Tenth 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

The cover design is a graphic representation of the National Heart, Lung, and Blood Institute. The intertwining spirals symbolize three separate components of the Institute—heart, lung, and blood—which evolve into and become a single unit—cardiovascular-pulmonary research.

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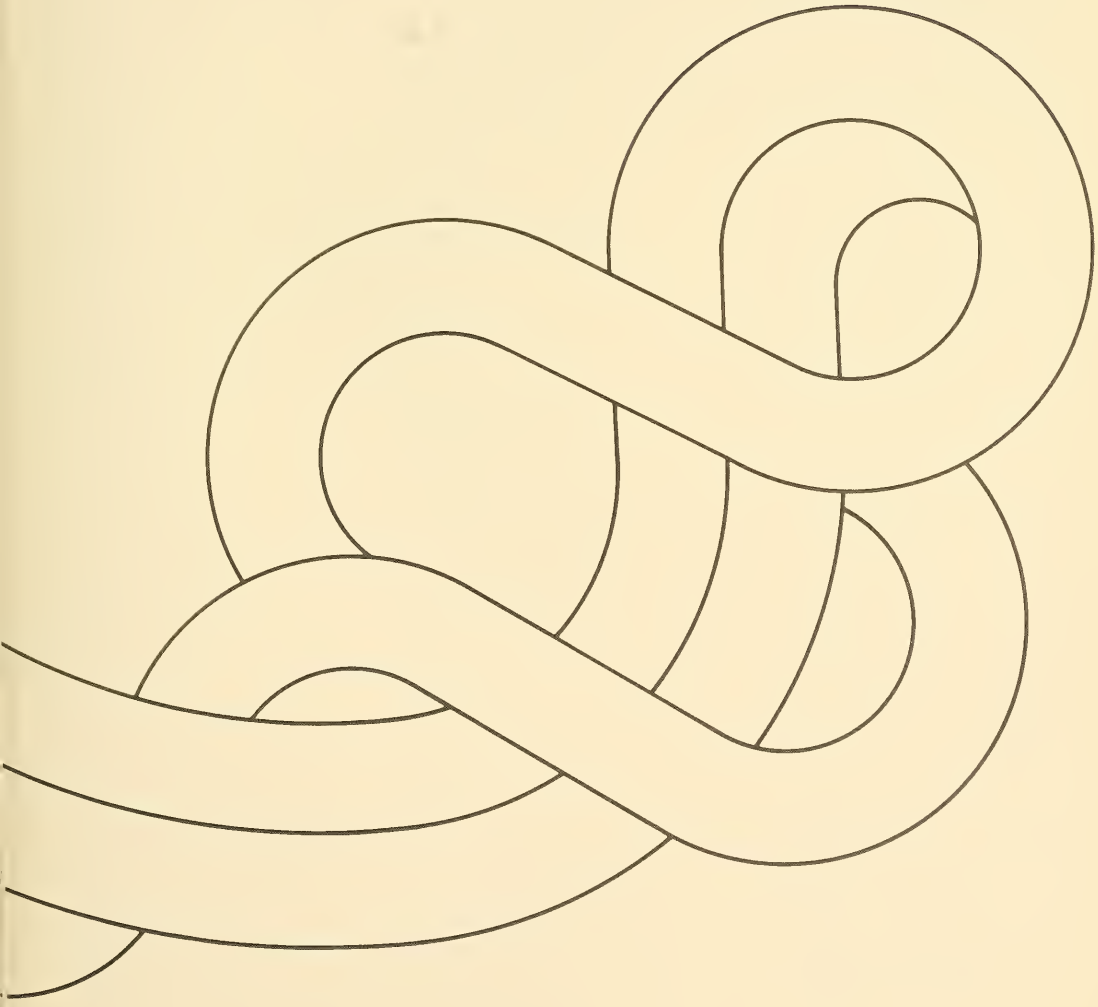

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
Bethesda, Maryland 20205

NATIONAL HEART, LUNG, AND BLOOD INSTITUTE

September 24, 1982

The President
The White House
Washington, D.C.

Dear Mr. President:

We, the members of the National Heart, Lung, and Blood Advisory Council, are pleased to submit to you, and to the Congress, our tenth report on the progress of the National Heart, Lung, and Blood Institute's effort to control and prevent diseases of the heart, lungs, and blood. The report has been prepared in accordance with Public Law 95-622.

In forwarding this report, the Council wishes to thank you for the opportunity we have been given to serve you, the Congress, and the Institute, and also the people of this country and throughout the world who benefit from the programs the Institute sponsors.

Respectfully,

The National Heart, Lung,
and Blood Advisory Council

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Contents

Introduction

The *Tenth Report of the National Heart, Lung, and Blood Advisory Council* deals with the response of the Institute to opportunities for improvements in prevention and treatment of heart, lung, and blood diseases that kill about 60 percent of the American people. Three examples from these diseases have been selected: heart attack, acute respiratory failure in the adult, and sickle cell anemia. Since recent advances in the prevention and treatment of these conditions are more often based upon systematic studies that have gone on for several years than on some sort of a "breakthrough," the evolution of our understanding of the mechanisms of these conditions and their treatments is presented. A solution to one problem often raises new questions that must be addressed and new opportunities for further improvements in prevention or therapy. For example, development of effective inhospital treatment of life-threatening electrical disturbances in the heart has decreased the death rate in these patients during the first week by about 50 percent and has brought to the fore the need for development of more effective methods for treatment of the decreased pumping action of the heart and recurrent electrical disturbances in the months following the attack.

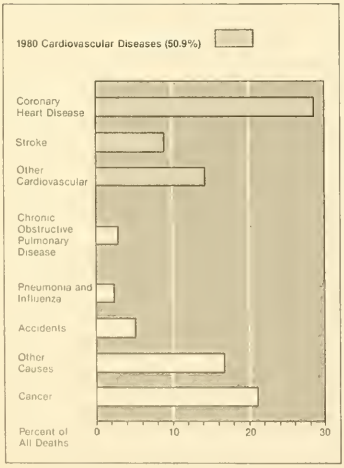
The causes of some diseases within the responsibilities of the National Heart, Lung, and Blood Institute, such as acute respiratory failure in the adult, have proven difficult to understand and little progress has been made despite intensive research efforts. These unsolved research problems remain the highest priority for the Institute and need to be addressed both through investigator-initiated research and Institute-initiated programs. Followup on knowledge arising from basic research offers the best chance to improve patient care and education, both for prevention and treatment of disease.

Limitations on resources are significantly impairing the Institute's ability to support high priority research that promises to improve the quality and length of life of the American people. For example, the program that was begun to provide stability by setting a minimum of 5,000 grants and 10,000 trainees to be supported by the National Institutes of Health has evolved into a "ceiling" on the Institutes' activities. The hope for stability in research support has turned into instability and threatens to destroy clinical investigation in this country by discouraging the young physician from entering a research career. Clinical investigation is a vital segment in the progression from basic research to prevention and treatment of disease and is of fundamental importance for the programs of the National Heart, Lung, and Blood Institute.

Heart and Vascular Diseases

Heart Attack: Improved Knowledge Leads to Treatment Advances. The leading cause of death in adults in the United States is coronary heart disease, usually from heart attack. Although the death rate from this disorder has begun to decline in recent years, it still claims nearly 600,000 lives each year in this country and tends particularly to strike men in their working years. Since coronary heart disease is associated with a high rate of sudden death and decreased life span in those suffering their first heart attack, prevention of this disease is the primary strategy in dealing with the epidemic of heart attacks that currently affects the American people. Continued epidemiologic studies have established firmly the relationships of the major risk factors—high blood pressure, serum cholesterol, and cigarette smoking—to the risk of coronary heart disease. An effort has begun to assess the precursors of risk factors in childhood because it is now realized that the maximum preventive effect will probably require modification of risk factors early in life. By 1980, about two-thirds of American families had changed their eating patterns for health reasons. Consumption of eggs, dairy fat, and meat has declined and the mean serum cholesterol level of middle-aged U.S. men decreased. The proportion of smokers in the adult population has decreased continuously since the 1960's. Unfortunately, the use of cigarettes by teenagers increased. In the 1970's, millions of American adults began to exercise during their leisure time. However, further research is needed to clarify the links between the risk factors identified in studies of populations and the causes of atherosclerosis (the underlying basis of heart attacks).

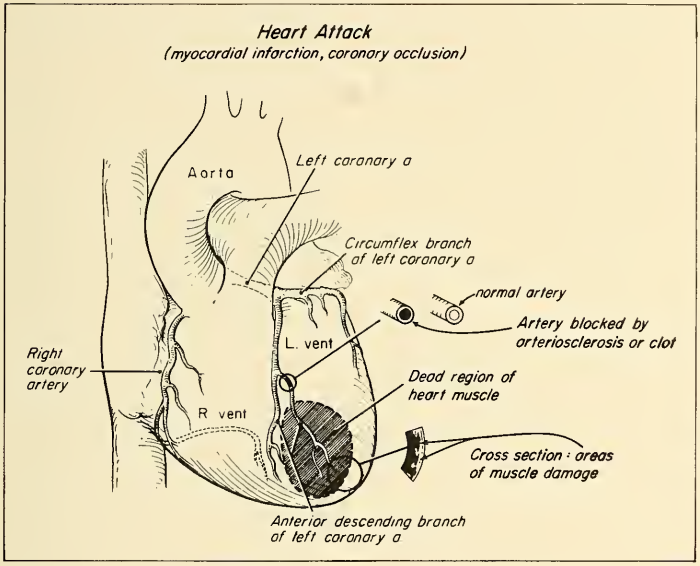
In 1980, cardiovascular diseases accounted for one-half of all deaths in the United States, and one-third of all deaths were directly attributable to coronary heart disease.



In those already affected with coronary heart disease, laboratory, clinical, and population research discoveries have led to improved clinical care and reduction of the high mortality associated with a heart attack, and recent research findings suggest that further progress will be forthcoming. Other selected areas of heart research in which significant advances have been made are highlighted at the end of this section.

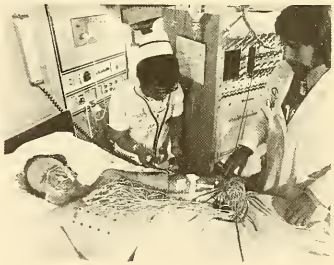
Usually a heart attack begins with sudden blockage of one of the three major blood vessels which supply the heart (the coronary arteries), an event which results in death (infarction) of the region of heart muscle (myocardium) supplied by that artery. Hence, the scientific term for heart attack is "myocardial infarction," sometimes also referred to as a "coronary occlusion," or simply "a coronary." Severe pain in the chest almost always accompanies the attack, lasting for at least 30 minutes and often longer. Electrical disturbances of the heart resulting from the lack of blood flow to the involved region pose a serious danger and lead to rhythm disorders which are sometimes immediately fatal. Indeed, many patients experiencing a heart attack die suddenly before reaching a hospital from a rapid, disordered electrical activity of the pumping chambers, referred to as "ventricular fibrillation." Even if electrical disturbances are not serious, the loss of coronary blood flow leads to poor contraction of the heart muscle in the involved region, which in turn impairs the output of blood from the heart and may lead to a serious decline in blood pressure early after the event.

