Ninth Report of the National Heart, Lung, and Blood Advisory Council

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
National Institutes of Health

Ninth Report of the National Heart, Lung, and Blood Advisory Council

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
National Institutes of Health

NIH Publication No. 81-2334
September 1981

National Heart, Lung, and Blood Advisory Council.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
Bethesda, Maryland 20205

September 24, 1981

The President
The White House
Washington, D.C.

Dear Mr. President:

The members of the National Heart, Lung, and Blood Advisory Council are pleased to submit to you, and to the Congress, our ninth report on the progress of the National Heart, Lung, and Blood Institute's efforts to control and prevent diseases of the heart, blood vessels, lungs, and blood. The report has been prepared in accordance with Section 418 of the Public Health Service Act.

In forwarding this report, we wish to thank you for the opportunity to serve you, the Congress, and the Institute, and the people of this country and throughout the world who benefit from the programs the Institute sponsors.

Respectfully yours,

The National Heart, Lung, and
Blood Advisory Council

National Heart, Lung, and Blood Advisory Council

Arthur R. Ashe, Jr.
Washington, D.C.

J. David Bristow, M.D.
University of Oregon Health Sciences Center
Portland, Oregon

Dorothy L. Brown, M.D.
Meharry Medical College
Nashville, Tennessee

Celia J. Flinn, M.D.
University of Miami
Miami, Florida

Peter C. Gazes, M.D.
Medical University of South Carolina
Charleston, South Carolina

Roberta M. Goldring, M.D.
New York University
New York, New York

Oscar Gonzales
First Interstate Bank of Arizona
Tucson, Arizona

Maryl R. Johnson, M.D.
University of Iowa
Iowa City, Iowa

Howard E. Morgan, M.D.
The Pennsylvania State University
Hershey, Pennsylvania

Louise M. Nett, R.N.
University of Colorado
Denver, Colorado

Alan K. Pierce, M.D.
University of Texas
Dallas, Texas

Harold R. Roberts, M.D.
University of North Carolina
Chapel Hill, North Carolina

John Ross, Jr., M.D.
University of California, San Diego
La Jolla, California

Russell Ross, Ph.D.
University of Washington
Seattle, Washington

Jeremiah Stamler, M.D.
Northwestern University
Chicago, Illinois

Douglas M. Surgenor, Ph.D.
Northeast Regional Red Cross Blood Program
Needham, Massachusetts

Doris F. Tulcin
Cystic Fibrosis Foundation
Rockville, Maryland

Vallee L. Willman, M.D.
St. Louis University
St. Louis, Missouri

Robert I. Levy, M.D. (Chairman)*
Director
National Heart, Lung, and Blood Institute
National Institutes of Health
Bethesda, Maryland

Ex Officio

William P. Baker, M.D., Ph.D.
National Naval Medical Center
Bethesda, Maryland

Thomas F. Newcomb, M.D.
Audie L. Murphy Veterans Administration Hospital
San Antonio, Texas

Denis J. Prager, Ph.D.
Office of Science and Technology Policy
Washington, D.C.

Thomas E. Malone, Ph.D.*
Acting Director
National Institutes of Health
Bethesda, Maryland

Richard S. Schweiker*
Secretary
Department of Health and Human Services
Washington, D.C.

*Did not participate in the preparation of this report.

Contents

Introduction

A major advance in the treatment of serious illness is less often a sudden "breakthrough" than is commonly believed. Rather, important progress is often based upon knowledge provided from work that has systematically gone on before. Following this principle, the advisory council of the National Heart, Lung, and Blood Institute (NHLBI) describes in this year's report basic and clinical research which has resulted in recent improvements in health care. NHLBI-sponsored progress in the management of one prototype illness for each of the three divisions of the Institute—heart, lung, and blood—is presented. We outline research which has permitted these advances in the care of important clinical problems. The relationship of research information to improved health care is the major theme developed.

At the end of each section, a brief summary of other areas of interest is presented.

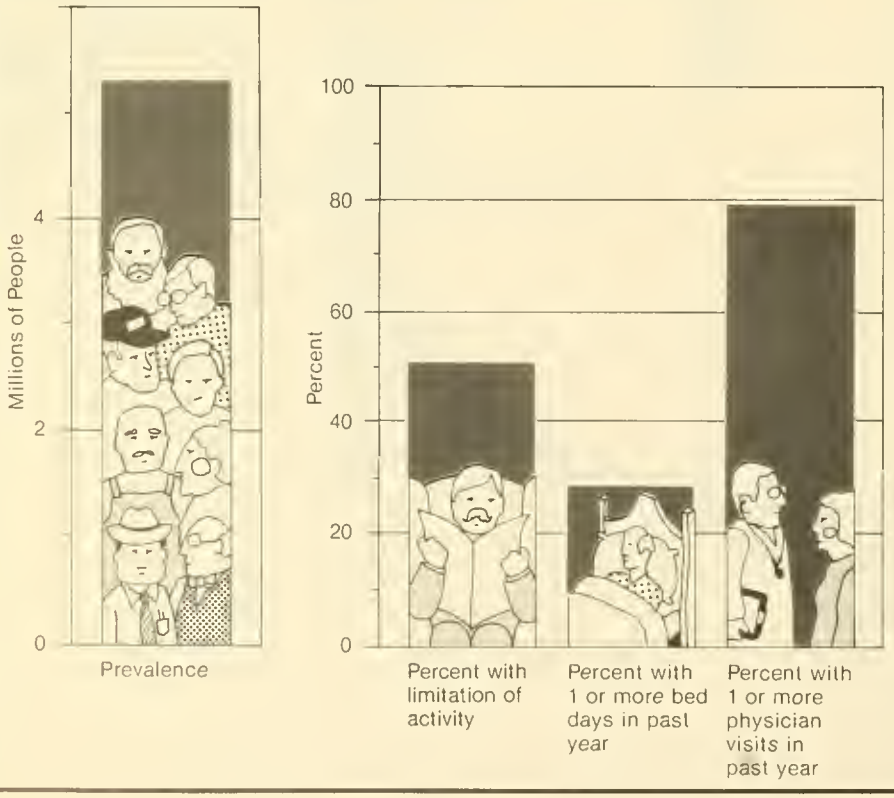
Heart and Vascular Diseases

Many thousands are debilitated by coronary heart disease in the United States each year. (Data from the National Center for Health Statistics)

Despite a substantial decline in mortality in recent years, cardiovascular diseases still account for more than half of all deaths in the United States, numbering about 968,000 in 1979. Over 200,000 of these deaths happened before age 65 and another 200,000 between 65 and the average life expectancy of 69 for men and 77 for women. These premature deaths amount to 12 million potential years of life lost each year.

In 1979 there were more than 550,000 deaths from coronary artery heart disease, the most common form of cardiac disorder, accounting for more than half of all the deaths from cardiovascular disease. In addition to the incalculable toll of human suffering, there are huge economic consequences of heart disease. For example, about 5 million hospitalizations per year are the result of cardiovascular disease in our country, and at least 40 percent of these are due to coronary artery disease.

Estimated Total Number of People with Coronary Heart Disease in the United States (1979)



Coronary artery disease (ischemic heart disease) is the predominant form of heart disease, causing as many as 1.5 million heart attacks each year, and affecting 5 million persons in the Nation. This portion of the report of the NHLBI Advisory Council is focused on recent advances in the surgical treatment of this disorder.

