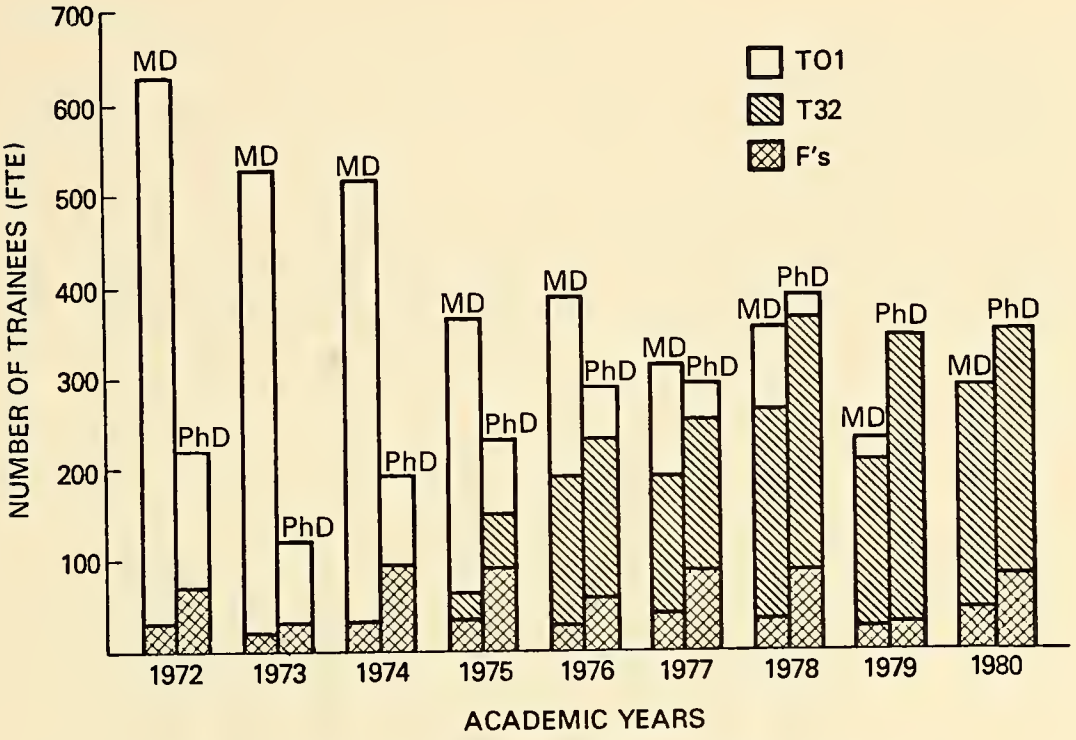


Figure 18. Postdoctoral Traineeships and Fellowships of the DHVD (Awarded) by Academic Year (7/1 to 6/30) and by Degree