Past Progress. During the last 20 years, important improvements in the treatment of heart attack have gradually become standard clinical practice in hospitals throughout the world. Particularly noteworthy were the advent of the coronary care unit for intensive care monitoring and treatment, the development of cardiopulmonary resuscitation (CPR) techniques (closed chest compression of the heart, mouth-to-mouth breathing, and electric shock to defibrillate the heart) which could be used both in and out of the hospital, and development of inhospital treatment of serious heart rhythm disturbances and low blood pressure. Other factors have also contributed to a lowering of mortality from heart attack, including the use of coronary care ambulances manned by specially trained paramedics, the development of better drugs to treat heart rhythm disturbances, and earlier ambulation and rehabilitation of heart attack victims. Important problems remain, however, in that the stricken individual frequently delays seeking help, or help may not be immediately available in some areas of the country, leading to continued high out-of-hospital mortality. Expert care is needed immediately if the full benefits of research are to be realized.



Heart muscle death (myocardial infarction) occurs when normal blood flow in the coronary artery is obstructed.

In the coronary care unit, the monitoring of heart rhythm disturbances is one of several techniques which has led to improved survival rates among hospitalized patients.



Once the hospital and a coronary care unit are reached, electrical disturbance of the heart's rhythm can be monitored electronically and treated with drugs or electric shock to the chest wall, if necessary. These approaches have resulted in lowering of the death rate in hospitalized patients from 20-25 percent to 10-12 percent. In fact, such electrical disturbances are now treated so effectively that the largest cause of mortality in patients who reach the hospital is no longer related to electrical problems (as was the case prior to the coronary care unit) but rather to heart failure or shock (that is, low blood pressure due to inadequate output of blood by the failing heart). The occurrence of heart failure and shock are largely determined by the location and size of the damaged area. Uncommon complications, such as rupture of the muscle supporting a heart valve, continue to pose a serious threat, but advances in medical and surgical therapy have now brought reductions in the death rate from even these severe complications.

Recent Progress

The Cause of Heart Attack. In individuals who die following a heart attack, a major coronary artery is almost always found to be severely narrowed by a region of atherosclerosis involving its wall. In such regions, fats and cholesterol build up in the blood vessel wall, thickening it and producing an irregular obstruction within the channel of the artery. For many years, it was controversial whether or not a clot was formed on such a damaged area to produce a sudden coronary occlusion, because postmortem examinations carried out many hours after the event often failed to reveal a blood clot. However, recent research has produced an important advance in our understanding of the onset of heart attack. More aggressive early treatment of heart attack had led some investigators to perform a special test in patients early after the onset of heart attack, a test involving injection of a liquid that is opaque to x-rays directly into the opening of a coronary artery to allow visualization of the vessel channel (coronary arteriography). Such studies have now demonstrated that a blood clot is the cause of the blockage of the artery in 80-90 percent of patients who are examined within a few hours of the onset of chest pain. This highly important

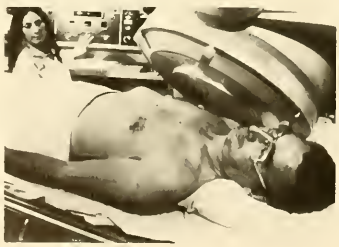
new finding carries significant implications for developing new forms of treatment for heart attack, as we shall see subsequently.

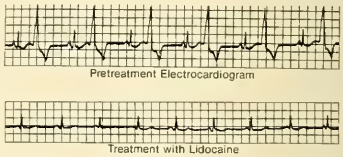
Other factors which may contribute to the sudden blockage of a coronary artery, or influence the amount of blood that reaches the zone of potential muscle damage are also under intensive investigation. For example, a number of events may cause damage to the lining of the blood vessel and promote attachment of elements carried in the blood that produce clot formation. Chemical or nervous influences on the heart may cause spasm of the muscle in the wall of the coronary arteries, further contributing to the degree of blockage. On the other hand, small extra blood vessels (collateral vessels) that naturally "bypass" an area of obstruction in a coronary artery may be present. In some patients such vessels can help to minimize damage to the heart muscle caused by blockage of the main coronary artery.

Prehospital Coronary Care. As already suggested, the fact that some individuals die almost instantly or within a few minutes after the onset of a heart attack is a major obstacle to further reducing the number of deaths following heart attack. In fact, over 50 percent of patients who die from a heart attack do so before they ever reach a hospital. Much has been learned from experiences with mobile coronary care units. Research supported by the National Heart, Lung, and Blood Institute has now clearly shown the potential usefulness of city-wide mobile emergency care systems. In Virginia, for example, it has been demonstrated that the operation of such a system saved the lives of 15 heart attack victims aged 30-69 years per 100,000 population, a lowering of out-of-hospital coronary deaths by 17 percent in that age group. In Seattle, Washington, a highly effective paramedic program and mobile care system has been developed and evaluated, and innovative programs also have extended the availability of CPR through training of citizens to give effective early treatment. So-called "bystander-initiated" cardiopulmonary resuscitation has now been shown to effectively supplement the paramedic team and, when properly applied, it can result in further saving of lives during the critical period prior to hospitalization.

Diagnosis and Treatment of Heart Attack in the Hospital. Better ways of diagnosing an acute heart attack have recently been developed which are more specific than the ordinary electrocardiogram and can estimate the amount of heart muscle damage. For example, enzymes released into the blood stream which originate only from damaged heart muscle can now be measured accurately (such as one form of creatine kinase, or "CPK"). In addition, it has been discovered that certain substances, when injected into the blood stream, are taken up only by damaged heart tissue, whereas others are taken up only by normal tissue. Labeling of these substances with a small amount of radioactivity allows pictures to be taken of the heart using a special camera, so that the damaged regions can be identified.

The gamma camera, seen here, permits noninvasive detection of damaged, as well as normal heart muscle of a patient.





These electrocardiographic tracings illustrate the benefit of treating heart rhythm disturbances with lidocaine. On the pretreatment strip, abnormal, extra beats can be seen as tall, wide spikes. However, on the strip below, these abnormal beats have been completely suppressed after continuous administration of lidocaine.

Treating Electrical Disorders. It was shown a number of years ago that when fatal heart rhythm (ventricular fibrillation) occurs, death can almost always be prevented by electrical shock to the heart followed by treatment with the drug lidocaine, provided the rhythm disorder does not occur in patients who also have shock. Research in patients who are admitted to the hospital early after the onset of symptoms of heart attack has now shown that early treatment with lidocaine can almost completely prevent or abolish the development of ventricular fibrillation. A number of other new medications have become available for use when this drug occasionally proves ineffective.

Electrical pacemakers have been found to reduce mortality in patients with heart attack who develop a very slow pulse rate due to "heart block" (a failure to conduct the electrical impulses from the heart's own pacemaker to its pumping chambers). Also, implantation of a permanent electrical pacemaker in these patients prevents fatal slowing of the heart's rhythm in the months following discharge from the hospital.

Treating Heart Failure. Many factors determine how much heart muscle will survive in the region normally nourished by the blocked coronary artery, but precisely what mechanisms are responsible for irreversible death of the muscle cells continues to be unknown. The death of a zone of heart muscle in the major pumping chamber of the heart (left ventricle) can, of course, seriously affect the ability of the heart to pump blood and maintain the blood pressure. In patients who survive a heart attack, the area of muscle damage undergoes scar formation, but how much limitation of activity the patient will later experience depends on the size of the involved zone.

Detailed studies of pressures and flows within the hearts of patients undergoing a heart attack were safely carried out in Myocardial Infarction Research Units and more recently in Specialized Centers of Research in Ischemic Heart Disease, sponsored and supported by the National Heart, Lung, and Blood Institute. In this research, special methods were developed for measurement of the effects of the damage zone on heart function and the circulation, permitting grouping of patients into those at high and low risk. Also, with such research came improved understanding of those factors which are deleterious and tend to increase the zone of potential damage, as well as those factors or drugs which are beneficial. New drugs that lessen constriction of the blood vessels throughout the body and thereby reduce the work of the heart, as well as drugs that stimulate the contraction of the surviving heart muscle, were found to be helpful in cases of heart failure. In addition, temporary artificial support systems for the heart have also been evaluated.

This improved ability to completely characterize the heart and circulation in patients during the acute phase of a heart attack led directly to the development of emergency surgical treatment for severe complications, including repair of certain forms of heart rupture, or insertion of an artificial heart valve when necessary.

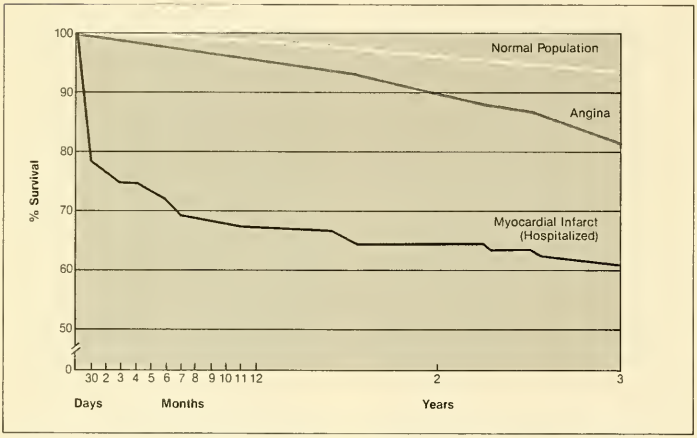
Recent research has also sought to devise approaches for making the amount of heart muscle damage smaller than it would have been without treatment, as discussed later in this report.

Opening Blocked Vessels. The most direct approach for limiting the zone of damage during heart attack would be, of course, to reopen the coronary artery and resupply blood to the threatened area as quickly as possible. Basic animal research supported by the National Heart, Lung, and Blood Institute a number of years ago showed that even when a coronary artery is blocked completely for a few hours, some of the heart muscle is not irreversibly damaged and can be saved if the vessel is reopened and blood flow restored.

Recently, research in patients in the Specialized Centers of Research on Ischemic Heart Disease and elsewhere in the world has been aimed at dissolving the thrombus, or clot (a process called "thrombolysis") within the coronary artery by infusing an enzyme (streptokinase) directly into the obstructed coronary artery within a few hours after the onset of chest pain. Initial studies have been successful in a number of patients, and this exciting new development is now under intensive study to determine whether or not it will lead to smaller areas of muscle damage and reduce the death rate from heart attack.

Drugs to Limit Heart Muscle Damage. Other approaches to limiting the size of the damaged zone are offered by the use of new drugs. Some drugs can reduce the oxygen needs of the endangered area, while others can improve blood flow through accessory coronary blood vessels or improve the diffusion of metabolic fuels to the partially damaged zone. Basic research in animals and pilot clinical trials showed sufficient promise that the National Heart, Lung, and Blood Institute has implemented a multicenter clinical trial (Multiple Investigation of the Limitation of Infarct Size) to determine whether or not certain drugs (propranolol and hyaluronidase) can improve heart function and favorably affect the size of the damaged zone.

The coronary arteriogram on the left shows a blood clot completely blocking a large coronary artery of a heart attack victim. On the right, after enzyme infusion, the blocked vessel is opened, restoring blood flow.



Following hospital admission, heart attack patients experience a mortality of about 20 percent in the first 30 days, as compared to a normal age-matched population and a population with chest pain (angina pectoris).

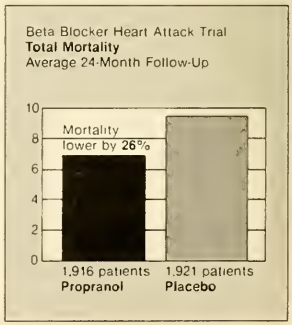
Late Treatment After a Heart Attack. It has been established that the risk of death is relatively high in the early months after a heart attack and then drops off rapidly after 6 months to 1 year. Often, deaths in these early months occur suddenly, or result from another heart attack. Research in patients that have survived a heart attack is now leading to improved methods for predicting, in each patient, just how great this risk is. Factors such as previous heart attack, electrical rhythm disturbances, and signs of heart failure during the heart attack, and the statistical prediction techniques which are leading to improved detection of these high risk patients should eventually result in improved treatment. One approach currently under study by the National Heart, Lung, and Blood Institute involves coronary artery bypass surgery in selected patients within 1 or 2 months after a heart attack. The answer to whether or not this approach is effective in selected patients should be forthcoming from the clinical trial on the effects of bypass surgery (Coronary Artery Surgery Study).