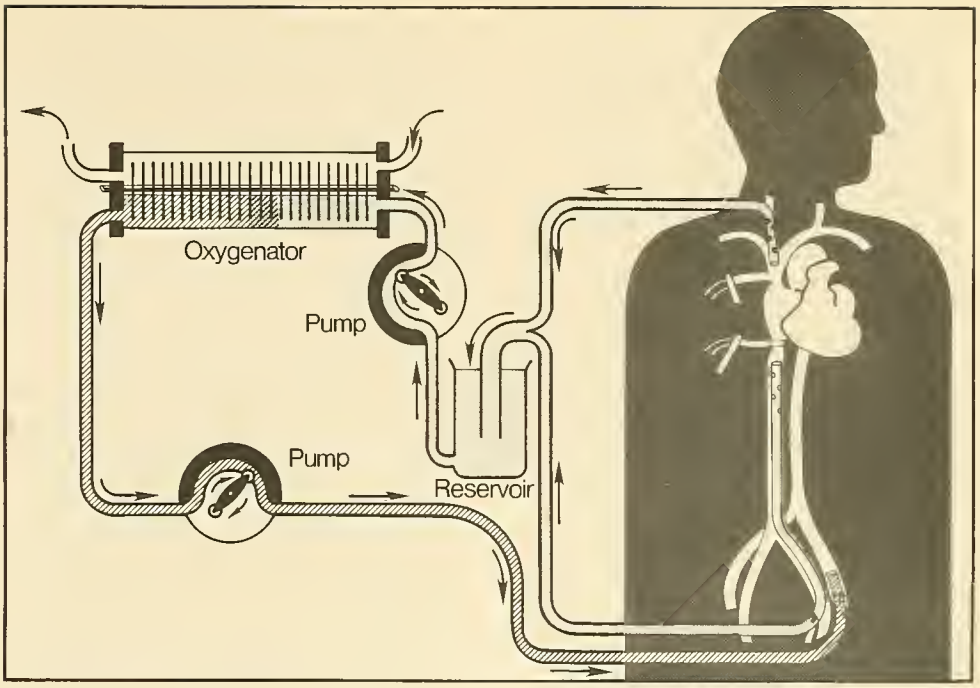
Coronary Artery Bypass Graft Surgery

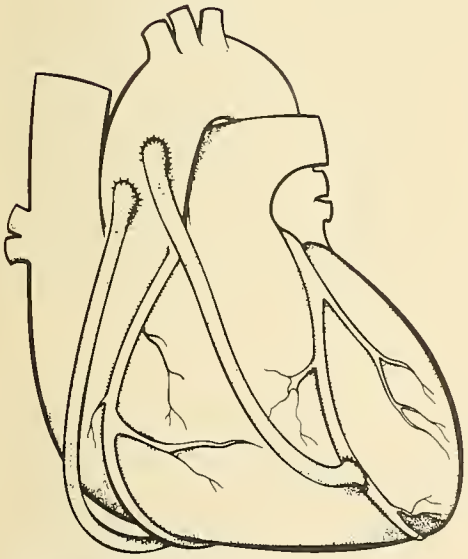
Coronary artery bypass graft surgery is one of the most dramatic advances in the care of problems produced by arteriosclerosis, or hardening, of the coronary arteries. The operation's record in improving physical activity, preventing chest pain, and enhancing a sense of well-being in sufferers of coronary artery disease has been striking, and the operation has received wide application throughout the country. It is estimated that over 100,000 coronary artery bypass operations are now performed each year. In the 13-year history of this procedure, there has been progressive improvement in its results and safety.

The coronary arteries supply the heart muscle with blood. Coronary artery atherosclerosis (arteriosclerosis) is a buildup or deposit in the inner lining of these arteries. The deposits, referred to as plaques, contain lipids and cells, and a blood clot sometimes forms on the surface. These plaques prevent a normal amount of blood from getting to the heart muscle, a problem known as ischemia. In huge numbers of Americans the arterial narrowings caused by atherosclerosis produce disabling cardiac symptoms. For example, angina pectoris is chest pain provoked by physical effort, and is the commonest symptom and the most frequent cause of disability from this disease. Heart attacks, heart failure, and cardiac arrest are also common results of coronary artery atherosclerosis. Some of these problems have been radically changed by coronary bypass surgery.

The surgical principle in coronary grafting is a simple one. A leg vein is removed and one end is connected to the aorta, the main artery

During heart surgery, the patient's circulation is taken over by a heart-lung machine. This diagram of cardiopulmonary bypass shows how the blood is removed, externally oxygenated, and returned to the patient, facilitating surgery on the resting heart.





Schematic diagram of coronary artery bypass.

of circulation. The other end is connected to a coronary artery, to bypass a narrow region in that artery. This grafted vein serves as a detour, to establish more normal coronary blood flow. During the operation, the patient's circulation is supported by a heart-lung machine, a process known as cardiopulmonary bypass.

Several important research developments in the past decade have produced better results for coronary bypass surgery. Operative mortality has decreased to about 1.5 percent, due to prevention of damage to the heart muscle during anesthesia and surgery and improvement in operative technique and postoperative care. Long-term results are also better because of a higher graft patency rate (prevention of closure of grafts) in the years following operation.

Improvements in Operative Technique and Postoperative Care

Prevention of heart muscle (myocardial) damage during induction of anesthesia. In the patient with coronary artery disease, the stress of surgery can lead to inadequate coronary blood flow (myocardial ischemia) and infarction or heart attack. Recognition of these dangers has led to the use of anesthetics that avoid excitement of the patient and of drugs to control blood pressure and heart rate.

Cardiopulmonary bypass techniques. A heart-lung machine takes over the circulation during most heart operations, in a procedure known as cardiopulmonary bypass. Among the improvements in cardiopulmonary bypass, one of the most important was the development of hypothermic (low-temperature) solutions to stop the heart. In addition to the advantage of improved myocardial protection, this technique allows the surgeon to operate in a clear, quiet surgical field and to retract the heart to obtain exposure, making the operation easier. In addition, the use of hypothermia associated with blood dilution (hemodilution) allows less damage to blood cells. Several studies have shown that hemodilution is associated with decreased use of blood products, decreasing transfusion risk for the patient and using less of this important resource.

Biomaterials. A great advance in biomaterials came in 1967 with the introduction of the disposable bubble-oxygenator for heart-lung machines. Before that, disc-oxygenators were used. They were time-consuming to maintain, and even though these oxygenators were thoroughly cleaned, foreign material could remain on the discs and cause postoperative fever.

Another improvement was the development of arterial filters. Studies demonstrated that aggregates of blood cells as well as particulate matter from the tubing were found in the pump circuit. With the removal of this microscopic debris, use of the heart-lung machine has become safer.

With increased awareness of clotting problems, blood use has been markedly reduced. It has been recognized that aspirin is an inhibitor of blood platelet function; stopping the use of aspirin before surgery has resulted in a decrease in postoperative bleeding. Also, the use of heparin as an anticoagulant during the bypass procedure was made safer by new methods for laboratory monitoring of heparin levels in the blood and other clotting tests. Transfusion need has also been reduced by improvement in salvage methods which retrieve the patient's own red blood cells from the surgical field and the retransfusion of these cells. In addition to conserving blood, the risk of hepatitis is decreased. These advances have resulted both from laboratory research and engineering progress.

Postoperative care. New methods for cardiac blood flow measurement have been perfected. Catheters that are easily "floated" into place are used to measure pressure in the cardiac chambers and blood flow during and after operations. Use of such catheters allows maximal cardiac function to be obtained by administering the optimal amount of blood or other intravenous fluids. Advances in biomaterials development have led to the availability of these tools.

The use of computerized monitoring also aids postoperative patient management. Postoperative trends can be followed and problems anticipated more precisely with this technique. The common use of cardiac pacing equipment facilitates the diagnosis of postoperative irregularities of the heartbeat, and also provides a means of maintaining the most appropriate heart rate for the patient.

An important improvement in postoperative lung function was the development of positive end-expiratory pressure as a method of improving oxygen delivery. By using this technique oxygenation is better maintained and the length of time the patient must receive breathing assistance on the ventilator after surgery is reduced. Recovery is speeded.

A significant advance in the care of the postoperative patient was the introduction of drugs to control blood pressure precisely. In the immediate postoperative period, resistance to blood flow in the body is increased in patients who have been perfused at low temperatures. The use of blood pressure reducing drugs decreases the work of the heart and prevents myocardial ischemia.

Heart muscle protection during surgery. Blood flow to the heart is interrupted during coronary bypass surgery and the body's circulation is provided by the heart-lung machine. For a time, the heart remains capable of essentially full recovery; the period during which interruption of blood flow can be safely tolerated depends upon the mechanical activity of the heart and its resultant demand for the remaining oxygen and energy reserves. Protection of the heart during surgery has involved decreasing its energy needs, providing materials for energy production, and protecting the cellular components in the heart muscle.

Therapy to protect the myocardium from damage during coronary bypass surgery has been predicated on basic studies of energy metabolism of the heart. These studies reveal that cardiac muscle has the highest rate of oxygen need and the largest extraction of oxygen from blood of any tissue in the body. The extraction of oxygen on a single passage of blood through the heart is about 70 percent compared with extraction of less than 10 percent for glucose or fatty acids. Therefore, oxygen supply is the first limitation to energy production when coronary blood flow is reduced, and energy production is essential to maintain cardiac function.

Reduced oxygen supply results in an undesirable cascade of events that eventually affect every metabolic and functional process of the heart. The detrimental factors include accumulation of breakdown products of glucose and fatty acid metabolism and loss of the pool of chemicals that serve to store energy within the heart cells. *One of the major advances in open heart surgery* in recent years has been prevention of cardiac energy depletion with "cardioplegic" solutions to preserve chemical energy levels and prevent waste accumulation during the period that coronary blood flow is stopped during the operation. The protection of the heart during coronary bypass surgery is one of the best examples of a practical use of detailed basic research to improve the results of surgery and to decrease deaths.

Improvements in graft patency. It is obviously important that coronary bypass grafts remain open (patent) and transporting blood. There has been a striking improvement in graft patency rates during the past decade. This improvement has been attributed to the use of new suture materials, as well as methods that allow the extremely delicate handling of the vein that will be used as the bypass conduit.