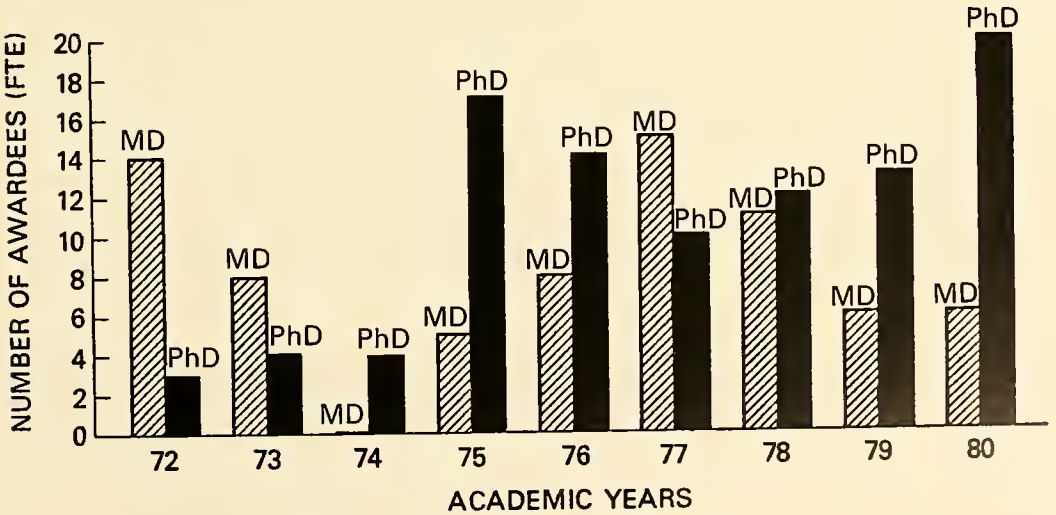
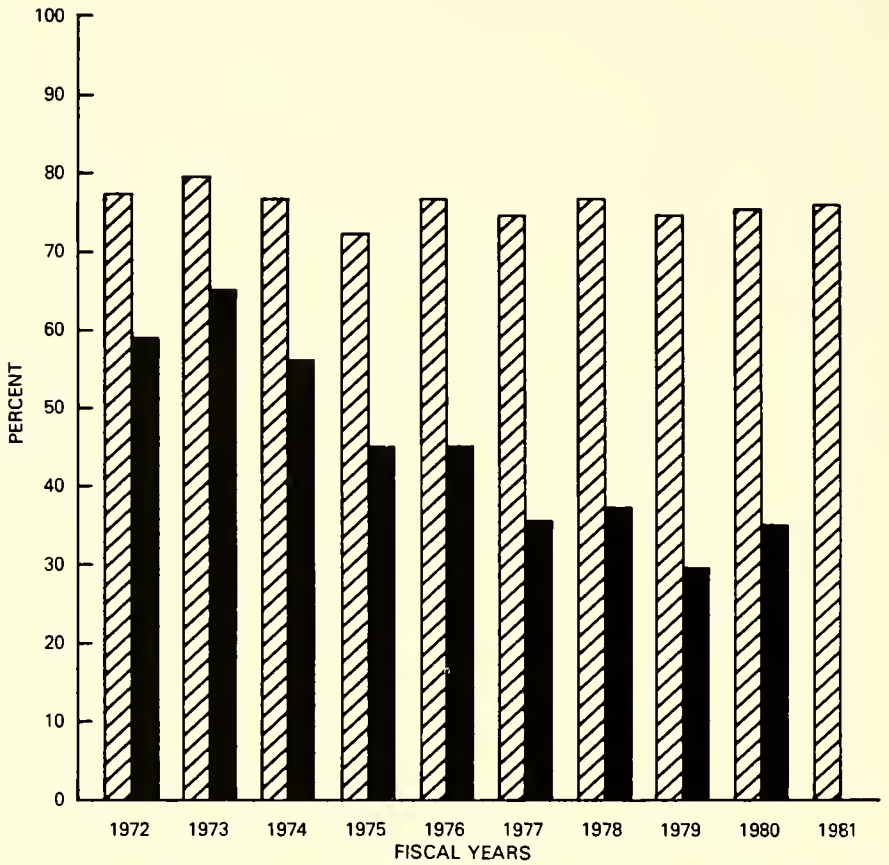


Figure 19. New Research Career Development Awards of the DHVD by Academic Year and Degree



	1972	1973	1974	1975	1976	1977	1978	1979	1980	1981
Percentage of Grantees Who Hold the PhD	78	79	77	72	77	74	77	74	75	76
Percentage of Grantees Who Hold the MD or the MD and the PhD	59	64	56	44	45	35	37	29	34	—
MD's as a Percent of PhD Grantees	75	81	73	61	58	47	48	39	45	—

Figure 20. Distribution of Postdoctoral Trainees and Fellows Supported by the DHVD and Percentage of MD's in Cardiovascular Research by Year

Arteriosclerosis and Lipid Metabolism

It is evident from the progress of research and research training from 1972 to 1982 that the rapid increase of fundamental knowledge about arteriosclerosis requires a cadre of scientists with very different types of training than was the case in 1972. Especially needed are basic scientists in the fields of pathobiology, lipid or lipoprotein biochemistry, physics, immunology, and biophysics. Also, in view of new concepts and new approaches of molecular biology, it is anticipated that many new scientists will be needed to explore the use of genetic mechanisms as a means of modifying the rate of development of atherogenesis. At the beginning of the 1980's, there was recognition of a rapidly growing deficit of medical scientists with basic science training who are interested in, trained for, and ready to enter a career of research in atherosclerosis and lipid metabolism.

A recent analysis of the numbers in training indicates that there may be as few as 161 full-time training positions directly related to atherogenesis and lipid-lipoprotein-cholesterol research, with much of the shortfall due to fewer physician scientists entering the field.