The Beta-Blocker Heart Attack Trial. A more generally applicable form of late treatment was recently evaluated in a large clinical trial begun in 1978 by the National Heart, Lung, and Blood Institute and completed just this year. The study involved nearly 4,000 patients who had experienced a heart attack 1 to 3 weeks earlier. Among these patients, 1,916 were started on the drug propranolol (which slows the heart by partially blocking the nerve supply to the heart and the effects of adrenalin) while the remaining 1,921 patients were assigned randomly to a placebo pill. The results of this study were so promising that the trial was terminated early, when clearly beneficial effects of propranolol were shown to occur during the first year after the heart attack. The drug produced a 26 percent reduction in mortality over the followup period, a saving of 45 lives among the 182 patients expected to die if the group had not been treated with propranolol. The effect was seen in all types of patients (male, female, high risk, low risk), although some patients with certain associated conditions are not able to take the drug. This type of drug is now likely to become a standard form of treatment after heart attack for most patients.

Highlights of Other Research Advances

• For the first time, transplantation of both the heart and the lungs in patients with otherwise inoperable heart and lung disease has been accomplished, due in part to the development of a new drug, cyclosporin A, which suppresses the immune response to organ transplantation. Three of these patients are living and this pro-

During a 24-month followup, results from the NHLBI Beta-blocker Heart Attack Trial show heart attack patients treated with propranolol had a 26 percent lower mortality rate than did patients treated with placebo.



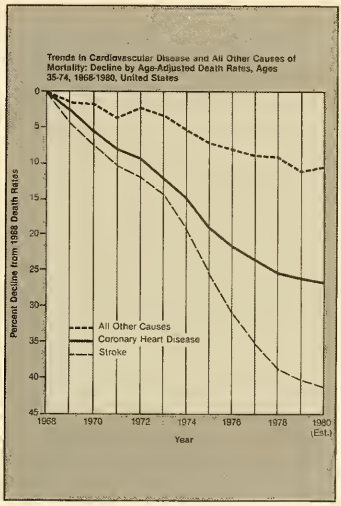
gram is continuing in California with support from the National Heart, Lung, and Blood Institute.

• The Institute has sponsored the formation of a registry of patients who have been treated by the new nonsurgical procedure of "balloon angioplasty of the coronary arteries." The procedure involves dilatation of lesions causing narrowing of a coronary artery, by passing an inflatable balloon through a tube or catheter into the coronary artery. This important new technique is receiving widespread application, and through the registry over 2,000 case histories are now available which indicate an initial success rate of 65-80 percent.

• An important advance has been the development of thermal energy systems for powering artificial heart pumps suitable for total heart replacement, or partial assistance to the heart. An engine with a thermal battery has now been developed that is of sufficiently small size to permit implantation, and it will soon be ready for testing in animals.

• A permanently implantable device has been developed to allow automatic electrical termination (defibrillation) of potentially lethal electrical disturbances of cardiac rhythm. The device, developed at a Specialized Center of Research in Ischemic Heart Disease, has been implanted in more than 30 patients and has successfully terminated a number of such episodes in patients who did not respond to ordinary drug treatment.

• Basic research continues on the causes of atherosclerosis, which is the underlying process responsible for coronary heart disease. New methods have been developed to study, in intact animals, those factors that stimulate overgrowth of the lining of arteries and of the muscle cells in their walls; these methods utilizing radioactive labeling of different cell populations. Various



physiological factors and drugs which affect the growth of these cells can now be studied much more readily in the experimental setting.

• A remarkable decline in mortality from coronary heart disease and stroke has been observed over the past 15 years in the United States, and recent epidemiologic research has shown important regional differences in this decline. Since 1967, heart disease mortality has declined more rapidly on the west coast, and deaths from heart attack have also declined considerably more rapidly than in the East. The reasons behind these differences need further investigation.

Current Opportunities and Problems

Despite advances in the development of animal models for studying the causes and treatment of sudden cardiac death, there has been slow progress in preventing this occurrence in patients. It appears that a clinical trial of the various new drugs now available to control serious electrical disturbances should be considered soon in selected patients at high risk of sudden death.

Research continues on various ways to reduce the damage from heart attack, and the new technique for dissolving clots in a coronary artery offers a means of opening up the coronary artery and reducing the damage. Despite its increasingly widespread application, this technique has not yet been fully evaluated, and it is possible that trials should be organized to study this form of therapy in a controlled manner.

New techniques are becoming available for the visualization of arteries to the limbs and head by "noninvasive" x-ray and ultrasonic techniques. However, coronary arteriography (which requires insertion of a tube directly into the artery) is still required for accurately visualizing the coronary arteries, because they lie deep within the chest and move continuously during the heart beat. Research is needed to develop noninvasive techniques capable of obtaining images of the coronary arteries.

Exercise is often used in the treatment and rehabilitation of patients with disease of the coronary arteries, but there is little direct information about whether or not it has beneficial effects on the heart. Although widespread use is made of exercise training, more research is necessary in this area.

Regions of fat deposition (so-called "fatty streaks") are common in the arteries of children. Although fatty streaks are thought to be precursors of atherosclerotic lesions, the question is unsettled. Techniques may now be available to answer this question, and research is urgently needed in this important area.

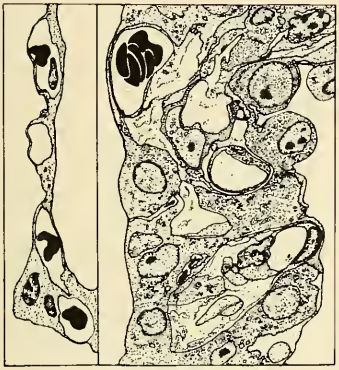
Acute Respiratory Failure in the Adult: A Frequent But Poorly Understood Phenomenon. Respiratory failure is a frequently fatal condition in which damage to the lung is so severe that gas exchange between the air sacs, called alveoli, and the blood is insufficient to meet the metabolic requirements of the body. When this happens, levels of carbon dioxide, the primary metabolic product in the blood, also become excessive. Sometimes this condition occurs in patients with chronic bronchitis, emphysema or other chronic pulmonary disorders when an acute insult to the lung, such as pneumonia, causes chronic respiratory insufficiency to progress to respiratory failure. But more often, respiratory failure is a complication of nonpulmonary disease or trauma in persons whose lungs were previously normal. This distinct clinical entity—the adult respiratory distress syndrome (ARDS)—may be a consequence of drug overdose, major surgery, trauma from accidents, viral pneumonia or other serious illness. Because alterations in the lungs of these patients are similar despite such diverse triggering factors and because their pulmonary condition is not complicated by preexisting lung disease, most research on respiratory failure is addressed to the adult respiratory distress syndrome. Because of the high mortality associated with ARDS, the immediate concern of the physician is better management through earlier recognition of impending failure, more accurate diagnosis, and development of more effective therapies. The major research focus is on fundamental investigations to determine the mechanisms of lung injury and to find ways of preventing or reversing this progression.

To date, ARDS can be defined only in terms of a clinical syndrome: (1) it is usually found in association with a serious illness or injury that requires hospitalization that often does not involve the lungs initially; (2) there is usually a latent period after hospitalization of several hours to a few days during which respiratory involvement is minimal or absent; and (3) after the latent period, acute respiratory failure develops that may progress relentlessly and cause the patient's death.

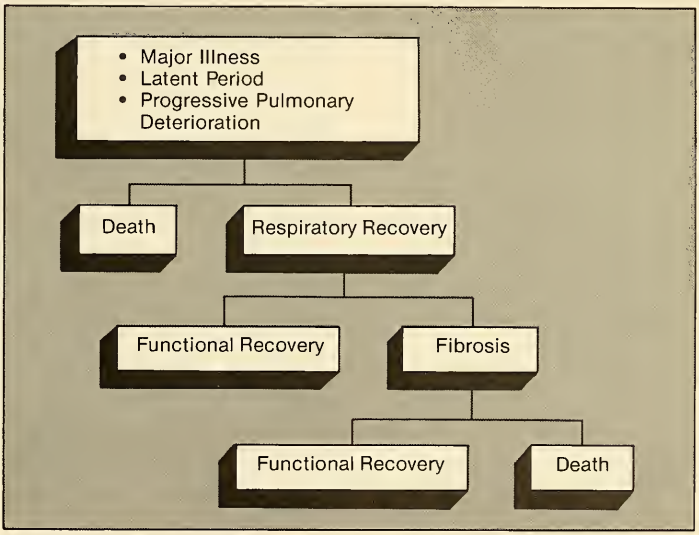
Common anatomical features at autopsy include heavy, airless, congested, red lungs with fluid accumulation in the lung tissue and air spaces and with hemorrhage and, at later times, increased numbers of lung cells and formation of scar tissue. The diagnosis rests on clinical and laboratory features especially because the illnesses are of short duration. Important clinical features include shortness of breath, rapid breathing, grunting, inadequate oxygen content of the blood, and poor response to oxygen. Chest x-rays often show minimal findings early, and later show increased density in portions of the lung in the middle of the chest in contrast to air-filled bronchi. Laboratory findings indicate that movement of oxygen from the alveoli to the blood is impeded, that blood passes through the lungs without optimal exposure to the alveoli, and that the lungs are stiff and expand poorly.

Prevalence and Prognosis of the Syndrome. It is difficult to collect reliable data about ARDS because of inherent difficulties in establishing the diagnosis

Trauma is the leading cause of adult respiratory distress syndrome (ARDS) and onset of symptoms usually occurs within 24 to 48 hours.



These illustrations depict the marked difference between alveolar septa in the normal and ARDS state. Alveolar walls in the ARDS patient become thickened by fluid accumulation in the alveolar cells and air spaces.



Clinical Progression of Adult Respiratory Distress Syndrome

of such an ill-defined disorder. The Institute's Task Force on Research in Respiratory Diseases estimated that 150,000 cases occur each year and emphasized that many of these were in young, previously healthy persons. The overall mortality rate is impossible to obtain because the actual incidence is unknown. However, of some 90 patients, most of whom had ARDS, enrolled in the Extracorporeal Membrane Oxygenator Study supported by the National Heart, Lung, and Blood Institute, only 8 survived (91 percent mortality). Data from the nine centers participating in the study revealed that of 600 patients who received mechanically assisted ventilation using air with an oxygen concentration of greater than 50 percent, a group that includes a high percentage of patients with ARDS, more than 75 percent died. At a large metropolitan hospital during a 3-year period, 119 patients (or 7 percent of all admissions to the respiratory and surgical intensive care units) were diagnosed as having ARDS; of these, 53 percent died. Thus, the incidence of the disorder is appreciable and once ARDS develops, the prognosis is poor.

Past Progress

In the early 1970's little was known about the mechanisms of acute lung injury and repair. Factors helping to protect the impaired lung were not identified. Little was known about the mechanism by which the triggering factors caused the respiratory distress syndromes. Almost no descriptions of lung tissue in the electron microscope or biochemical changes were available. The role of accumulation of fluid in the lung in both injury and repair was undefined. Conventional respiratory support measures were ineffective and specific therapy directed against the mechanisms responsible for the syndrome were lacking. A few patients with severe respiratory distress had survived after extracorporeal perfusion with membrane oxygenators.