Effects of Coronary Bypass Surgery on Longevity

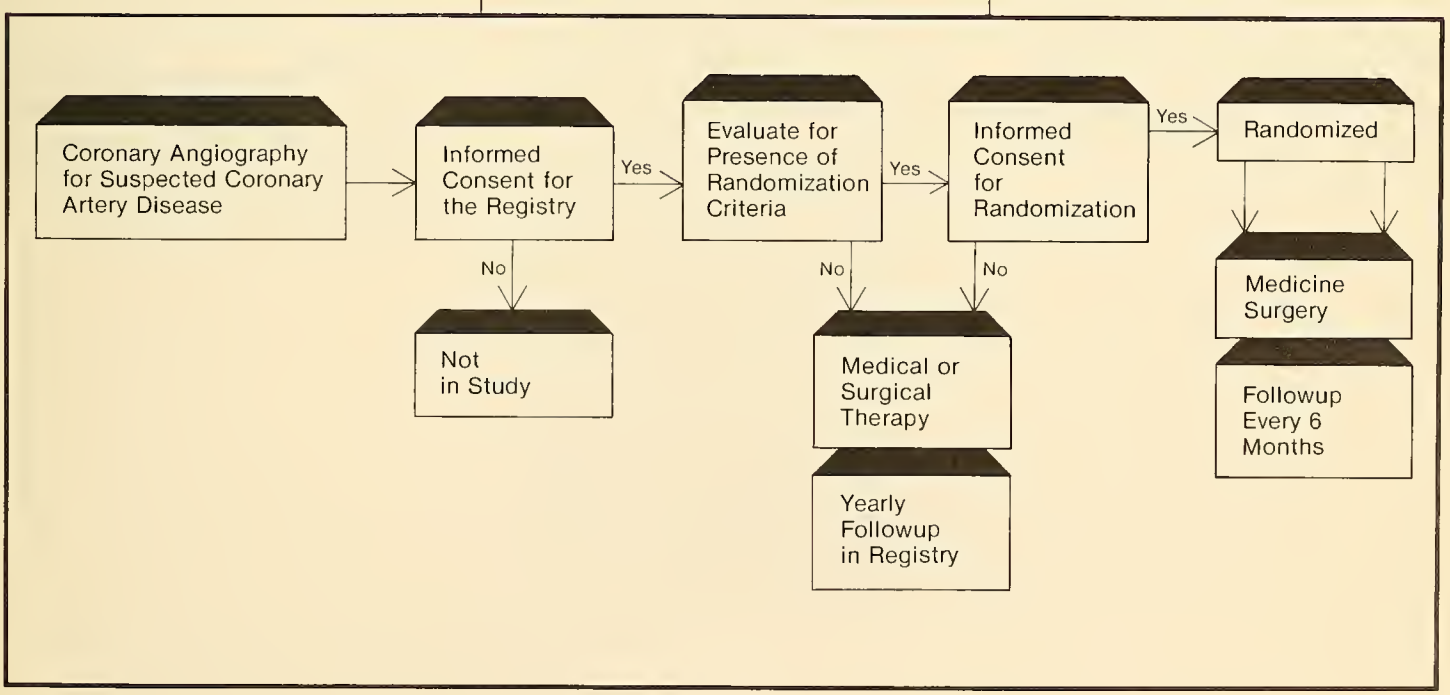
The effects of coronary bypass surgery in improving or abolishing symptoms of coronary disease in many patients are striking. In those whose coronary anatomy is suitable for surgery, disabling symptoms of chest pain with exertion or at rest are often dramatically improved. Another goal for the operation, however, is to prevent premature death. One particularly threatening situation is presented by atherosclerotic involvement of the left main coronary artery. Several studies have confirmed that the death rate in the first few years after recognition of this problem is cut substantially by coronary bypass surgery.

The disease, however, may involve the coronary arteries in other patterns that are highly variable from person to person. Thus there can be obstructions limited to one, two, or all three of the major coronary artery branch systems. The impact of the operation on increasing the survival of patients with these patterns of coronary disease has led to extensive debate. It is well-recognized that interpretation of results of treatment to prolong life expectancy in coronary disease is difficult, both for surgically treated and medically treated patients, as there have been improvements in both areas.

A limited number of randomized surgical trials and other studies of unoperated patients to assess the effects of surgery on long-term survival have led to conflicting results. It has been evident for some time that additional research is needed before a firm conclusion can be reached about improved survival in many of the patterns of coronary arterial involvement. This issue is especially important in those patients with known coronary disease whose symptoms are mild or absent. For these reasons, two clinical trials were undertaken with NHLBI sponsorship to define the value of coronary bypass surgery in extending life expectancy in these patient groups.

Coronary Artery Surgery Study

The Coronary Artery Surgery Study (CASS) is a prospective randomized trial designed to compare results of medical and surgical treatments in a well-defined group of patients with angiographically proven coronary artery disease. After 2 years of planning, CASS enrolled patients from 1974 through 1979 with followup to continue through May 1983. Three groups of patients were randomized: (a) patients with less than severely



Enrollment sequence for the NHLBI Coronary Artery Surgery Study.

disabling angina but normal cardiac function, (b) patients with less than severely disabling angina and reduced cardiac function, and (c) patients who had recovered from a heart attack (myocardial infarction). Those with severe angina pectoris were excluded from the study because coronary artery bypass surgery had already been shown to significantly improve the "quality of life" in this group. The randomization procedure was designed to equalize the number of patients with single-, double-, or triple-vessel coronary disease in the surgically and medically treated groups. Specific endpoints for followup include mortality, rate of myocardial infarction, and "quality of life." By the end of the enrollment period, 780 patients were randomized. In addition, a registry of consecutive patients undergoing coronary arteriography at the 15 participating sites in the United States and Canada was established. The purpose of the registry is to describe the natural history of the coronary artery disease and the choice of treatment in nonrandomized patients. By the end of the enrollment period, 24,959 patients had entered the registry. Results of the randomized trial will be available shortly after patient followup ends in May 1983. There are 15 clinical centers, a coordinating center, and a central laboratory for interpretation of electrocardiograms involved in the study. This project should provide important answers about the ability of coronary artery surgery to prolong life.

Unstable Angina Pectoris Trial

A syndrome suggesting impending myocardial infarction (heart attack) and characterized by a progressive increase in chest pain at rest or with minimal exertion has been recognized for decades and known as unstable angina pectoris. With the advent of coronary bypass surgery, patients with this symptom were considered in many centers to be candidates for emergency surgery. The goals of therapy for unstable angina, whether medical or surgical, are: (1) to prevent death, (2) to prevent myocardial infarction, (3) to relieve the patient of pain, and (4) to prolong useful life. If immediate bypass surgery is to be clearly justified, a reduction in myocardial infarction and early death must be demonstrated.

In order to provide a more reliable assessment of the efficacy of medical treatment as compared with coronary artery bypass graft surgery, the Unstable Angina Pectoris Trial was initiated in 1972 by the NHLBI. The extent of coronary vascular disease was defined by angiography so that similar patients could be compared. The results for the 288 patients entered into the randomized trial were first reported in early 1977, after all patients had had at least 1 year of followup since entry; their long-term results are still being followed. During the total study period, the hospital mortality for the surgical and medical groups was not significantly different.

The results of the Unstable Angina Pectoris Trial indicate that patients with this threatening syndrome can be managed in the emergency setting with intensive medical therapy, including the administration of drugs such as propranolol and nitrates. This vigorous medical approach will achieve adequate control of pain in most cases with no increase in early mortality or heart attack rates. Later, elective surgery can be more safely performed with low risk and good clinical results if the angina fails to respond to the intensive medical therapy.

Coronary artery bypass graft surgery has become the major treatment for many patients with coronary artery disease. The operation's record of safety and success has continually improved during the last decade because of the increased understanding provided by research at both fundamental and clinical levels. The NHLBI has had a key role in supporting these activities. The future role of coronary artery surgery will be further clarified by ongoing, NHLBI-sponsored projects.

Other Areas of Research

Coronary artery bypass surgery was selected for the foregoing section as an example of laboratory and clinical research which can be easily translated into patient care. The NHLBI Division of Heart and Vascular Diseases also supports a wide spectrum of research in other areas. A few of the many other topics are cited.

Atherosclerosis is the most common serious health problem in our Nation. An intense program of research is supported by the NHLBI to learn the causes and mechanisms which produce this disease. The relationship of blood cells and clotting to atherosclerosis is an exciting avenue of research, with the ultimate goal of prevention.

Work continues on attempts to limit the amount of heart muscle damaged by heart attacks, to understand the ways in which the heart's rhythm of beating becomes seriously upset, and to learn how to prevent the most drastic rhythm disturbances that may lead to sudden unexpected cardiac death.

There is a successful program for development of mechanical devices to aid the failing circulation, which has helped lead to systems that are available for clinical care at this time. Methods for identifying the presence of coronary arterial lesions, which do not depend on catheterizing the heart and circulation, are also being developed.

The Hypertension Detection and Follow-up Program, an NHLBI-sponsored trial, was recently completed and was presented in some detail in the *Eighth Report of the National Heart, Lung, and Blood Advisory Council* (NIH Publication No. 81-2104). It exemplifies research at the clinical level which has direct relevance to health care.