The following areas in need of research scientists should receive special attention. Most were identified by the NHLBI Working Group on Arteriosclerosis in 1981.

- Medical scientists with a primary interest in the cellular and molecular biology of atherogenesis.
- Biochemists for studies of lipid and lipoprotein metabolism and the metabolism of the artery wall.
- Laboratory investigators for studies of tissue metabolism and regional blood flow during atherosclerosis-induced impairment of circulation of heart, brain, and limbs.
- Clinical scientists (physicians) in all fields, with emphasis on cerebrovascular and peripheral vascular diseases.
- Geneticists for studies of the genetic substrate of atherosclerosis.
- Epidemiologists and biostatisticians for research surveys and new clinical investigations, and for trials in the atherosclerosis area.
- Behavioral scientists to study the social, psychosocial, and behavioral mechanisms influencing the basic process of atherosclerosis, the behavioral procedures needed

for clinical treatment and rehabilitation, and the social influences that are important in preventing arteriosclerosis.

- Pathologists with a primary interest in the pathogenesis of atherosclerosis in human subjects and experimental animals.

- Biomedical engineers with expertise in cardiovascular pathophysiology to improve and accelerate the development of noninvasive diagnostic instrumentation and to increase its quantitative potential to measure lesions sequentially.

- Investigators with specialized training in endocrinology and metabolism to study the complex interactions among atherosclerosis, diabetes, and other hormonal aberrations.

- Pediatric cardiologists and other clinical scientists who are knowledgeable in nutrition and growth, metabolic factors, and development to study the origin of adult risk factors and how they can be modified.

- Investigators with knowledge of blood coagulation to study the relationship of thrombus formation to atherogenesis and to the complications of atherogenesis as they affect the heart, brain, and lower extremities.

Hypertension

Research training in the basic science of hypertension has been undertaken by physiologists, biochemists, biophysicists, and pharmacologists. Training in clinical investigation has been generally undertaken by internists or pediatricians with subspecialty expertise in cardiology, nephrology, endocrinology, or clinical pharmacology. More recently, the necessity of interdisciplinary research and training has been appreciated. It is difficult, however, to project numbers of research personnel needed because of the limited data available on which to base projections.

Areas of multidisciplinary research identified as offering various needs and opportunities in hypertension include: neural control of the circulation and hypertension; vascular smooth muscle and hypertension; local and systemic hemodynamics; the renin-angiotensin, prostaglandin, and kallikrein-kinin systems; genetics; and pediatrics.

Cardiovascular Epidemiology and Biostatistics

In 1974, the Institute estimated that there were about 175 cardiovascular epidemiologists in the United States. About one-third of this group were nonphysicians, and only about one-third of the physicians had formal training in epidemiology. A shortage of such personnel was already apparent, and it was intensified by the emergence of large-scale multicenter studies and clinical investigations. It was estimated that no more than 8 or 10 cardiovascular epidemiologists were produced each year by schools of public health. An immediate need was seen for at least 72 cardiovascular epidemiologists. Similar needs for biostatisticians were cited. To remedy the situation, a survey by the National Institute of General Medical Sciences concluded that about 15 to 20 new epidemiologists per year and a similar number of biostatisticians were needed for the Nation's cardiovascular research programs.

A recent summary of the present status of Division-funded cardiovascular epidemiology and biostatistics training programs shows that there are 10 programs in epidemiology (4 of these programs also involve biostatistics) and 5 programs in biostatistics. In 1980-1981, there were 18 postdoctoral and 14 predoctoral students enrolled in the epidemiology program, and 6 postdoctoral and 18 predoctoral students enrolled in the biostatistics program. There is still difficulty filling postdoctoral training programs in epidemiology, but postdoctoral training programs in biostatistics and predoctoral programs in both areas are virtually full.

The estimates on the current number and the identified need for independent researchers in the fields of epidemiology and biostatistics indicate that it may be necessary to double the number of epidemiologists and biostatisticians within 5 years and then to replace these scientists at the rate of 7 percent, or about 30 new persons per year.