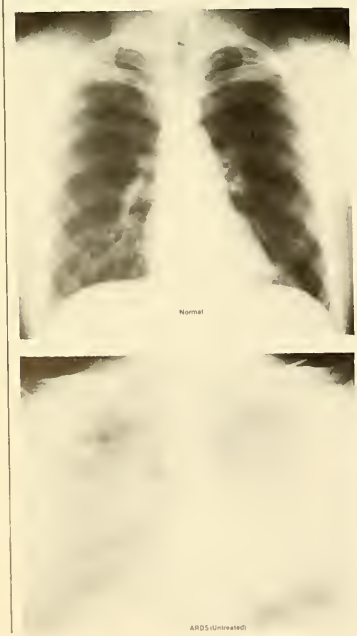
Although ARDS was recognized as a widespread and highly lethal clinical condition, the syndrome was in part a product of the rapid development of sophisticated techniques of providing respiratory support to patients who otherwise would have died of oxygen lack or carbon dioxide accumulation. It was not known whether respiratory support techniques were responsible for the development of ARDS or

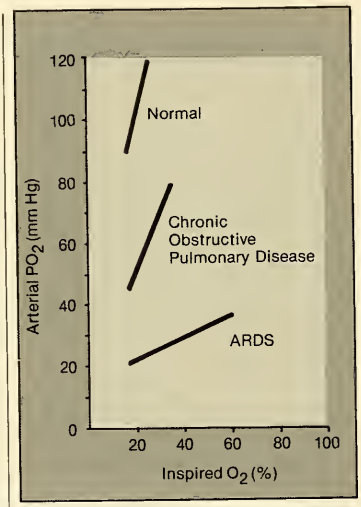
whether the support techniques merely permitted the natural course of the disease process to continue long enough for the syndrome to develop.

Current Treatment

The primary objective of respiratory care for ARDS is to augment the performance of the diseased lungs and to protect the lungs from further injury. Care is based on sound physiologic principles and is available in intensive care units of many large hospitals throughout the country.

Early in the course of adult respiratory distress syndrome, the chest x-ray may be normal. Subsequently, signs of pulmonary injury gradually appear. The opacity of the x-ray below indicates much fluid accumulation and very little air in the lungs.





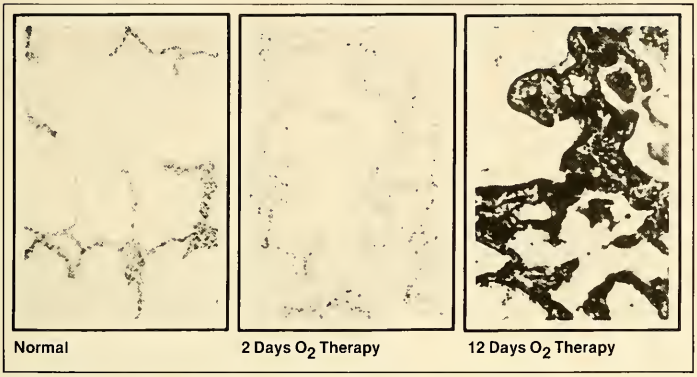
Arterial blood oxygen level of an ARDS patient receiving oxygen therapy is considerably less than levels achieved in the normal person and chronic obstructive pulmonary disease patient, thus indicating severe loss of gas exchange capability.

Respiratory care of severely ill patients requires careful monitoring, nursing and intelligent management of a large number of variables. Patients are hospitalized in special care units wherein one nurse cares for only one or two patients. A physician is available within a few minutes. The unit contains special ventilatory and resuscitation equipment and electronic devices to monitor the electrocardiogram, arterial blood pressure in the lungs and elsewhere in the body, pressure in the veins supplying blood to the heart, temperature, and respiratory rate. The levels of oxygen and carbon dioxide in arterial blood are measured frequently. The amount of blood pumped by the heart is measured intermittently by automated methods.

Mechanical ventilation, increased oxygen concentration in the supplied air, and maintenance of a small positive pressure against which air must be expelled are the three cornerstones of conventional respiratory support therapy. Mechanical ventilation is provided patients by tubes placed in the windpipe (trachea) and by pumping either a certain volume of air or air at a certain pressure using mechanical respirators. Machines can be adjusted to provide controlled ventilation. Sedation and sometimes drugs to paralyze the chest muscles are used to control the patient's own respiration so that the machine can assist or control ventilation.

Increased oxygen concentrations in the supplied air are provided by oxygen-air blenders. Increased oxygen content in the air helps to overcome the barrier to oxygen diffusion into the blood. Unfortunately, prolonged exposure to oxygen concentrations above 70 percent is toxic and in time causes accumulation of fluid in the lung and congestion of blood flow. Toxicity, which is related to both oxygen concentration and duration of exposure, limits the therapeutic value of high oxygen concentrations; however, increased oxygen concentrations in nontoxic ranges in air supplied to the patient are a most important means to increase oxygen content of the blood.

Elevation of the pressure against which the lungs must expel air during spontaneous or mechanical ventilation is also an important technique of respiratory support. The increased pressure effectively increases the functional volume of the diseased lungs and helps to prevent collapse of diseased alveoli. The maneuver usually increases the oxygen content of arterial blood. In some patients, however, breathing out against a high pressure can reduce the amount of blood pumped by the heart or can cause escape of air into the



Prolonged exposure to high-oxygen therapy induces pulmonary damage leading to development of ARDS.

space around the lung (pneumothorax) or the heart (pneumomediastinum).

Other aspects of conventional respiratory care are designed to prevent complications and to control the disease process. Use of warmed humidified gasses, proper positioning, chest physiotherapy, intermittent hyperinflation of the lung, and aspiration of airway secretions all help to prevent collapse of the lung and pneumonia. Frequent studies of airway secretions are done to detect the earliest signs of infection; antibiotics are given to further reduce the risk of superimposed bacterial pneumonia. Careful management of fluid balance and nutrition is also essential for respiratory care of seriously ill patients.

Thus, conventional respiratory therapy embraces a variety of techniques to enhance the performance of diseased lungs and to prevent early deaths from lack of oxygen or accumulation of carbon dioxide. However, some investigators have obtained data showing that few patients survive if respiratory support therapy is required for more than 1 to 2 days. Unfortunately, conventional therapy does not rest the diseased lung. Indeed, injuries induced by prolonged exposure to high oxygen concentrations in the air and to repeated mechanical expansion of the lung or both are a recognized complication of usual medical management. As a result, treatment may worsen lung injury and prevent recovery.

Current Research and Opportunities

Until recently, the major emphasis of research on ARDS was directed at providing improved forms of early detection along with frequent measurements of oxygen and carbon dioxide content in the blood and sophisticated regimens of artificial respiratory support, including oxygenation of the blood outside the body by membrane oxygenators (extracorporeal oxygenation). Despite this aggressive treatment, however, recent controlled studies show that the mortality rate of these patients remains very high. There is a general recognition that more effective therapy can only come from an improved understanding of the mechanism of lung injuries associated with the syndrome.

Several Institute programs have been expanded through vigorous and timely pursuit of new opportunities for research into mechanisms of lung injury and repair. Three Specialized Centers of Research in Adult Respiratory Failure were initiated in 1979 and were designed to establish interdisciplinary research programs to investigate changes associated with the progressive lung damage that results in ARDS. This was the first attempt to initiate a program to study adult respiratory failure with a major emphasis on acute lung injury and repair rather than on technology of respiratory support. Two of the special aspects of this center program are that clinical treatment units offer an opportunity to study, in more detail, the natural history of the disease and that patients are carefully investigated in various research projects.

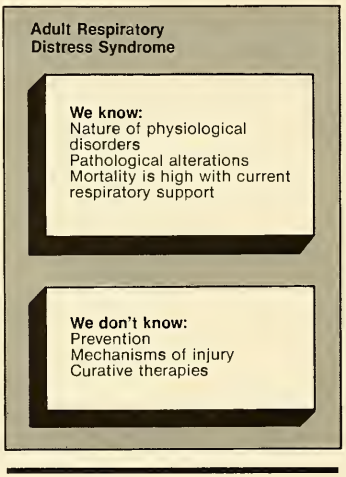
The pervasive nature of the lesion in adult respiratory distress syndrome is reflected in the diversity of current research approaches. These include examination of changes in the alveolar lining that affect lung expansion and diffusion of oxygen and carbon dioxide, alterations in the lining of the pulmonary blood vessels that lead to excess leakage of fluid into the lung, formation of scar tissue that develops in many patients who recover from ARDS, and the roles of the blood clotting and immune systems in development of ARDS.

A dog model of ARDS, produced by a single injection of n-nitroso-N-methyl-urethane, is of interest because it incorporates the essential abnormalities of the syndrome, including mechanical changes. The injury produced by this chemical results from damage to a single-cell system, the lining of the alveoli, and results in

decreased formation of surface-active lipids and stiffness of the lung. In recent clinical studies, surface-active lipids obtained from the bronchi of patients with ARDS showed abnormalities of these lipid components, but as healing of ARDS progressed there was gradual normalization of the composition of surface-active lipids, perhaps due to repair of the alveolar lining.

Recent studies of the immune systems indicate a previously unsuspected mechanism that may enhance or perpetuate the alveolar wall injury in ARDS. A component of the immune system, complement $C5_a$, is known to cause an intense inflammatory response when activated. Complement is a series of interacting serum proteins that play a role in the body's defense system and is activated when proteins known as antibodies interact with foreign bodies known as antigens. When complement $C5_a$ was instilled into rabbit lungs, there was a marked accumulation of white blood cells and damage to the alveolar lining and capillaries similar to that seen in ARDS. This line of inquiry is being pursued to examine further the role of complement $C5_a$ in attracting white blood cells and to determine whether tissue injury is induced by secretions of the white blood cells. Other recent investigations have shown the effect of complement $C5_a$ to be inhibited by treatment with adrenal steroids. These studies have important implications for therapeutic interventions to arrest or prevent changes associated with ARDS.

While fundamental studies of mechanisms underlying respiratory failure have the ultimate goal of preventing or arresting lung damage, other studies are concerned with amelioration of the clinical consequences of respiratory failure and with improving survival of patients with ARDS. As discussed elsewhere in this report, oxygen administered in greater than normal concentrations or at greater than average pressure may result in oxygen toxicity. This problem is the focus of studies of protective enzymes to increase tolerance to oxygen. In addition, efforts continue to develop devices for extracorporeal oxygenation of the blood and for artificial pacing of respiration by stimulation of nerves to the diaphragm. The problem of lung transplantation is also still being pursued with particular emphasis on animal studies to improve preservation of donor lungs and to reduce immunologic rejection after implantation.

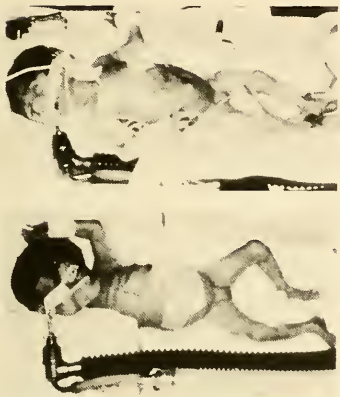


Because of their debilitated condition, ARDS patients are easy victims to hospital-acquired infections of the respiratory tract, a major cause of mortality. Recent studies have shown that pneumonias may be caused by a bacterium that is a common inhabitant of the colon, but is rarely found in the respiratory tract of healthy individuals. It has now been shown that this bacterium can form colonies in the respiratory tract of ARDS patients and that their presence is associated with a sudden change in the surface cells of the respiratory tract, making it possible for the bacteria to adhere to the lining cells. Hence, the bacteria are not cleared by the respiratory secretions.