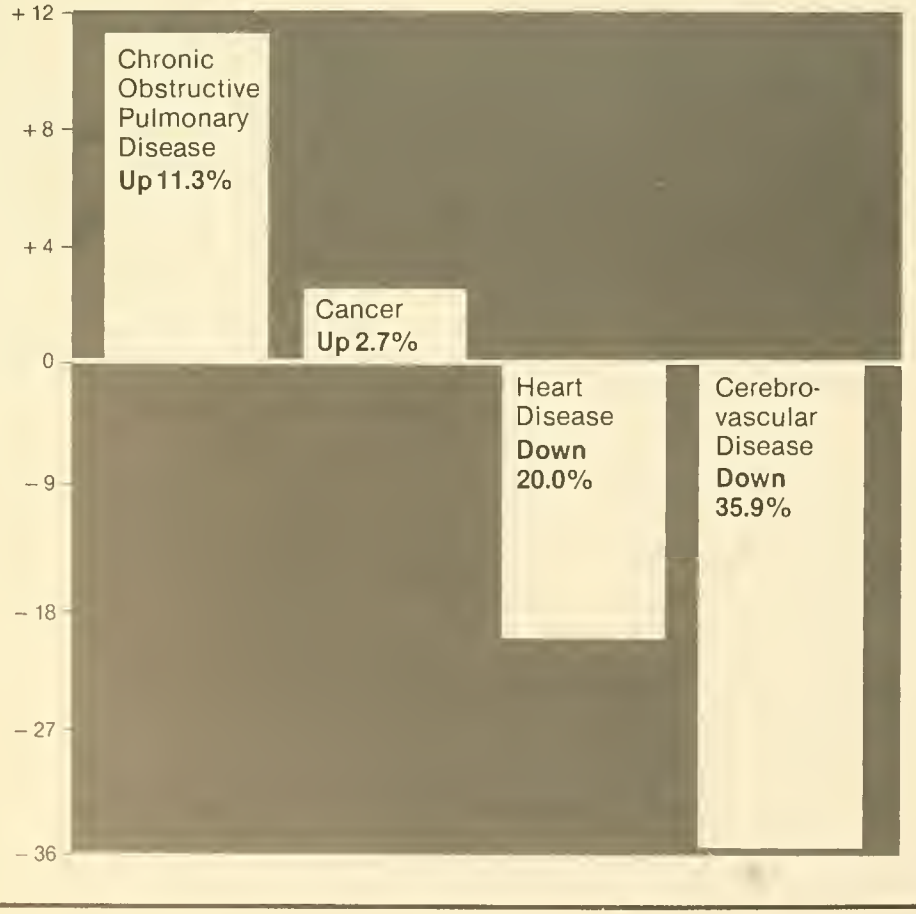
The NHLBI Division of Heart and Vascular Diseases sponsors research that spans a broad spectrum from cell chemistry to clinical trials of new treatments for heart disease. What have been described above are areas of important progress, progress that has been based on research translated to better care of patients. These represent dramatic changes in the care and treatment of heart disease patients; we can justifiably be proud of this improvement and progress. However, heart disease remains the Nation's number one serious illness and much remains to be done.

Lung Diseases

Chronic obstructive pulmonary diseases are progressive, debilitating conditions that affect millions of Americans, severely limiting their activities and shortening their lives. It is estimated that approximately 9 million Americans suffer from chronic bronchitis and emphysema, the two most prevalent forms of chronic obstructive pulmonary disease (COPD). Indeed, COPD is the fastest rising cause of death in the United States, accounting for about 2.5 percent of deaths annually. While mortality rates for most of the other leading causes of death have declined over the last 10 years, mortality from COPD has increased by about 1.4 percent per year. The cost of this disease category, in health care and in wages and time lost from work, now exceeds $15 billion annually.

*Among these four diseases, leading causes of death in the United States, COPD is the fastest rising. (*Data from the National Center for Health Statistics; adjusted for the aging of the population)*

Percent Change in Death Rates per 100,000 Population* 1970-1979



Attack on Chronic Obstructive Pulmonary Diseases

The NHLBI Division of Lung Diseases has recognized that the attack on COPD must be a multifaceted one, and has taken that approach. Fundamental research is required in order to elucidate the biochemical and physiological processes through which the diseases develop. Such an understanding is a basic requirement of any attempt to control or eliminate disease. When the Division was established in 1972, very little progress had been made either in achieving such a grasp of the disease process itself or in clearly recognizing the characteristics of the population "at risk." The latter was a separate and extremely important goal: to identify common factors among the many millions of COPD patients in order eventually to be able to predict and ultimately to control the disease. The fact remained, however, that even if basic biochemical research and epidemiological studies were to begin to shed light on its causes and risk factors, millions of Americans were already suffering from irreversible COPD. It was therefore also necessary to examine existing treatment and to seek new methods, so that this segment of the population could look forward to improved and longer lives.

Bronchitis

Both emphysema and chronic bronchitis are disorders associated with obstruction of the airways in the lungs. Bronchitis is characterized by an accumulation of mucus in the bronchial passages which results in a persistent, productive cough. The production of mucus is a normal mechanism by which the lung protects itself against external irritants. However, in bronchitis, mucus is produced in such excess that the air passages become obstructed, both due to the excess mucus itself and to inflammation and attendant thickening of the bronchial walls. Severe chronic bronchitis is the cause of many millions of hours lost from work and can result in death.

Epidemiological studies have begun to produce information that

may allow the occurrence of severe chronic bronchitis to be predicted and its frequency decreased. For example, persistent wheezing and repeated respiratory tract infections in young children may be linked to the development of COPD later in life. Much more work is needed to clarify these relationships. Smoking is a clear risk factor for bronchitis, and one which magnifies the effects of any other factor. The importance of each of these factors, and the ways in which risk can be minimized or controlled, are areas that urgently need further study.

Emphysema

Emphysema is a condition which actually causes an alteration of the lung structure. In emphysema, the walls of both the small air passages (bronchioles) and air sacs (alveoli) are progressively destroyed, losing their elasticity and ability to force air out of the lungs. Concomitantly, the air spaces in the lung become enlarged and so thin-walled that they tend to collapse during exhalation. Thus, stale air containing excess carbon dioxide becomes trapped in the lungs. The structural damage done by emphysema is essentially irreversible, debilitating, and life-shortening.

Basic research over the last 10 to 15 years, much of it supported by the NHLBI, has made some inroads into an understanding of the fundamental process of emphysema. The loss of elasticity of the alveolar walls results from destruction of elastin, a major structural protein of the lung. This breakdown of elastin is caused by action of the enzyme elastase, one of a large class of enzymes known as proteases. A third substance, an antiprotease, can protect lung tissue from injury. In the normal lung, there is a balance between elastase and the antiprotease alpha-1-antitrypsin, which limits the breakdown of elastin. By contrast, in emphysema this balance is believed to be disturbed and excess destruction of elastin results. With this biochemical information in hand, researchers have begun to look for the causes of the protease-antiprotease imbalance and for ways to detect such an imbalance before the disease has progressed irreversibly.

Genetic factors and early diagnosis. In some individuals, a genetic deficiency of alpha-1-antitrypsin disturbs the protease-antiprotease equilibrium. It is estimated that between 20,000 and 80,000 Americans have this deficiency, and therefore lack a fundamental weapon against emphysema. Because of the low level of alpha-1-antitrypsin, the lung tissue is especially vulnerable to destruction by elastases, and such destruction may be precipitated easily by lung inflammation such as occurs with virus infections, smoking, or exposure to air pollution. It is hoped that people with this type of emphysema will be helped in the future by replacement or supplementation therapy with alpha-1-antitrypsin. This would provide a truly basic attack on the underlying problem in this one form of emphysema.

The concept underlying this type of therapy may open the doors to a new attack on at least some forms of emphysema, but other fundamental questions remain. For example, the natural course of alpha-1-antitrypsin-deficiency emphysema, first described by two Swedish investigators, Laurell and Eriksson, in 1962, is not known. What is known is that most of the patients with this type of emphysema often exhibit symptoms in their thirties and forties, a younger age than other emphysema patients. This type of emphysema also affects men and women equally, unlike more common forms of emphysema associated with smoking, where a male predominance exists. If an individual with this predisposition also smokes, emphysema may manifest itself at an especially young age. Other questions concern the age at which the destructive process begins, whether pneumonias or other chest infections enhance the destructive process, and whether this process can be halted by smoking cessation, treatment or prevention of infection, or use of anti-inflammatory drugs.

The vast majority of emphysema sufferers, however, have no genetic deficiency of alpha-1-antitrypsin, but nevertheless are thought to exhibit a protease-antiprotease imbalance. This imbalance may be caused by any of a number of factors: excess production of elastase in the lung, release of excess elastase into the lung, inactivation of alpha-1-antitrypsin, or some combination of these factors. Research has recently shown that even when alpha-1-antitrypsin is neither deficient nor inactivated, there can be an excess of elastase and a protease-antiprotease imbalance. It now appears that two kinds of lung cells produce elastase, leukocytes (white blood cells) and alveolar macrophages. If either or both of these cells are increased in number in the lung, there may be excess elastase produced. Several studies, both *in vitro* and in animals, have shown that exposure to cigarette smoke increases the numbers of both leukocytes and macrophages present in the lung. Such studies provide good evidence of a direct connection between smoking and emphysema, a connection that epidemiological studies dramatically substantiate. Many investigators are studying the very complex relationships between proteases and antiproteases.

Diagnostic tests. In addition to basic biochemical research into the causes of emphysema, many studies are attempting to discover methods of detecting the disease in its early stages. Finding emphysema before the disease has done substantial irreversible damage is a challenge not unlike the recently conquered challenge of finding hypertension before it has caused

heart attack or stroke. One existing method of diagnosis involves use of the spirometer, a tool that was first used in 1846. For a long time, it was complicated to use and expensive to purchase, and it has not been widely used. However, this important diagnostic tool is now simplified and available at reasonable cost, and should eventually be a fundamental tool in any doctor's office and every hospital in the country. Basically, it is a device which records the volume and flow of air from the fully inflated lungs. There is a range of normal values of lung volume (capacity) and flow for both men and women of all age groups, and it is believed that even mildly abnormal lung function, ascertained by comparison to this range, may be an important indicator of early airways disease. Studies have shown that cessation of smoking can forestall or even prevent lung deterioration. This points out how critical early diagnosis is.