Cardiovascular Surgery

The era of open-heart surgery began in the 1950's with the development of heart-lung machines, first employed successfully in the treatment of congenital heart disease. This was followed in the 1960's by the development of artificial heart valves and the use of homografts and xenografts for replacement of diseased mitral and aortic valves. Methods for surgical treatment of coronary artery disease followed, and they were accompanied by widespread use of coronary bypass surgery. Research on myocardial preservation with various forms of cardioplegia was prevalent in the 1970's, and it continues at present. Cardiac transplantation has been used successfully in a few centers in the United States.

Circulatory assist systems, especially balloon assist devices, are also in wide use.

Despite a clear need for research training, support for trainees came primarily from mechanisms other than training grants. These mechanisms included research and program project grants, fellowships, and contracts. Moreover, during the last 25 years, this training of cardiovascular surgeons has been primarily in the setting of clinical practice. A real need exists for cardiovascular surgeons trained to conduct research in cardiovascular physiology and pharmacology, bioengineering, methodology of clinical trials, experimental design, biostatistics, biophysics, and molecular cardiology and immunology.

An important area that has received little attention is peripheral vascular disease, for which more research personnel are needed to extend scientific and methodological advances to improve understanding and control.

Behavioral Medicine and Preventive Cardiology

The special need for training more behavioral scientists with expertise in the cardiovascular area remains acute in the early 1980's. The first of the institutional training grants in behavioral medicine was awarded in 1975, and by 1981 the number grew to 10. Currently, the Division has 23 predoctoral and 33 postdoctoral trainees supported by institutional training grants and 2 postdoctoral students supported by individual fellowships, for a total of 58 trainees in DHVD-supported behavioral science and other biomedical science areas related to its interest.

Many other such trainees are apparently being supported for careers in areas of interest to the Division by other mechanisms (for example, by university fellowships, loans, private foundations), but the numbers of such trainees are unknown. The existing cadre of NHLBI predoctoral and postdoctoral trainees in the behavioral sciences may not be adequate to meet future needs.

A second source of research personnel to help meet the needs of the Division will continue to be the pool of established and mature investigators in the various behavioral sciences, who, as in the past decade, will continue to be attracted to research in the cardiovascular area.

The third and potentially most valuable source of research scientists that will help the Division meet its needs is the large supply of students from many behavioral sciences who are currently in predoctoral and postdoctoral programs not directly related to the interests of the NHLBI. The experience of academic leaders

and of DHVD-supported training program directors during the past 5 years indicates that many students now in training could be induced to transfer into areas of interest to the Division if the number of NHLBI predoctoral and postdoctoral traineeships in the behavioral sciences could be increased.

Cardiovascular Disease in the Young

In 1970, 244 pediatric cardiologists were identified in the United States, and at that time there were 103 unfilled positions. In the same year, 6 percent of the effort of these pediatric cardiologists was devoted to research. The limited amount of time devoted to research could be attributed to the shortage of pediatric cardiologists. Also in 1970, the goal of most training programs was the training of clinicians. A lack of facilities in pediatric departments also limited research opportunities.

During the 1970's, a number of fields of research were identified and research training began in the fields of normal and abnormal cardiovascular physiology of the fetus, electrophysiology of the conduction system, noninvasive methods of evaluating the circulation, followup of corrected congenital heart disease, and preventive cardiology.

It is currently estimated that 25 percent of pediatric cardiologists now spend 50 percent or more of effort in basic or clinical investigation. This change can be attributed to the recognition that a track for research training of pediatric cardiologists during their formative years is essential. Also shown in this trend is a recognition of the importance of interdisciplinary training, including behavioral and educational research that addresses issues of modification of health habits of the young in an attempt to prevent disease.

Cardiovasular Biomedical Engineering

Four cardiovascular biomedical engineering training programs presently exist, which support 15 predoctoral and 17 postdoctoral trainees. Of the 17 postdoctoral trainees, 12 hold the MD and 5 hold the PhD. Training programs have been designed to produce investigators who can make significant contributions to four important areas of cardiovascular research: ultrasound, electrocardiography, microcirculation, and biomaterials.

Support for training in cardiovascular biomaterials was initiated in July of 1981 and seems particularly timely. Cardiovascular biomaterials research has increasingly emphasized the understanding of the physical and biological mechanisms that underlie tissue-material interactions. Some functional implants

place demands on intrinsic properties of materials that are as close to the limits of current technology as any other engineering application. For instance, the flex life expected of a polymer to be used in a long-term cardiac replacement device exceeds the specifications formulated for any other application.