Highlights of Other Research Advances

• In 1976, a clinical trial was initiated to establish whether nocturnal low-flow oxygen therapy would be as effective as continuous oxygen therapy in patients who suffer from chronic obstructive pulmonary disease and oxygen lack. Long-term oxygen administration is an expensive form of treatment, yet little scientific evidence was available to suggest that continuous oxygen therapy was necessary, especially since patients are known to suffer their most severe episodes of oxygen lack while sleeping. The results from this clinical trial provided convincing evidence that patients on nocturnal oxygen (12 hours) have twice the mortality rate of those on continuous oxygen therapy. This finding, which has been widely disseminated, is expected to have a major impact on the treatment of patients with the disease.

• Preliminary results of a major clinical study on neonatal respiratory distress syndrome (NRDS) indicate that a synthetic steroid drug called dexamethasone can lower the incidence of NRDS among newborn infants when administered to mothers who are at high risk of premature delivery. Infants born prematurely are more likely to suffer from NRDS because their lungs have not developed sufficiently to meet their oxygen needs at birth. Up to 60 percent of premature infants have NRDS and as many as 10,000 deaths among live born infants are attributed to NRDS each year. This form of therapy has the



Twins, born prematurely, receive treatment for neonatal respiratory distress syndrome (NRDS).

potential to prevent at least 15,000 cases of NRDS and thus save over $200 million per year for neonatal intensive care.

• Investigations into how basic processes at the cellular level influence the etiology and treatment of pulmonary diseases continue to yield new and useful information. For example, the role of the extracellular matrix (composed of collagen, elastic fibers, proteoglycans, and fibronectin) in the development of both emphysema and adult respiratory distress syndrome has recently been recognized.

• The discovery of surface-active lipids, called pulmonary surfactant, led the way toward the recognition of the lung as an active metabolic organ. Interest in pulmonary surfactant continues to expand and grow. The awareness of its vital function to prevent the collapse of alveoli has prompted extensive investigation of its complex physical properties, composition, metabolic pathways, and physiological regulation. Dysfunction of the surfactant system in the respiratory distress of the newborn or in adult lung disease is still not completely understood. However, knowledge gained from basic studies of the surfactant system should continue to contribute to our knowledge and treatment of both neonatal and adult lung diseases.

• Pulmonary hypertension usually occurs as a secondary disease in association with either congenital or acquired heart disease or chronic lung disease; however, it can occur as a primary disorder. Although this disease is relatively uncommon, it appears to be increasing. It can occur in both children and adults and carries with it a poor prognosis and high mortality rate. The disease is poorly understood and probably arises from diverse causes and involves a variety of pathogenetic mechanisms. Effective therapeutic measures currently available for treating the disease are limited. In 1981, the NHLBI established a patient registry to collect data on primary pulmonary hypertension from over 30 clinical centers. Emphasis will be given to criteria used to diagnose the disease and the regimen used to treat these patients. It is hoped that through the analyses of these pooled data new insights will be gained into the diagnosis, pathogenesis, and treatment of primary pulmonary hypertension.

As a result of NRDS treatment advances gained through NHLBI-supported studies, the same twins, seen here at two years of age, now enjoy a normal, healthy childhood.

Current Opportunities and Problems

• Chronic obstructive pulmonary disease is the fastest rising major cause of death in the United States; over 56,000 deaths were recorded in 1980. Existing evidence supports the hypothesis that small airways dysfunction is an early manifestation of chronic obstructive pulmonary disease and that long-term controlled trials to screen for abnormalities of lung function could be an effective means of preventing the serious consequences of chronic airflow limitation in a large number of people.

• During the last 10-year period, a significant scientific accomplishment has been the isolation, maintenance, and characterization of various types of lung cells in tissue culture. Cellular biologists and biochemists must now characterize the structural and functional features of the various types of lung cells, study interrelationships between the different cell types, and investigate cellular modification associated with lung injury and disease. Although the endocrine role of the lung has been recognized for many years, there is now heightened interest in the system of diffuse endocrine or endocrine-like cells which are scattered throughout the epithelium of the lung. These cells have been well characterized in the gut and brain and have been shown to be responsible for the production and/or storage of many different types of polypeptides or hormones. Their abundance in fetal lungs is well documented, but their precise roles have not been well-defined in either the fetal or the adult lung.

• Cigarette smoking is believed to be associated with 90 percent of lung cancers, 75 percent of chronic bronchitis and emphysema, and 15 percent of other respiratory diseases. It also interacts additively, and sometimes synergistically, with exposure to occupational risk factors and community air pollution. Programs to discourage smoking have grown in terms of the types of people they address and the range of procedures and levels of intervention they employ. Several projects have successfully encouraged pregnant women, children, or adolescents to quit or not to start smoking. Successful new approaches to this problem include instruction in self-control skills, self-help manuals, mass communication interventions, individualized encouragement by a physician, and extended group and individual treatment as part of the Multiple Risk Factor Intervention Trial comprehensive program for heart disease risk reduction. Research in chronic smoking patterns and in relapses following cessation indicates that the smoking habits of family and friends, social support for maintained cessation, and stress may be critical targets of future programs in this area.

Blood Diseases and Resources

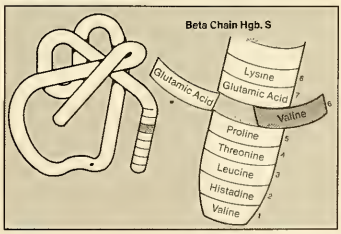
Sickle Cell Anemia: A Molecular Disease and Its Treatment

The Division of Blood Diseases and Resources of the National Heart, Lung, and Blood Institute supports basic and applied research related to blood diseases and blood resources. The following programs are encompassed in the Institute's blood program: 1) bleeding disorders, including hereditary diseases such as hemophilia and acquired bleeding due to platelet disorders; 2) disorders related to thrombosis, i.e., blood clots that obstruct blood flow, leading to such conditions as heart attacks and strokes; 3) disorders of red cell metabolism and enzymes and hemoglobin structure such as Cooley's anemia which affects many Americans, primarily of Mediterranean descent; 4) sickle cell disease which affects approximately 50,000 Americans, mostly black, but also is infrequently seen in Americans of Hispanic, Italian, Mediterranean and Mideastern ancestry; and 5) blood resources which supports activities related to three essential areas: namely, transfusion of blood and blood components (including red cells, white cells, platelets, plasma and plasma products), blood substitutes, and hepatitis.

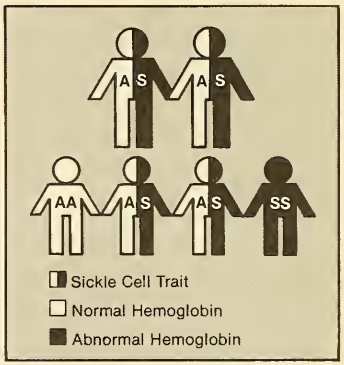
Blood diseases, if one includes thromboses resulting in heart attacks and strokes, are the greatest cause of morbidity and mortality in the United States. This section summarizes progress made at the basic and clinical levels in blood diseases and resources with emphasis on sickle cell disease and to demonstrate that support of this biomedical research has clinical applicability and has been beneficial to millions of Americans.

Sickle Cell Disease. Sickle cell disease is a hereditary disorder of the red blood cells. Although first described in 1910, it was not until the late 1940's that sickle cell disease was found to be caused by an abnormal hemoglobin leading to "sickling" of the cells. This was the first description of a "molecular disease." The principles derived from the study of sickle cell disease have resulted in wide application to a variety of other disorders. Hemoglobin, the protein which carries oxygen to tissues throughout the body, is composed of two pairs of protein chains, called alpha and beta. In 1956, the precise genetic defect in sickle hemoglobin was identified and found to involve a single amino acid, valine, that was substituted for glutamic acid in the sixth position of the beta chain in the hemoglobin molecule.

Sickle hemoglobin, the result of a single genetic defect, occurs when the amino acid valine replaces glutamic acid in the sixth position of the hemoglobin chain.



Sickle cell anemia is inherited as an autosomal recessive, i.e., both parents of an affected offspring are carriers of what is referred to as sickle cell trait (AS). Individuals with sickle cell trait have few if any clinical symptoms, since they carry only one abnormal hemoglobin gene and normal hemoglobin A is the predominant hemoglobin. Patients with sickle cell anemia inherit two abnormal hemoglobin genes (SS, one from each parent).



When each parent carries one normal hemoglobin gene (A) and one sickle hemoglobin gene (S), there is a one in four chance they will have a child with sickle cell disease.

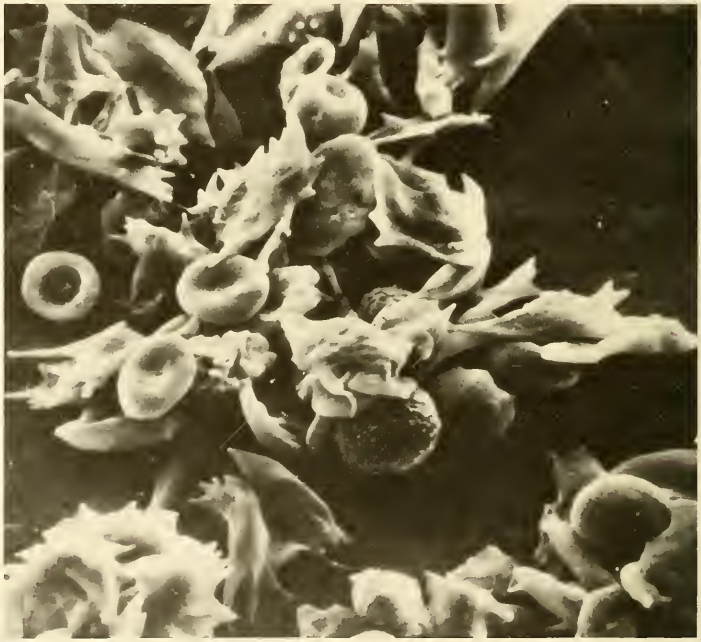
Sickle Cell Disease Program. The sickle cell disease program was established in 1972 to meet the national mandate of the National Sickle Cell Anemia Control Act for research in the diagnosis, treatment, education, and counseling in sickle cell disease. Over 50,000 black Americans have this disorder which, unlike acquired diseases, lasts a lifetime and takes a heavy toll on the individual and the family. Medical costs per patient are staggering and, throughout the Nation, are estimated at over $500 million annually. These costs must be borne by the patient, third-party reimbursements, or the Nation's social service system. In addition, the problems associated with insurability, discrimination in job opportunities, and the psychological impact of any chronic disease place this

disease as one with significant economic and social impact and, therefore, deserves national support. The sickle cell disease program supports basic research, targeted research, and activities in education, screening and counseling.

Research Advances

Basic research has enhanced understanding of the pathophysiology of sickle cell disease. Sickle hemoglobin is less soluble than normal hemoglobin and upon losing its oxygen to the tissue cells (deoxygenation), it aggregates and forms fibers within the red cell, distorts the cell and produces the "sickled" shape. Unlike normal red blood cells which are round and pliable, sickled cells are rigid, tend to stack up and have difficulty traversing the small capillaries, leading to occlusion of small blood vessels. Tissues and organs are thereby deprived of oxygen, and this chronic obstruction leads to organ damage. Almost every organ of the body can be involved with this disease process, and the recurrent painful episodes or "crises" are the clinical hallmark of sickle cell disease. In addition, the lifespan of the red cell is shortened from the normal 120 days to approximately 20 days, thus causing a chronic anemia.

Observations of the cells which have a shortened survival, the irreversibly sickled cells, have led to new information on the role of the red cell membrane in sickle cell disease. During deoxygenation, remarkable events occur. As hemoglobin sickles, the membrane is deformed and the repeated cycle of sickling and unsickling leads to a membrane defect with a demonstrable loss of intracellular water and potassium and an increase in calcium.