Another exciting possibility has emerged very recently. It has been observed that elastin fragments can be detected in serum and urine samples. Sensitive new techniques are being used to detect extremely small quantities of these fragments. Preliminary studies show that there are elevated concentrations of elastin fragments in the urine of both emphysema patients and smokers. If it were possible to correlate the elastin fragment concentration with the progression of disease, then such methods might be useful for early detection of emphysema. This promising approach, which uses sensitive immunologic detection methods such as radioimmunoassay, is being pursued by several investigators supported by the NHLBI.

Important Unresolved Issues

Researchers are making progress in learning about the fundamental processes of COPD, and epidemiological studies are revealing considerable information about external factors that either cause or aggravate the conditions. Much additional work both in basic and in epidemiological research is needed. For example, there is now no question that of all the risk factors identified, smoking is clearly the primary one. But many questions still remain. Is it possible to reduce smoking in individuals with initial lung dysfunction and thereby to permit lung restoration to begin? Or must smoking be eliminated altogether? Why are all smokers not afflicted with COPD? How can individuals be persuaded to give up smoking before irreversible lung damage has been done? In addition to these are many other difficult questions which involve additional risk factors as well, such as exposure to environmental pollutants, alcohol consumption, exposure of nonsmokers to cigarette smoke, allergies, family history of respiratory disorders, and others. One ongoing project will attempt to establish a so-called index of risk of COPD, which will match age, sex, and various risk factors against present lung function. Using such an

Measurement of lung function with a spirometer.

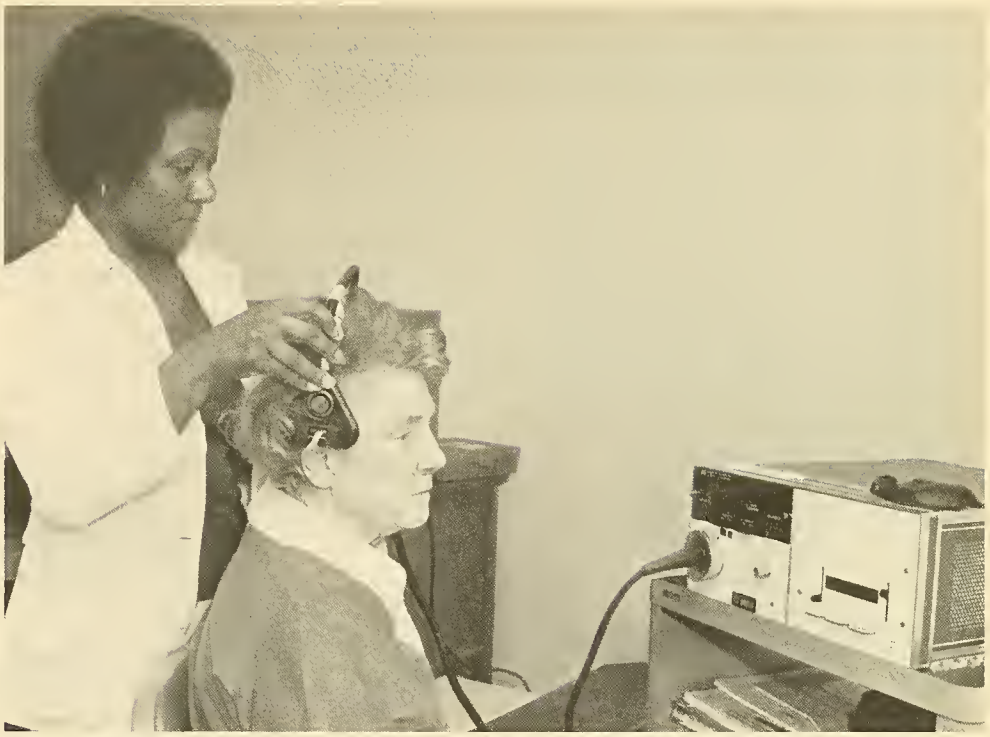
index might allow a physician to predict, for example, not only the likelihood of a patient's getting emphysema, but also the timeframe for disease progression under the existing circumstances. The patient could then be advised on lifestyle changes that might forestall, minimize, or prevent irreversible disease.

Advances in Management of the Diseases

Many millions of Americans are suffering and dying from COPD. Evaluation, improvement, and development of therapy must therefore be important parts of an integrated attack on airways diseases. A number of approaches to the treatment and management of COPD are being supported and sponsored by the NHLBI.

Intermittent positive pressure breathing. One treatment regimen that is presently being examined is intermittent positive pressure breathing (IPPB). This therapy has long been in use, but without controlled studies of its actual effectiveness. The technique involves mechanically assisted inhalation, used intermittently. It has been thought that such therapy would be beneficial to patients whose lungs are not being sufficiently ventilated. The Division of Lung Diseases is sponsoring a controlled clinical trial of IPPB, to examine the long- and short-term benefits of the treatment as well as possible undesirable side effects. It is anticipated that the results of this trial will define the effectiveness of IPPB in comparison to a compressor nebulizer in ambulatory COPD patients.

Continuous oxygen treatment. A recently completed clinical trial has established with greater certainty the role of another therapeutic regimen, long-term continuous oxygen, in modifying the late course of advanced chronic obstructive pulmonary disease. This multicenter oxygen trial, completed in 1980, indicates that continuous oxygen therapy (i.e., 24 hours per day) is more effective than 12-hour oxygen therapy in prolonging life for individuals



An oximeter is used to measure the oxygen content of the blood. Expanded use of this noninvasive tool is under investigation. (This emphysema patient is also on oxygen therapy.)

This emphysema patient, supported by 24-hour oxygen therapy, pursues a favorite activity.

suffering from oxygen-deficient, chronic lung disease. For patients followed for 2 years, mortality was 22.4 percent in the former group and 40.2 percent in the latter. In this controlled trial, patients had been randomized to a program of 12-hour-per-day oxygen or continuous (24 hours) oxygen. All patients were carefully matched by important factors such as age and sex. Other therapy was equal and all patients were carefully supervised by research teams in six North American cities. This study was a landmark in our understanding of the effectiveness of oxygen in patients with low blood oxygen and advanced obstructive lung disease.

Without oxygen therapy, the predicted lifespan for this group of patients would be 1 to 2 years, with a major proportion of this time spent in a hospital or nursing home. Previous studies indicated that 24-hour-per-day oxygen reduced hospital days, increased the quality of life, and added an additional 1.5 to 2 years of life for patients living at high altitude. The results of the new six-center study confirmed the previous belief about the value of continuous oxygen and extended those concepts to a broader population. Again, improved survival was found. Of perhaps greater importance was the improved quality of life in patients with a terminal illness. Important reductions in hospital days were an additional benefit to the patient, the family, and the community at large.

Reports of this study have been disseminated to the medical community by publication in medical literature and presentation of the results at national and international meetings and at postgraduate courses aimed at the practicing physician and other health care deliverers. Further analyses of the study are currently in progress. The industrial community has already responded to meet the needs for home oxygen therapy by providing new devices to supply oxygen in the home. This response by the biomedical community has provided equipment that will help meet the needs of large numbers in both urban and rural areas, making this advance in therapy potentially available to all sufferers from severe emphysema who require this form of therapy. Further advances in technology, stimulated by this research, promise to make oxygen in the home even less costly and more convenient.

Challenge for the Future

More basic investigation will be required to deal with the fundamental problems of lung injury resulting in emphysema. However, recent advances now clearly show that something can be done for emphysema. The late course can be palliated by oxygen. Life can be extended and made more worthwhile.

Chronic obstructive pulmonary disease is one of the most vexing and expensive health problems faced by our citizens and by medicine today. The future requires an even greater and more concerted effort linking basic, clinical, and epidemiological research, training, and patient care in order to solve this problem.