The contributions of cardiovascular biomedical engineering trainees and their mentors from 1972 to 1982 are significant. The increasing application of the sophisticated technology used in computers, microprocessors, and digital instrumentation suggests a continuing demand for this training. The success of trainees in acquiring suitable academic positions indicates that there have been sufficient numbers of vacant academic positions to absorb biomedical engineering graduates. The present and projected shortage of engineering faculty and the highly promising developments in medical imaging suggest that increased emphasis on cardiovascular biomedical engineering training is justifiable.

Cardiovascular Physiology and Pharmacology

During the past decade, basic research in cardiovascular physiology and pharmacology has yielded significant contributions to understanding normal and abnormal states of the cardiac and vascular system. Training grants in cardiovascular physiology and pharmacology presently support 74 predoctoral and 114 postdoctoral trainees on 25 institutional training grants.

Training grants have produced the mature investigators who continue important research activities in cardiovascular physiology and pharmacology. Current trainees have also added many significant contributions to cardiovascular research. Trainees were the first authors of over 250, or 30 percent, of the approximately 800 cardiovascular physiology papers published in the 1980-1981 academic year from institutions that have cardiovascular physiology or pharmacology training grants.

The professional opportunities for trainees who are clinically qualified and who have completed these training programs are excellent; however, there is a growing shortage of clinical investigators. There are some indications that the number of predoctoral trainees for the PhD in cardiovascular physiology and pharmacology may exceed needs in the near future. It appears desirable to consider some mechanism for documentation of good professional opportunities for the PhD in cardiovascular physiology and pharmacology in the proposed area of training.

Cardiovascular Imaging

Between 1972 and 1982, significant accomplishments occurred in cardiovascular ultrasonic and nuclear imaging and in subtraction radiography. The advances in ultrasound research include the development of real-time B-mode ultrasonic scanners for the diagnosis of arteriosclerosis, the diagnosis of extracranial carotid artery occlusive disease, improved visualization of cross-sectional images of the heart for evaluating patients with ventricular wall dysfunction, aneurysms, and mural thrombi, and the development of diagnostic ultrasonic imaging techniques to evaluate patients with peripheral arterial occlusive disease.

Fourteen cardiovascular radiology trainees are presently supported by four DHVD training grants. All are physicians who have completed residency training. Further, 5 of the 32 trainees supported on cardiovascular biomedical engineering institutional training grants (discussed elsewhere) are engaged in cardiovascular ultrasound imaging research. Institutional training grants in departments of medicine also support ultrasound, radiographic, and nuclear imaging research.

The cardiovascular imaging accomplishments of the past decade, combined with several promising new imaging and image-enhancement modalities, suggest a considerable need for physicians trained in research techniques to evaluate, interpret, and improve these important sources of diagnostic information.

Program Goals 1982 to 1987

Research training and research career development programs of the Division have been instrumental in attracting outstanding scientists and in fostering the high level of scientific accomplishments in heart and vascular disease research. Continuation and expansion of such productive programs are considered essential for continued progress of heart and vascular disease research in the future. Program goals in research training and development are:

- Continue those research training and career development programs that have a demonstrated need and have been productive in providing the training of research scientists for advancement of heart and vascular diseases research.

- Continue to develop fellowship or training programs that attract outstanding young potential scientists into cardiovascular research careers to provide the leaders needed to enhance scientific progress in the future.

- Undertake programs at predoctoral years that attract the most gifted and motivated young individuals into biomedical research, and undertake additional programs in postdoctoral years directed to attracting creative young physician scientists into research in cardiovascular disease.

- Improve the research training capabilities, including multidisciplinary opportunities, in research training programs in order to provide the highest quality of training with the best qualified scientists and the finest research environment.

- Investigate the needs for research training in special discipline areas that may provide particular contributions in emerging areas of research so that new techniques in other fields are rapidly incorporated into research training in cardiovascular disease research.