Most of the red blood cells in this scanning electron micrograph have abnormal shapes with projections of distorted membranes (sickle cells). The biconcave discs present are normal red blood cells.

These cells are dehydrated and rigid, with an increased intracellular hemoglobin and deformation of the red cell membrane. Some of these cells do not resume their round shape upon reoxygenation and are irreversibly sickled. Alterations in arrangement of the distribution of fatty substances in the red cell membrane and subsequent surface charges have been reported to influence the interactions of the sickle cell with the surface of small blood vessels.

Early observations that sickle hemoglobin migrates differently than normal hemoglobin in an electrical field permitted accurate and rapid diagnosis of sickle cell disease and sickle cell trait through the process of hemoglobin electrophoresis. The refinement of this technique made possible the diagnosis of sickle cell disease in newborn infants. This approach offers the potential for preventing life-threatening events occurring in early infancy

through early family education and entry of the infant into a closely supervised health care delivery system.

Recombinant DNA technology has made a significant contribution to our knowledge of human genetic diseases. Mapping hemoglobin genes on the chromosome using genetic (cDNA) techniques has led to the identification of the genetic locus for the beta globin gene on chromosome 11. The substitution of a single base in the genetic code, i.e., thymidine for adenine, leads to the substitution of valine for glutamic acid at the sixth position of the beta chain of hemoglobin. This point mutation is responsible for sickle cell disease.

Making use of these new technologies for the prenatal diagnosis of sickle cell disease has made a significant contribution to the whole field of molecular genetics. Prior to 1978, a sample of fetal blood, obtained through the process of fetoscopy (observing, through instruments, the fetus still in the womb), was required for biochemical analysis of globin chains to determine whether the fetus was affected. This approach has largely been replaced through gene mapping of DNA fragments produced by enzymes that split DNA at specific sites. For couples at risk for birth of a child with sickle cell disease, it is possible to obtain fetal cells (fibroblasts) from amniotic fluid, thereby avoiding the risk to the fetus which occurs with fetoscopy. More recently, an enzyme has been shown to cleave DNA at the specific point of the beta mutation. This valuable new diagnostic aid should facilitate the prenatal diagnosis of sickle cell disease. This is a major contribution to modern medicine with important implications for other genetic disorders.

Evidence that increased amounts of fetal hemoglobin increase the survival of red cells in patients with sickle cell disease and delay the onset of sickle cell disease in the newborn is explained by the fact that fetal hemoglobin carries oxygen more efficiently than sickle hemoglobin. Mechanisms regulating the "switch" from fetal to adult hemoglobin during the first year of life have been a major area of targeted research along with efforts to increase synthesis of fetal hemoglobin. Animal models have been used to manipulate the expression of gene coding for globin chains, with recent reports of stimulating fetal hemoglobin production in the mature baboon. However, initial high levels of fetal hemoglobin could not be sustained and further investigations in this area remain a high priority.

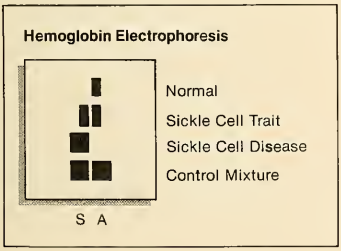
The architecture of the structure of sickle hemoglobin when it crystallizes has been at the center of research investigations for many years because detailed knowledge could point to therapeutic approaches which interfere with its formation.

The possibility of developing drugs to treat sickle cell disease was suggested by observations that urea and cyanate inhibited sickling in the test tube. However, cyanate, when given to patients orally, caused undesired side effects. A new approach involves treating red blood cells with cyanate outside the body (extracorporeal carbamylation) and removing the excess cyanate before giving the blood back to the patient. This procedure is promising, but further clinical studies are needed to determine the clinical effectiveness of this agent.

A recent development is the specific chemical modification of the hemoglobin molecule to prevent its aggregation. Until now, it has been difficult to find antisickling agents with high specificity for hemoglobin and minimal reactions with other proteins. Bissalicylates, referred to as "two-headed aspirins" have been synthesized and these agents significantly reduce the tendency for sickle hemoglobin to aggregate. Thus, a new class of agents has been identified for further research.

More recent evidence based on biophysical studies of the abnormal hemoglobin, shows that even if the cells are not morphologically deformed, the crystallized hemoglobin renders the cells rigid, thereby hampering easy passage through small blood vessels. These biophysical methods employ light scattering, nuclear magnetic resonance, and viscosity measurements. The kinetics of polymer formation suggest that there is a specific time interval for this process to occur during circulation of the blood and an approach which could keep the cells from forming polymers for the 30-40 seconds required for blood to traverse the smallest blood vessels would have great clinical potential. Other therapeutic approaches include attempts to prevent the leak of potassium and water from the cells, to modify the red cell membrane, to increase oxygen affinity, and to prevent sickle hemoglobin polymerization.

Hemoglobin electrophoresis, a technique used for early diagnosis of sickle cell disease, shows the migration of various hemoglobins. Persons with hemoglobin A have normal hemoglobin, those with sickle cell trait have both A and S hemoglobin, and those with sickle cell disease have only hemoglobin S.



Clinical research has progressed at a swift pace over the past decade and has provided much heretofore unknown clinical data about sickle cell disease, primarily reported from a very small population of patients across the country. However, there remains a tremendous imbalance between what we know and our understanding of the disease as it affects the patient. The variability of clinical severity ranges from very mild to very debilitating. This observation continues to challenge the researcher and the clinician. Only recently has the medical community begun to appreciate the spectrum of this illness. The National Heart, Lung, and Blood Institute supports a multicenter prospective study to elucidate the "natural history" of sickle cell disease from birth through adulthood. Over 3,500 patients, ranging from newborns to patients in the sixth and seventh decade, are enrolled in this 5-year study. Major unanswered questions related to acute and chronic complications, growth and development, splenic function, risk factors, infections, organ damage, and definition of "crises" are under investigation. Classification of clinical severity, a major objective, should permit a more rational use and evaluation of therapy in patients and identify fertile areas for future research.

Advances through support of clinical studies of eye complications of sickle cell disease have been rewarding. A national classification of sickle cell eye disease has been established, and routine eye examinations of sickle cell patients has increased early diagnosis of these problems. The treatment of blood vessel abnormalities in the eye by means of light photocoagulation has reduced the overall visual loss. Ongoing studies continue to assess other approaches to determine the best modality for future treatment of ocular complications.

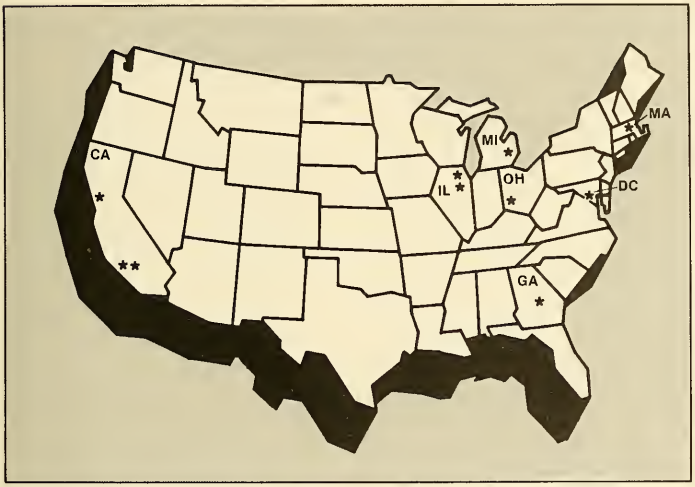
The immune response and increased susceptibility to infections in sickle cell patients remain a challenge. The particular importance of this complication in early childhood cannot be minimized, as infection accounts for the major cause of mortality in the young pediatric population. An important contribution to our understanding of this phenomenon has been data from investigations of splenic function. Although the spleen of the young patient may be large and palpable, it does not function normally and does not protect the sickle cell disease patient from infection. The pneumococcal vaccine, licensed for use in patients over 2 years of age, may prove to be of some benefit for the older child with infections,

With NHLBI-supported research, children with sickle cell disease can look forward to improved quality of life through better methods of management and treatment of the disease.

but overwhelming infection in the sickle cell pediatric patient is still unresolved.

Even though treatment is mostly supportive, a significant number of patients are treated with repeated blood transfusions for complications such as stroke, crises, and pregnancy. Newer techniques using exchange transfusions as well as young red cells, "neocytes," offer the possibility of improving the anemia of patients with longer intervals between transfusions.

Comprehensive Sickle Cell Centers. Serving as a prototype of similar complex programs developed in categorical disease areas, the Comprehensive Sickle Cell Centers program was the first supported by the National Heart, Lung, and Blood Institute which incorporated an active educational component into the same administrative structure as the research projects. Centers bring together basic and clinical research, clinical applications and demonstration programs in diagnosis, education and counseling for a coordinated approach to sickle cell disease. As knowledge is gained at the molecular, cellular and clinical levels, the mechanism is available through the centers to transfer findings rapidly and effectively into clinical use, thereby bridging the gap between the research community and the health care delivery system. Pneumococcal vaccine, readily applied through the population of patients in sickle cell centers, is an example of this process, and led to licensure of the vaccine.



Ten Comprehensive Sickle Cell Centers supported by the NHLBI, conduct a multifaceted program for the alleviation of the many problems associated with sickle cell disease and related disorders.

The 10 centers, dispersed throughout the country, provide a cadre of well-trained hematologists, internists, pediatricians, obstetricians, social workers, and psychologists for a comprehensive approach to disease management. These teams have greatly improved the monitoring of patient care and reduced the previously episodic and impersonal relationship with the health care providers.

Education of the public and the patient has changed the perception of sickle cell disease in the community, as reflected by participation in appropriately developed screening programs, with counseling and followup. Health educators and other professionals are trained to develop educational programs and to disseminate accurate information to all segments of the community. There is no "animal model" for sickle cell disease and therefore it is imperative that patients be educated about their disease, understand its ramifications, and participate in research protocols. Professional education through inpatient hospital visits and continuing education programs under sponsorship of the sickle cell centers have had a "multiplier" effect in keeping physicians knowledgeable about current research and management procedures for sickle cell patients.

In the center environment, a "critical mass" of outstanding research scientists pursue basic and clinical investigations in a wide range of interrelated disciplines and have contributed to our knowledge base and led to new and productive areas of investigations. The center as a "concept" for serving the needs of the scientist, the patient, the clinician, and the general community, in an integrated approach to sickle cell disease, has been an effective mechanism and warrants continued support.

Future Prospects

Even though there remains a wide gap in our knowledge of molecular events in sickle cell disease and care for the patient, prospects for the future are optimistic. One example of potential application of basic research is the use of genetic engineering. There is preliminary evidence in experimental animals to show that the normal hemoglobin human gene can be inserted into primitive bone marrow cells that give rise to the adult red cell. If the normal hemoglobin gene could be inserted into the primitive bone marrow cells of a patient with sickle cell disease, so that the transformed cells containing the normal hemoglobin had a growth advantage over the abnormal sickle hemoglobin cells, it would theoretically be possible to cure this disease. While such an event may be years in the future, many of the techniques are now available and experiments have been performed on animals. The clinical application has far-reaching significance for other hemoglobin abnormalities as well, i.e., Cooley's anemia.

New animal models for studying regulation of fetal hemoglobin production to determine factors influencing the "switch" mechanism hold promise for possibly maintaining the production of fetal hemoglobin in adult life and thereby ameliorating the symptoms of sickle cell disease.