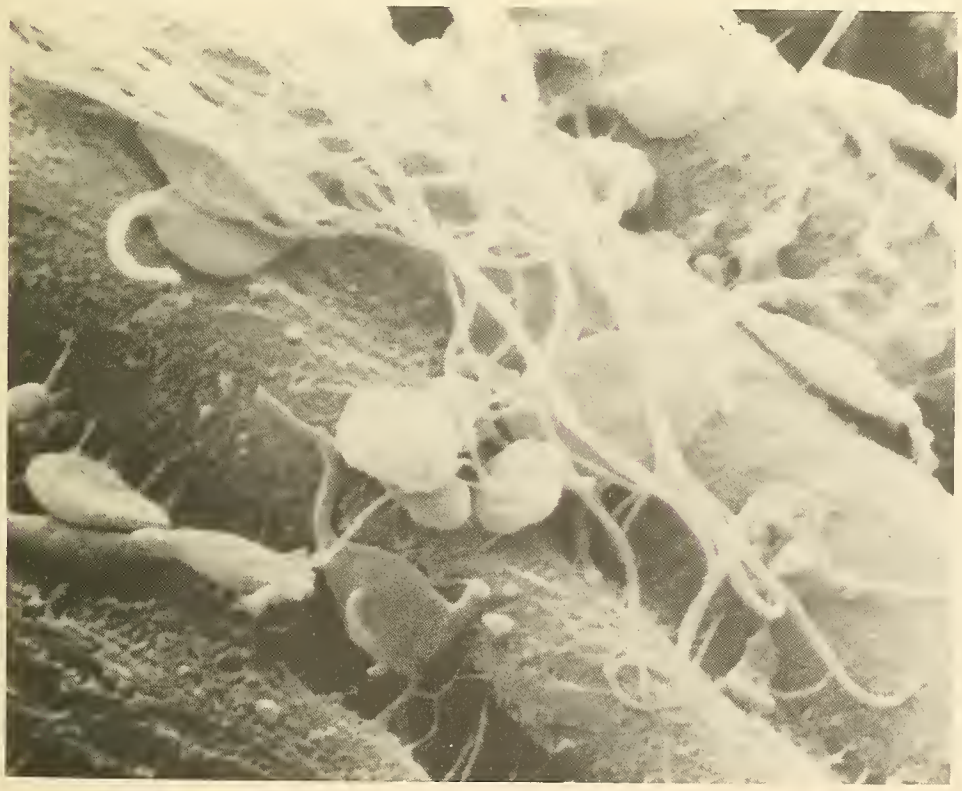
Other Areas of Research

The Division of Lung Diseases has a broad program of research related to the normal structure and function of the lung and the causes, recognition, and management of lung diseases which affect both children and adults. Research programs in cystic fibrosis, neonatal respiratory distress syndrome (hyaline membrane disease), and asthma receive attention, as do disorders of the lungs' blood vessels, problems related to the toxic effects of oxygen, and immunologic reactions in the lung. Studies of gas exchange in the normal lung and alterations associated with exercise, high altitude, and disease states are among the fundamental investigations supported by the Division.

A carefully developed program of research into lung function and disease has grown during the past decade. The resulting improvement in understanding of the lung has been dramatic. This understanding, combined with continued research, should one day lead to effective prevention.

Blood Diseases and Resources

Scanning electron micrograph of a blood clot forming. The surface of this major artery (an animal aorta) has been injured, and a layer of platelets is replacing the surface cells. The injury has stimulated the coagulation mechanism, and fibrin strands can be seen forming across the site. (Electron micrograph provided by Dr. James G. White, University of Minnesota.)



The NHLBI Division of Blood Diseases and Resources supports basic and applied research on diseases which literally affect millions of Americans. Such research has had great impact on the health of people of this country. Some areas of interest are hemorrhage, thrombosis (a major contributor to heart attack and stroke), sickle cell anemia, blood transfusion, and transplantation. It is possible to illustrate, with just a single disease, how basic research can result in improved clinical care of patients and lead to recognition of new diseases with clinical applicability of broad ramifications. This kind of illustration can also be extrapolated to other programs.

The disease to be described is hemophilia, a hereditary hemorrhagic disease which, until recently, resulted in crippling, incapacitating arthritis, and, frequently, early death.

The NHLBI has supported many fundamental studies that have led over the years to vastly increased understanding of many bleeding disorders. Basic research has revolutionized the recognition, diagnosis, and treatment of hemophilia, so that patients who were once severely handicapped can now live more normal lives. It now appears that the research findings related to hemophilia may also be applicable to atherosclerosis and thrombosis, leading causes of death in the United States and in the world.

Hemophilia—A Great Mystery

Hemophilia was recognized as a bleeding disease even in ancient times. By late 1936, it had been discovered that patients with hemophilia were deficient in a plasma factor necessary for blood to clot normally. It became apparent that an understanding of hemophilia, a result of *defective* coagulation, would rest to a large extent on an understanding of *normal* blood coagulation. This was particularly apparent when it was noticed that transfusions of normal blood into hemophilic patients corrected their markedly prolonged clotting times. However, it was also obvious that new tests and more basic investigation were needed before the defect in hemophilia could be adequately understood, and before new approaches to treatment could be designed. At about the time of World War II, the "two-stage prothrombin assay" was developed, a test which permitted investigators to determine that normal plasma contains a plasma protein, or antihemophilic factor (now called factor VIII). It was also evident that to understand hemophilia, investigators would have to learn about genetic factors and develop basic biochemical and molecular biological techniques that would permit such studies.

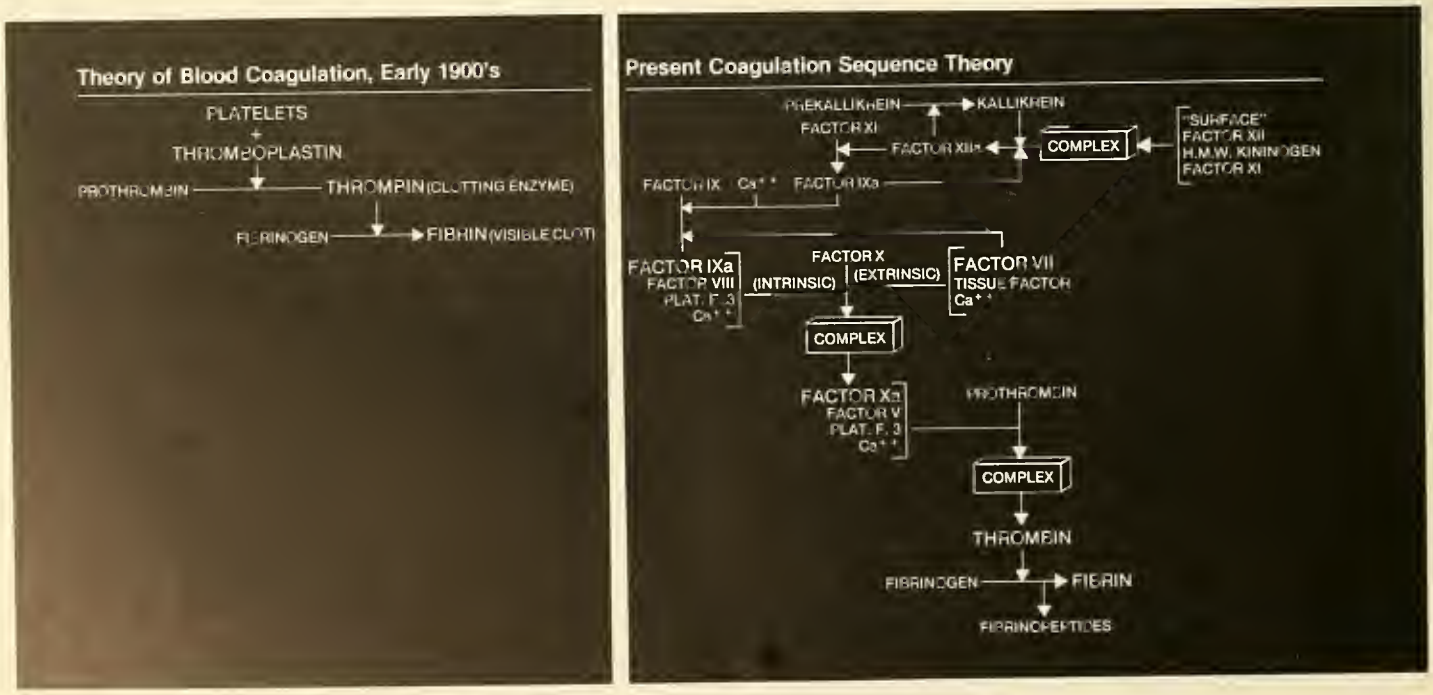
In the 1940's, an animal colony with hemophilia identical to that seen in humans was discovered and permanently established. This colony permitted direct confirmation of the human genetic pattern of inheritance of classic hemophilia; males are affected and females are carriers of the disease. Moreover, for the first time it was shown that females could have classic hemophilia.

Early work on hemophilia was retarded by the lack of a simple test to measure factor VIII (antihemophilic factor), the plasma protein missing in patients with classic

hemophilia. With NHLBI support, simple one-stage assays were developed to measure factor VIII. This allowed more basic biochemical studies on the nature of the factor VIII molecule, and led to techniques that permitted the identification and isolation of this complex and interesting molecule.

Early biochemical work on factor VIII. When tests for specific identification of factor VIII became available, investigators took normal human plasma and began to separate it into component parts by various procedures. One of these was a relatively simple technique involving the freezing of plasma and then thawing at ordinary refrigerator temperature (4° C). A cold insoluble material was left in the bottom of the container of plasma and could be separated from the thawed material. This cold insoluble material ("cryoprecipitate") was found to have high concentrations of factor VIII—a ten- to fifteen-fold higher concentration than in whole plasma. This cryoprecipitated factor VIII became immediately available for the treatment of hemophiliacs because it was so concentrated that it was much more effective in preventing bleeding than plasma transfusions alone. At about the same time, other investigators were able to achieve a 400-fold purification of factor VIII. This biochemical work resulted in preliminary characterization of the factor VIII molecule in terms of molecular weight, stability in storage, and role in normal coagulation. It also led to the development of clinically useful factor VIII concentrates for the treatment of classic hemophilia.