Opportunities 1982 to 1987

A long period of time is required to train highly specialized research scientists. The major challenge to the research training and development program of the Division is to provide research personnel for the needs of tomorrow and thereby avoid limitation and delay of future research endeavors because of shortages of research scientists. Current and future cardiovascular research opportunities stipulate a need for specially trained personnel in numbers that greatly exceed current levels of activity. The national research service award, both institutional and individual, and all other current mechanisms will continue to be the mainstay of the training programs. Multidisciplinary training will be encouraged. New awards will be considered, as appropriate, to provide for the evolving needs of cardiovascular research. Key research training opportunities include:

- Training of scientists who combine basic knowledge of atherosclerosis as a disease process with specialized training in the physical chemistry of lipids, proteins, and cell membranes.

- Collaboration of clinically trained investigators who have knowledge of new advances in biology with biologists who have an understanding of the problems of atherosclerosis and hypertension.

- Training of biomedical scientists in the study of multiphase lipid-protein systems, lipoprotein synthesis, secretion, and metabolism, the interaction of lipoproteins

with plasma membranes and subcellular organelles, and the application of improved methodology and physical instrumentation.

- Training of research investigators in the fields of neurovascular and peripheral vascular research.

- Training of epidemiologists and biostatisticians to study the clinical problems associated with heart and vascular disease.

- Training of highly skilled behavioral research scientists with an emphasis on interdisciplinary research that will allow them to work efficiently in cardiovascular health research.

- Increase in support for institutional and individual training in pediatric cardiology research in order to maintain and enhance the present quality of research.

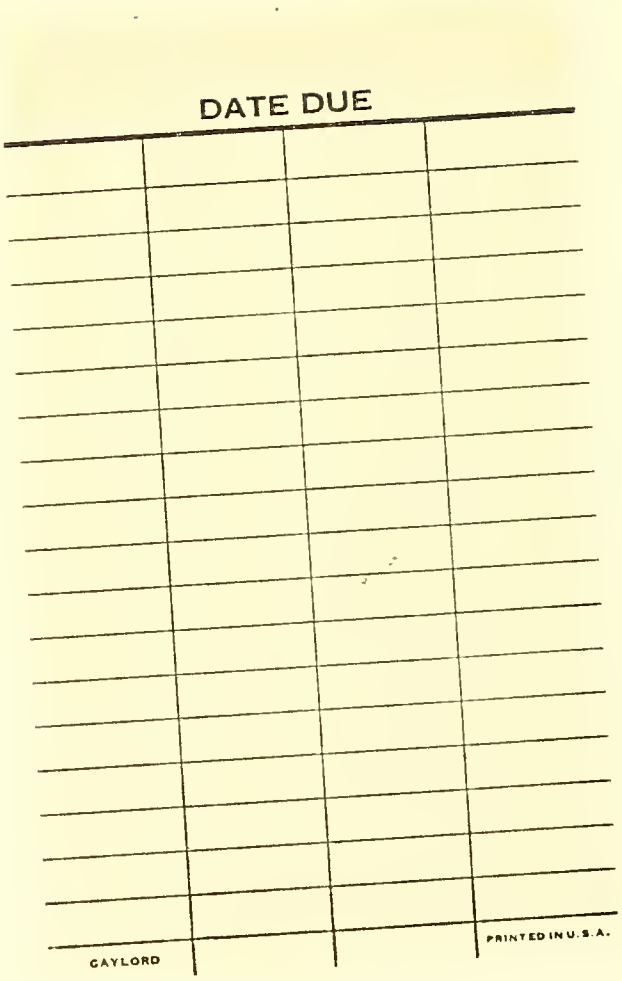
- Continuation of emphasis on biomedical engineering training to assure the availability of the highly trained personnel required for the development and effective utilization of this advanced technology.

- Increase in emphasis on research training in the basic understanding of cardiovascular function and in the importance of utilizing this understanding in diagnosis and in use of pharmacologic therapy.

- Fostering training opportunities in modern experimental cardiovascular pathology.

- Training of clinically qualified investigators who have the competence to develop, evaluate, interpret, validate, and improve cardiovascular imaging modalities and processes.

- Training in the field of nutritional sciences, especially as it applies to the regression and prevention of atherosclerosis.



Ten-Year Review and Five-Year Plan

National Heart, Lung, and Blood Institute

Volume 1. Progress and Promise
NIH Publication No. 84-2356

Volume 2. Heart and Vascular Diseases
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Volume 3. Lung Diseases
NIH Publication No. 84-2358

Volume 4. Blood Diseases and Resources
NIH Publication No. 84-2359

Volume 5. Companion Issues
NIH Publication No. 84-2360

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