Highlights of Other Research

Blood Diseases. The blood diseases program includes research on diseases caused by blood clots (thrombi, thromboembolic disease), bleeding (hemorrhagic diseases, platelet abnormalities), and abnormalities of the red blood cell, i.e. anemia, blood cell production, etc., as well as genetic anemias such as Cooley's anemia.

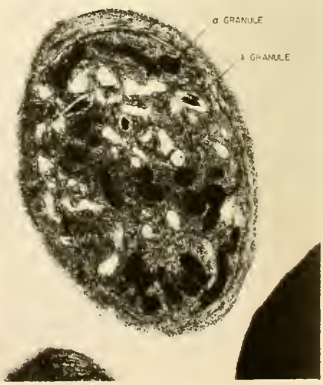
• The diseases related to the clotting mechanism are interrelated with atherosclerosis (hardening of the arteries). Recent research has shown that a swine animal model lacking a piece of blood clotting factor VIII seems to be protected against atherosclerosis as well as sudden death following induced heart attack. These pigs lack the von Willebrand factor and have von Willebrand's disease, a disease similar to that in humans who also lack the von Willebrand factor. When pigs with von Willebrand's disease are fed a high cholesterol diet, they are protected against atherosclerosis while normal pigs are not. Research is being supported to determine how the von Willebrand factor contributes to atherosclerosis and to find ways to interrupt this process therapeutically, without disrupting the normal clotting mechanism.

• Heart attacks usually occur because clots form in the coronary arteries, thereby obstructing blood flow to heart muscle with resulting death of muscle tissue. This observation has led to an exciting new therapeutic development, discussed earlier in this report, because agents that dissolve clots (thrombolytic agents) have been biochemically purified and characterized and have already been used to dissolve clots in the veins of the leg and the lung arteries. These thrombolytic agents (streptokinase and urokinase) have recently been used in patients who have had heart attacks. For example, within a short time after a documented heart attack, thrombolytic agents have been infused into the coronary arteries by placing a catheter directly into the arterial circulation. Clinical results have been promising and indicate that bathing the clot in thrombolytic agents results in dissolving the clot so that blood flow to the heart is increased and the area of damage to the heart muscle can be significantly decreased. Other investigators presented, at a 1981 NIH conference, suggestions that the thrombolytic agents might also be beneficial if administered by the usual intravenous route, a procedure which is simple and less risky than placing catheters in arteries. This type of clinical use of thrombolytic agents would not have been possible without basic biochemical studies on the isolation, purification and mechanisms of clot-dissolving agents. A potential new thrombolytic agent (hementin) has recently been isolated from the leech and this new agent could be more efficacious than those currently available.

• Another exciting advance is the further purification of heparin, a well known anticoagulant drug that prevents clots from forming. Current heparin preparations are impure and little is known about the precise biochemical nature of heparin preparations. A recent discovery indicates that more purified and more potent low molecular weight heparin preparations can be prepared. If this can be accomplished, more precise heparin doses and laboratory methods of monitoring the beneficial effects of heparin can be established. It is also very possible that purer heparin preparations will circumvent some of the adverse side effects of heparin such as heparin-associated thrombocytopenia (low platelet counts). This problem is now under active investigation by three of the four Specialized Centers of Research in thrombosis now funded by the Institute.

• Research related to platelets, blood cells smaller than white corpuscles, also shows promise of ameliorating those diseases related to atherosclerosis, heart attacks and strokes. For example, evidence has been acquired suggesting that when the blood vessel wall is damaged, platelets stick to the vessel wall and release agents that contribute to the atherosclerotic lesion. Specifically, the platelet growth factor is released and causes smooth muscle cells, a normal component of arteries, to multiply and pile up. Proliferation of smooth muscle cells is the hallmark of atherosclerotic plaques. Thus, if one could prevent platelet sticking and release of the platelet growth factor, atherosclerosis could be reduced. Aspirin prevents platelet sticking and has been shown to be efficacious in preventing strokes in

Alpha granules (α), as seen in this electron micrograph of a platelet, contain among other components, a growth factor thought to contribute to smooth muscle proliferation of vessels and hence, to the atherosclerotic lesion. Delta granules (δ) contain serotonin, a weak aggregating agent and blood vessel constrictor.



selected populations. These types of studies led to the discovery of a new antithrombotic agent, prostacyclin, synthesized by endothelial cells that line the blood vessel wall. Prostacyclin prevents platelets from forming platelet plugs and has been used in preliminary clinical trials in patients with atherosclerotic disease. The discovery of prostacyclin has been followed by attempts to make prostacyclin-like compounds that have antithrombotic activity, but do not have the adverse side effects of the natural prostacyclin compounds. The natural compounds cause low blood pressure and have a very short lifespan in the circulation. Hence, it would be of enormous benefit if synthetic prostacyclin without these drawbacks could be synthesized.

• The very basic studies on the blood coagulation mechanism have provided advanced techniques and methodology that may well lead to the development of ways to prevent thrombotic diseases or, if thrombosis occurs, to find better methods of treatment. More research is needed to understand the details of the interaction of the vessel wall with the blood circulating through the vessel. Further work on how blood cells themselves contribute to the clotting mechanism is needed. These studies are potentially applicable to cancer metastases since it appears that an intact clotting mechanism may enhance metastasis or that cancer cells possess intrinsic mechanisms by which they can anchor to tissues via the fibrin clot.

• It is always difficult to project future discoveries, but examples give some idea of how scientific progress is made. For example, who would have predicted that human urine, which contains a potent clot-dissolving substance (urokinase), would be used to isolate a thrombolytic agent and that this thrombolytic agent could be manufactured by pharmaceutical firms from tissue cultures of human kidney? Such advances depend upon detailed knowledge of the clot-dissolving mechanism, tissue culture techniques, biochemical purification procedures, toxicology studies, animal trials, preliminary trials in humans, and finally a clinically useful agent. Who would have guessed that protein C, a vitamin-K-dependent plasma protein, which only a few years ago had no known function, is now known to be a very important regulatory agent for the clotting mechanism which is activated by cells lining the blood vessel wall? Who would have known that this same protein would be found in 1981 to be lacking in patients who developed clots in veins? Thus, for some patients, replacement of protein C may protect them from thrombotic diseases. From these examples, one can safely predict that future support of both basic and clinical research will be rewarding and of benefit to the health of millions of Americans.

Blood Resources and Transplantation

This program supports, coordinates, and plans for the efficient use of, and access to, blood and blood products. Another important area of responsibility is the coordination of tissue and organ transplantation through a better understanding of transplantation biology.

• Over 10 million units of blood were collected for transfusion in the United States in 1979. The National Heart, Lung, and Blood Institute has been instrumental in promoting use of blood components rather than whole blood, i.e., the use of packed red cells, platelets, white cells, and plasma or isolated components given when specifically needed rather than the use of whole blood containing all of these components. The use of 8 or 10 components derived from a single unit of whole blood permits much more efficient use of this commodity and benefits more patients.

A laboratory technician tests blood samples for hepatitis virus.

• Recent advances include the development of a vaccine for hepatitis B. Transfusions of human blood products carry a significant risk of hepatitis due to contaminating viruses, one of which is the hepatitis B virus which can cause severe chronic liver disease that can result in lifelong disability. Therefore,

the development of a vaccine to protect against hepatitis B was met with great excitement. The incidence of detectable hepatitis was reduced from 35 percent in susceptible nonvaccinated subjects to 1.6-7.6 percent in vaccinated subjects. Thus, there is clear evidence that the vaccine is highly effective. This development is a milestone and widely applicable not only to recipients of blood products, but also to other population groups that have a high incidence of hepatitis B.

• Since clotting factor concentrates prepared to treat patients with hemophilia are made from large pools of plasma, the incidence of non-A, non-B hepatitis is also high in hemophiliacs. Preliminary evidence suggests that it will soon be possible to prepare clotting factor concentrates free of hepatitis virus, an advance that would reduce the overall incidence of hepatitis in the hemophilic population as well as in the population of all patients receiving blood transfusions or blood products. These two developments are of tremendous clinical significance.

• The blood resources program also supports research aimed at the development of blood substitutes. This research has resulted in the development of perfluorochemicals as blood substitutes, and preliminary trials attest to the efficacy of these products. One new application of perfluorochemicals has been recently developed. Evidence in animals suggest that administration of perfluorochemicals may aid in reducing the size of heart damage in experimentally induced heart attacks.

• The preparation of platelet concentrates from whole blood has greatly facilitated the treatment of bleeding episodes in patients who have low platelet counts, such as patients with acute leukemia. Indications for platelet therapy have been developed which permit efficient use of these labile components of blood.

• A great deal of progress has been made in the transplantation field, especially in the area of bone marrow transplantation in patients with aplastic anemia (those whose bone marrow reserve of blood cells has been depleted) and in patients with acute leukemia. These advances have been made possible because of basic research on tissue typing. Thus, for a marrow transplant to be successful, a compatible donor with the same tissue type (HLA-matched tissue) is needed. Even though HLA tissue typing may be identical, some recipients will still reject a bone marrow transplant. Recent evidence indicates that patients at risk for graft rejection might be identified by studying interaction of recipient and donor cells in a test tube.

• One area of need in the blood resources program is to find a way to fractionate a single unit of plasma into more useful components or derivatives. The blood resources program is supporting efforts to obtain other useful components from a unit of plasma that would otherwise be wasted. For example, if antithrombin III (an antithrombotic agent), plasminogen (a clot-dissolving protein), α_1 antitrypsin (defective in emphysema) and multiple other components could be made from a single unit of plasma, then the price of each product would be substantially reduced and more needed plasma products would be available for clinicians.

• Another pressing need in the blood resources area is the training of physicians expert in blood bank management. There is a national shortage of people qualified as blood bank directors. With the increasing use of blood bank techniques, such as exchanging a patient's unhealthy blood for normal blood, greater numbers of physicians expert in these sophisticated techniques are needed.

Priorities, Goals and Resources

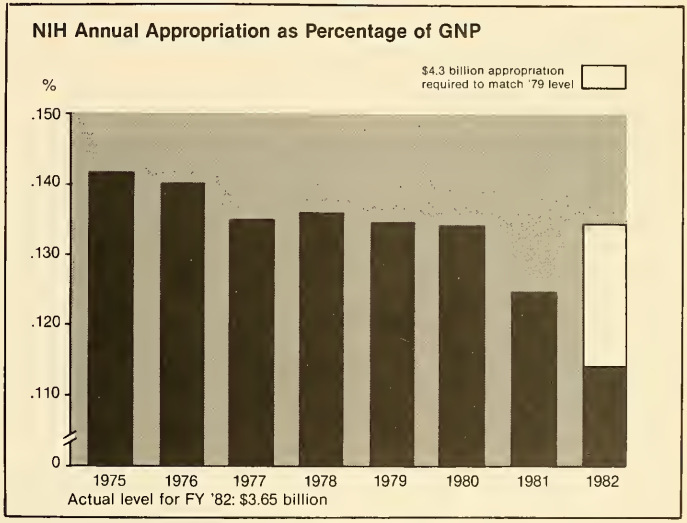
Since World War II, our understanding of biological processes has expanded in every direction. Progress can be measured not only in the scientific literature, but in achievements in disease prevention, declining mortality rates, new treatments, and better lives for those affected by heart, lung or blood diseases. Moreover, the basic research of the past has opened doors for new applied research that is ready to be pursued. The basic research of today will certainly do the same in the future. The possibilities being created daily truly make this the most exciting period in the history of biomedical research, and the most creative time in the prevention and treatment of human illness.