Clinical spin-off from early biochemical work. The transfusion regimen developed in the animal model was applied successfully to humans. By 1964, large-scale production of cryoprecipitate in blood banks was taking place; at the same time, dried, highly purified factor VIII fractions produced by pharmaceutical firms also became available. These therapeutic advances, based on NHLBI-sponsored basic research, led to a revolution in the treatment of patients with hemophilia. Factor VIII levels in hemophiliacs could be made *normal* (as long as factor VIII fractions were administered); hemophiliacs could safely undergo major surgery, even on the brain and heart;



Blood coagulation was once believed to be a simple process. Today, researchers know that the process is an extremely complicated one which is still not completely understood.

and the dried commercial concentrates of factor VIII could be taken home by patients and *self-administered,* the beginning of home therapy. Thus, factor VIII products became to hemophiliacs what insulin was to diabetic patients.

Physiology of factor VIII. Following the development of specific tests of factor VIII and the availability of factor VIII products, investigators supported by NHLBI found that the biological half-disappearance time of factor VIII in hemophiliacs was 8 to 12 hours. This meant that factor VIII replacement was necessary at least every 12 hours. It was also discovered that factor VIII was required for wound healing, and that part of the factor VIII molecule is made in the cells lining the inner surfaces of blood vessels.

Further biochemical and molecular biological investigations of factor VIII. Following the development of tests specific for factor VIII, investigators soon learned that a disease other than classic hemophilia was associated with a low factor VIII level. This disease became known as von Willebrand's disease. Unlike classic hemophilia, von Willebrand's disease affected both males and females, and had a different set of abnormalities of clotting tests, involving platelets. Platelets circulate in the blood, are smaller than white blood cells, and stick together to plug leaks in the blood vessels. Thus it was suspected that the factor VIII molecule was composed of at least two pieces—one called the von Willebrand factor (VWF), which is defective in patients with von Willebrand's disease, and one called the antihemophilic factor (AHF), which is defective in patients with classic hemophilia. It appeared that the von Willebrand factor was necessary for platelets to stick to the site of blood vessel injury while the antihemophilic factor was necessary for normal clotting.

This led to the basic discovery that the whole factor VIII molecule is quite large (molecular weight greater than 1,000,000). It was found that this molecule could be broken into one small piece (AHF) and one large piece (VWF). Moreover, it was learned that these two pieces could be reassociated. These investigations resulted in the current working model of factor VIII, a large molecule that circulates in the body.

But more was to be learned about the von Willebrand piece of the factor VIII molecule. Intensive study, still ongoing and sponsored by NHLBI, suggests that von Willebrand factor, in its interactions with platelets, could be related to the development of *atherosclerosis*—the major contributor to cardiovascular disease, including heart attack and stroke. The reason for believing this is that pigs with von Willebrand's disease and lacking the von Willebrand factor are more resistant to atherosclerosis than normal pigs when placed on normal or atherogenic diets. Currently, pig models are being used to study this relationship, which is important since it connects the clotting mechanism to platelets and the vessel wall. The interactions among these three components make it appear that when they are defective, hemorrhage, in one case, or clotting and atherosclerosis, could result. More recent biochemical work suggests that the antihemophilic piece of the factor VIII molecule can be isolated and that it acts with other clotting factors to accelerate clotting.

These studies of von Willebrand's disease provide another example of clinical application of fundamental research. The research described here has permitted a clear clinical distinction between classic hemophilia and von Willebrand's disease. In addition, purified concentrates of von Willebrand factor and antihemophilic factor have been developed, allowing better treatment of these two diseases. The clinical implications of the relationship between the von Willebrand factor and atherosclerosis are just now being explored in depth. For example, the Division of Blood Diseases and Resources is sponsoring a survey of elderly von Willebrand's patients in an attempt to determine whether their clotting disorder has protected them against atherosclerosis.

Immunology of factor VIII. Some patients with classic hemophilia develop antibodies against factor VIII resulting in neutralization of the factor. Therefore the treatment of such patients using factor VIII products is complicated and often ineffective. In an attempt to overcome this problem, new and different types of concentrates which *bypass,* by an unknown mechanism, the factor VIII requirement have been discovered—namely, prothrombin complex concentrates which possess activity that bypasses factor VIII. A recently conducted clinical trial clearly shows that hemophiliacs with inhibitors do benefit from treatment with prothrombin complex concentrates.

Of major importance is the use of new immunological methods to detect the antihemophilic factor. Thus, carriers of hemophilia can be much more reliably detected. Moreover, using a combination of clotting and antibody tests for factor VIII, *prenatal* diagnosis of classic hemophilia has become a reality. These tests were all developed in connection with NHLBI-sponsored basic and applied research and have made accurate, reliable genetic counseling for hemophilia accessible.

The question arises whether all of the basic findings related to hemophilia can be readily applied to the population of hemophiliacs, many of whom are poor, feel stigmatized, and all of whom hate to come to a hospital.

Comprehensive Hemophilia Diagnostic and Treatment Centers

As basic and applied knowledge of hemophilia (and other bleeding diseases) accumulated, it became apparent that the patients needed the care of pediatric hematologists, internal medicine hematologists, psychiatrists, orthopedic surgeons, nurse clinicians to supervise home therapy, social workers, dentists, and rehabilitation counselors. In federally supported hemophilia centers, these specialists now hold clinics where the patient can see a hematologist and, on the same day, see each professional needed for rehabilitative and preventive therapy —including instruction in home treatment. Any hemophiliac will now affirm that attendance at such clinics, and especially instruction in home therapy, has made life much easier and much healthier. There is improvement in daily activities; for example, a hemophiliac teenager can infuse himself with a factor VIII concentrate and go to a school dance without fear of severe bleeding. Hemophiliacs now have improved mobility. They lose fewer days from school and work, they have fewer days spent in pain, and they have decreased disabling joint disease. Further studies supported by the NHLBI and carried out through federally funded hemophilia centers have resulted in greater understanding of the natural history of antibodies to factor VIII and hepatitis (liver disease) due to viruses that may be present in some human blood products including factor VIII. Other ongoing studies supported by NHLBI are designed to determine the efficacy of preventive versus emergency treatment for hemophilia and to investigate other ways to administer factor VIII, besides the intravenous route.

With new information on techniques and tests, and with better therapeutic products on hand, the following are possible: (1) prevention of complications in hemophilic children; (2) restorative surgery in older hemophiliacs; (3) bypassing of factor VIII antibodies; (4) induction of adult immune tolerance to factor VIII products; and (5) use of a hepatitis B vaccine.

With further knowledge, possibilities in the foreseeable future include production of cheaper, purer factor VIII products by cloning techniques using recombinant DNA technology and possible cure of hemophilia in animal models using recombinant DNA techniques, under the guidelines defined by NIH.

Most of the developments in classic hemophilia have occurred in the past two decades, during which progress in basic science and clinical application for classic hemophilia alone has been truly astounding. Future potential developments now under way, are equally promising.

Hemophilia patients can administer medication at home, thanks to vast improvements in treatment.

Explosion of Knowledge About Other Clotting Factors

Studies on classic hemophilia have provided a model for subsequent work. Between 1944 and the 1950's many blood clotting factors were discovered, purified, and biochemically characterized; these findings have been applied to the diagnosis, treatment, and genetic counseling of patients deficient in these factors.

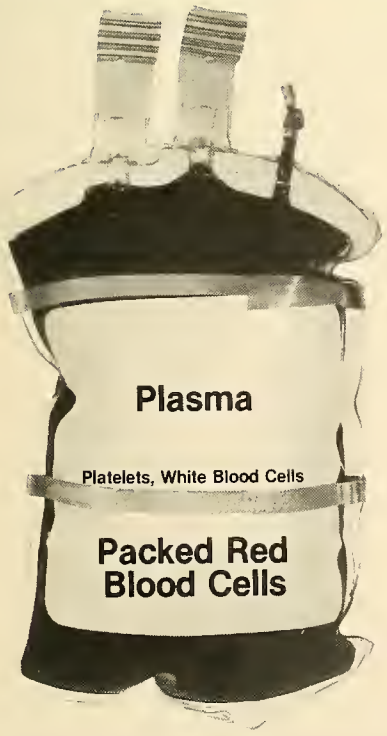
	Factor	Disease
1944	XIII	Factor XIII deficiency
1944	V	Parahemophilia
1951	VII	Factor VII deficiency
1952	IX	Hemophilia B
1953	XI	Hemophilia C
1955	X	Stuart factor deficiency
1955	XII	Hageman factor deficiency

Discovery of various factors in the blood has contributed over the years to an increased understanding of hemophilia.

Almost all "bleeders" were considered to have classic hemophilia until the 1950's, when it was discovered that the blood of some apparent hemophilia patients corrected the clotting times of the blood of known hemophiliacs. Cross-correction tests led to the identification of a number of factors in the blood.

Later, many other factors, important in host defense mechanisms and causing abnormal clotting tests, were discovered. The identification of these factors, most of which were discovered because of NHLBI-sponsored research, has led to a modern concept of how blood clots, what is wrong when it does not clot (hemorrhage), and what happens when it clots too rapidly (thrombosis).

It is now possible to isolate, store, and use many components of whole blood. This capability is a landmark in blood resources research and development. The diagram schematically illustrates that one pint of whole blood may be the source of numerous life-saving components.



Further processing of plasma yields:

Fresh frozen plasma
Cryo-poor plasma
Cryoprecipitate
Antihemophilic factor (AHF)
Specific immunoglobulins
Fibrinogen
Albumin
Plasma protein factor
Immune serum globulin
Factors II, VII, IX, IXa, Xa
α_1-antitrypsin
Fibronectin
Protein C
α_2-plasmin inhibitor
Cold insoluble globulin
Plasmin
α-thrombin

Further processing of packed red blood cells yields:

White-blood-cell-poor red cells
Frozen-deglycerolized red cells

Clinical Application of Basic Molecular Biology

With the story of advances in hemophilia and the other hemorrhagic diseases as background, it is clear that basic biochemical techniques initially designed for research purposes have now been successfully applied clinically, resulting in fractionation of plasma for therapeutic concentrates with excellent clinical effectiveness. Plasma fractionation is a prime example of the clinical application of basic research. The far-reaching impact of this application is a success story.

It becomes apparent that even the most esoteric research related to human disease may be applied one day at the clinical level. It also means that as a result of basic research, the sick can be cured and human misery can be alleviated.

Other Areas of Research

Research in bleeding and clotting disorders, of which hemophilia is only one example, is a major emphasis of the Division of Blood Diseases and Resources. The Division also sponsors work in many other important areas. Research is ongoing in sickle cell disease and Cooley's anemia. Understanding the mechanisms of the clinical problems these disorders produce is essential to the search for effective treatments.

In the area of blood resources, the Division is concerned with screening tests for hepatitis, to make the entire process of blood transfusion safer. Work is also in progress to develop blood substitutes which could be useful at the time of sudden massive hemorrhage and ultimately to decrease the need for transfused human blood. The Division also sponsors research in the judicious use of blood products and the management of the national blood resource.

Priorities, Goals, and Resources

The principal focus of this report has been on the translation of basic biomedical research results into effective treatment and management of disease, one important aspect of the mission of the National Heart, Lung, and Blood Institute. The ultimate goal of all biomedical research, however, is and must be the prevention of disease and the promotion of health. The NHLBI currently expends approximately one-quarter of its fiscal resources for programs that contribute directly to our understanding of how to prevent heart, lung, and blood diseases. A fundamental aspect of disease prevention is the translation of research results into information that contributes to public awareness of what causes these diseases and what can be done to slow disease processes once begun or to avoid them altogether.

A number of NHLBI-sponsored clinical trials seek to determine whether reducing or eliminating certain risk factors will produce a decline in disease incidence or mortality. For example, the Multiple Risk Factor Intervention Trial (MRFIT) was designed to learn how risk of heart disease is affected by lowering blood cholesterol levels, eliminating or reducing smoking, or lowering blood pressure. Results from this important trial will be available in approximately 2 years. The Coronary Primary Prevention Trial is a study of 4,000 men who have elevated blood cholesterol levels but who had no clinical evidence of coronary heart disease on entry into the trial. A cholesterol-lowering diet and the same diet supplemented with the cholesterol-lowering drug cholestyramine are being evaluated to determine their effects on rates of heart disease morbidity and mortality in this high-risk population.

There have been many studies indicating that smoking is the primary risk factor for lung disease and a serious risk factor for heart disease as well. Recently, researchers' attention has turned to the question of whether nonsmokers who are constantly and for long periods of time exposed to the cigarette smoke of others are also at increased risk. Spirometry has been used as a tool in one study to compare the lung functions of nonsmokers, nonsmokers chronically exposed to cigarette smoke, and smokers. The distressing discovery of this study was that nonsmokers exposed daily over a period of years to the cigarette smoke of coworkers exhibited significant deterioration of lung function. In fact, their lung functions were equivalent to those of individuals who smoke 10 cigarettes a day and inhale. Smoking cessation is clearly emerging as a critical prevention measure for smokers and many nonsmokers alike.

Epidemiological studies provide a great deal of information, about incidence and transmission of disease, that is significant to prevention. For example, identification of populations at high risk of contracting viral hepatitis was essential before trials could be undertaken to test new hepatitis vaccines. The occurrence of non-A, non-B hepatitis has been established epidemiologically and clinically to occur in 7 to 10 percent of posttransfusion patients. Until the viruses that cause this type of hepatitis are identified, it will not be possible to eliminate use of blood that contains those viruses. However, a recent study has indicated that non-A, non-B hepatitis occurs more frequently in patients receiving blood from donors who have high serum levels of the enzyme transaminase (ALT). Screening blood donors for elevated ALT levels may be an important interim detection method to reduce the incidence of posttransfusion hepatitis.

Extremely important approaches to disease prevention are public and professional education programs, to teach both the general public and health care professionals about how to prevent disease. Knowledge gained through basic, clinical, and epidemiological research is directly applicable to such programs. Wide use is now being made of television public service announcements to promote conscientious attention to high blood pressure. Data from a number of basic and clinical studies clearly support the theme of these announcements: "High Blood Pressure—Treat It and Live." Nutrition information prepared by the NHLBI is distributed through two new programs: *Food for Thought*, printed material for use in cafeterias; and *Foods for Health*, pamphlets and fact sheets available in some supermarkets. Voluntary health organizations cooperate with the NHLBI in distributing these and other educational materials. The Institute has also provided technical assistance to a number of U.S. corporations in developing worksite health promotion activities such as smoking cessation programs. Many more examples could be cited that illustrate the intense interest of the NHBLI in education for health promotion.

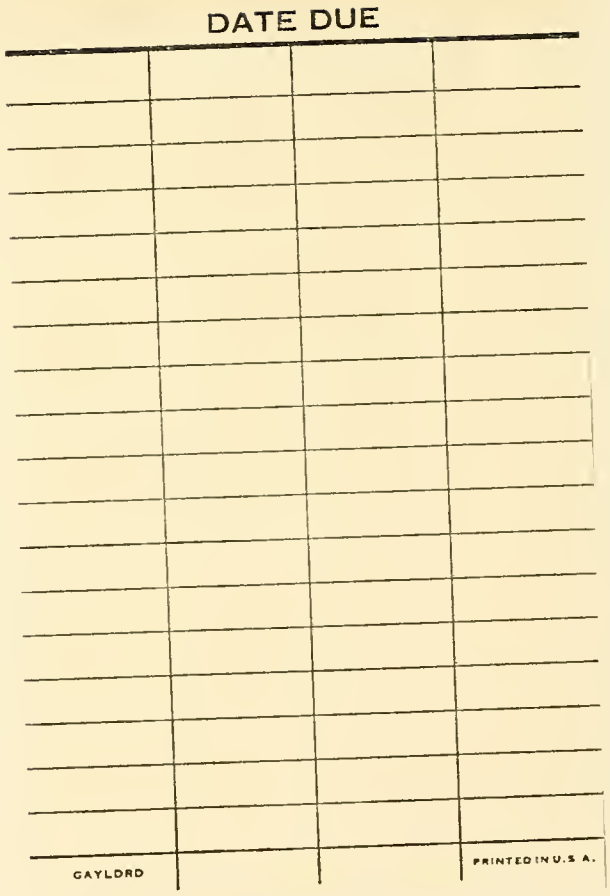
It is difficult to isolate the basic research and research training functions of the NHLBI from the goal of disease prevention. All of our efforts must be directed to that ultimate goal—prevention—for the most cost-effective and successful contribution to the health and well-being of the Nation.

Budget Recommendation

The advisory council has evaluated the National Heart, Lung, and Blood Institute's program of research and research training support and carefully assessed the needs for continuing programs in the attack on diseases of the heart, lungs, blood vessels, and blood. With due consideration of the economic status of the Nation, we have recommended an authorization budget that will not jeopardize the Institute's responsibility to meet the critical demands for continuing progress. However, it is less comprehensive than would be proposed during times of less economic stress. In other words, it is realistic but not optimal.

Reflecting the reality of the current fiscal situation, the recommended increases in the budget result from careful consideration of the highest priorities for health care research.

Program Activities	Fiscal Year (dollars in thousands) 1983	1984	1985	1986
Extramural Research Programs				
Heart and Vascular Diseases	389,000	423,000	453,000	480,000
Lung Diseases	97,000	108,000	125,000	140,000
Blood Diseases and Blood Resources	97,000	108,000	125,000	140,000
Prevention, Education and Control	65,000	75,000	80,000	90,000
Construction	20,000	20,000	20,000	30,000
Research Training and Development	60,000	65,000	75,000	85,000
Total Extramural Research Programs	728,000	799,000	878,000	965,000
Intramural Research Programs	60,000	65,000	70,000	75,000
Program Management and Program Services	52,000	56,000	60,000	65,000
Total	840,000	920,000	1,008,000	1,105,000



DISCRIMINATIO
enacted by Con
grounds of race
participation in
under any prog
education prog
tion, Executive
contractors ar
Executive Ord
criminate aga
race, color, re
Lung, and Bl
and Executiv

ons of applicable public laws
the United States shall, on the
ap, or age, be excluded from
be subjected to discrimination
s of sex, with respect to any
ral financial assistance. In addi-
nation on the basis of age by
nance of Federal contracts, and
y funded contractor may dis-
for employment because of
herefore, the National Heart,
in compliance with these laws

NIH Publication No. 81-2334
September 1981