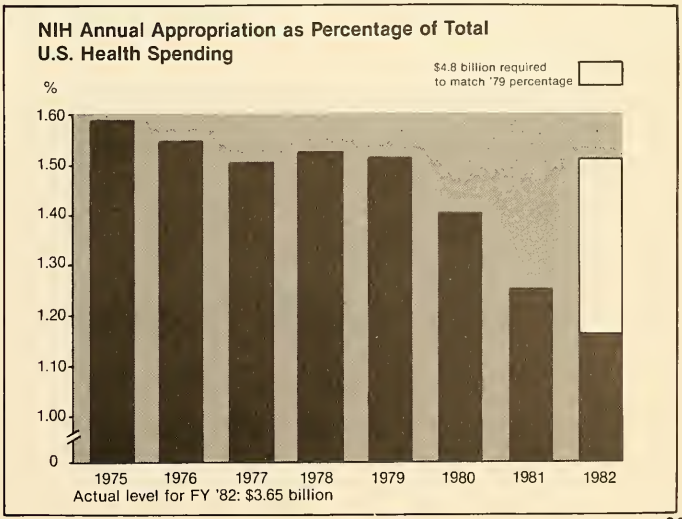
The members of this advisory council firmly believe that this Nation is well served by its investment in biomedical research. The earlier sections of this report, and the past reports of this Council, have documented some of the major advances in health care and disease prevention that have resulted from the work of the National Heart, Lung, and Blood Institute. Yet, as we review a number of trends, we must express our concerns.

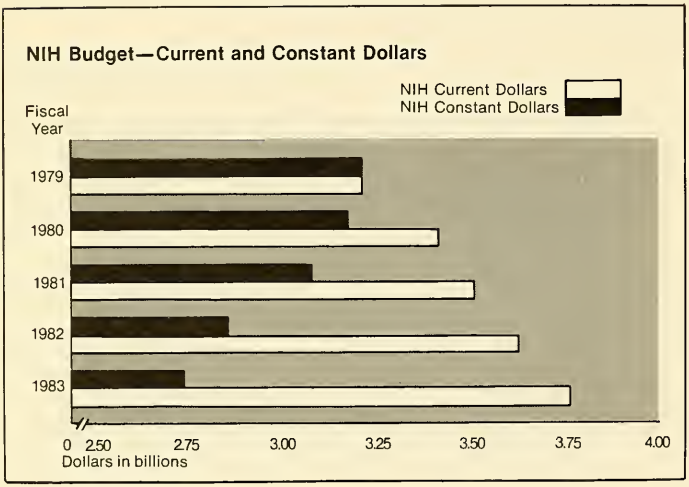
The most alarming factor is the declining level of real resources available to the National Heart, Lung, and Blood Institute and to the National Institutes of Health generally. Whether measured against GNP or the Nation's spending on health care, health research has not kept up.

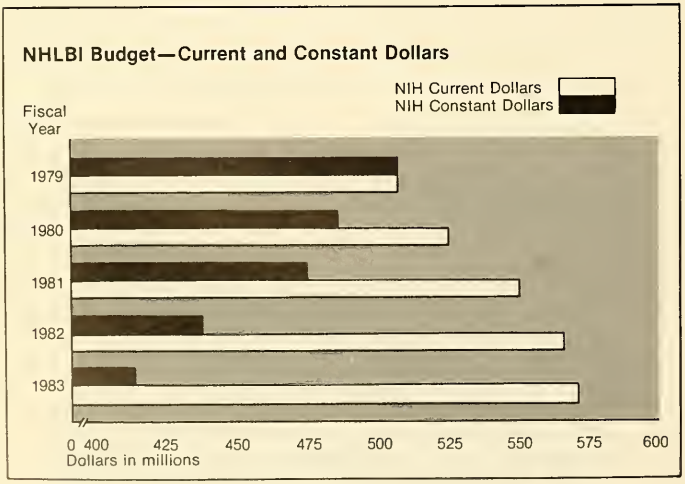
The last several years have seen small annual dollar increases for NIH, but these have not kept up with inflation.

In real terms, the NIH budget *shrank* by 4 percent per year in the 3 years since fiscal year 1979. The National Heart, Lung, and Blood Institute was even worse off, losing 6 percent of its real resources each year. The President's budget for FY 1983 offered no relief from these trends.







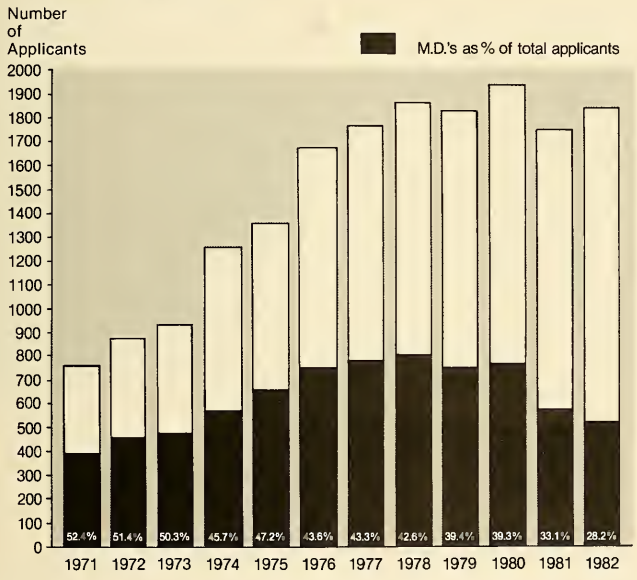


The effect is broader than simply one of fewer dollars. The money that is available is being increasingly concentrated in the support of investigator-initiated research grants at the expense of all other mechanisms of research funding. As recently as FY 1980, 33 percent of unobligated extramural funds were used for training, career awards, contracts, and new initiatives. In FY 1982, the Institute planned to use only 14 percent of available funds for those programs; research grants took $6 of every $7.

The National Heart, Lung, and Blood Advisory Council strongly believes that research to address critical health problems must be well supported along the entire continuum from basic research, to applied research, to clinical trials, to education, prevention, and transfer programs, and to research training. Much of this work is done through individual researchers, and we urge the continued availability of enough money to fund at least half the scientifically approved grant applications received each year. This, however, is only one priority among many:

- *Research training* must continue. The rapid development of science makes it imperative that there be a continuing flow of new people educated and trained in the new techniques. To assure that scientists are able to recognize the potential clinical value of research findings, the number of medically trained individuals in the research pool must be continually replenished. The Council commends the Institute for its leadership in this area, as National Heart, Lung, and Blood Institute training programs have among the highest ratios of M.D.'s to Ph.D.'s at the National Institutes of Health. Nevertheless, the percentage of medically trained individuals in the total applicant pool applying for research grants has declined from 52 percent in 1971 to 28 percent in 1982. This trend

Principal Investigators Applying to NHLBI for Research Grant Support



reflects the difficulty of attracting and retaining young clinical faculty in an environment where only about 30 percent of approved grants are funded and the prospects for future funding are very uncertain. Decline of clinical investigation represents a serious threat to the entire continuum that has led to declining mortality rates and better lives for those affected by heart, lung, or blood diseases.

• The state of *research resources* is an area of increasing concern to the Council. State-of-the-art science requires state-of-the-art instrumentation and equipment, yet many researchers are working in laboratories that are decades old, and funds for modernization are difficult to obtain. One solution is through expanded use of centers programs with their emphasis on resource sharing. We would also hope that the National Institutes' of Health Division of Research Resources will have the funds available to upgrade facilities at our major research institutions.

• Adequate *Institute staffing* is essential to the management of an effective program, and in the direction and assistance that can be given to the scientific community. During the past several years the National Institutes of Health have experienced increasing difficulties in the recruitment and retention of scientific staff and management personnel. Recently, the situation has deteriorated even further; it is now acute and prompt remedial action will be required if permanent and severe damage is to be avoided. Both the lay and scientific press have referred to this as a critical "brain drain" and their description is accurate.

During the past year, there has been great difficulty in the recruitment of individuals for the most senior and most responsible positions at the National Institutes of Health. The directorship of the National Institutes of Health and of approximately half of the research Institutes remained vacant for inordinately long periods of time. This cannot help but have a deleterious effect on the forward momentum and stability of the Nation's biomedical research programs.

These difficulties are the result of several factors. An unrealistic ceiling on salaries exists and it puts the National Institutes of Health at a severe competitive disadvantage. The fact that the same ceiling has existed for several years has led to several echelons of staff (as many as five or six) being at the same salary level despite major differences in their responsibilities. In September 1981, 10 percent of the civil service staff of the National Heart, Lung, and Blood Institute were at the salary ceiling.

A new Senior Executive Service has been established and was designed to have several attractive features and rewards for outstanding performance. The rewards and bonuses have, for the most part, not materialized and considerable disappointment and disaffection have resulted.

For some considerable period of time, a personnel recruitment freeze has existed so that recruitments have been limited to within the Department. Although special exemptions have been allowed, for the most part, a system of personnel transfers ("musical chairs") has been fostered.

In recent months, an absolute reduction in the number of Civil Service and Commissioned Officers has occurred in some parts of the Federal health enterprise.

In addition to all of these concerns, many National Heart, Lung, and Blood Institute staff members have also had to endure offices in grossly inadequate facilities.

Despite these many difficulties and burdens, the Institute staff has demonstrated a consistently high level of performance. The Council believes, however, that it is unreasonable to expect this continuing level of service and dedication. Prompt remedial action is required and is long overdue. Institute staff must be provided with the conditions and resources essential for their management functions, for the development and identification of biomedical research opportunities, and for their scholarly and intellectual enterprises.

• *Clinical trials and transfer programs* allow the final validation of research findings and their communication to the medical professions and the general public. The record of the National Heart, Lung, and Blood Institute in these areas is unmatched, yet funds for new initiatives are harder and harder to come by. In fact, the National Heart, Lung, and Blood Institute's most recent major clinical trial was started in FY 1978.

In the current year, seven new clinical trials were highly recommended by the advisory committees to the heart, lung, and blood divisions. Only one of these, "Antiarrhythmic Agents in the Prevention of Sudden Death," has progressed to the stage of implementation as a feasibility study; the other six studies were not implemented because of insufficient funds. These proposed clinical trials are intended to evaluate 1) scans for blood clots in the lungs, 2) high blood pressure that often occurs in the elderly, 3) calcium-blocking drugs to prevent coronary artery spasms, 4) drugs to prevent stickiness and clumping of blood platelets in patients recovering from a heart attack, 5) exercise after a heart attack, and 6) prevention of sudden death in people who survive serious disturbances of heart rhythm that occur in the non-hospital setting.

Budget Recommendation

It is difficult to define specific budget recommendations for several years in the future. Major opportunities may suddenly appear, while other promising areas may ripen more slowly than expected. Nevertheless, the Council believes that certain principles can be stated in the determination of funding levels:

1. The decline in real resources available to the National Heart, Lung, and Blood Institute (and NIH generally) must stop. Budgets must grow at least as fast as the cost of doing research.
2. The program levels last achieved in FY 1979 should be restored.
3. At least one-third of all unobligated funds should be used to support training, career awards, centers, contracts, and other research mechanisms each year, with the remaining two-thirds available for regular research grants and program project grants.
4. Funds should be sufficient to fund 50 percent of all approved research grant applications.

Using these principles, and assuming 9 percent inflation in 1982 and 8 percent thereafter, we recommend the following levels of funding for the National Heart, Lung, and Blood Institute for fiscal years 1984 through 1987:

FY 1984	FY 1985
$781.5M	843.7M
FY 1986	FY 1987
911.0M	984.0M

To adequately fund priority areas in addition to research project grants:

FY 1984	FY 1985
$803.5M	870.5M
FY 1986	FY 1987
939.2M	1012.9M

For comparative purposes, these needs are shown with funds necessary to prevent decline in future funding from the current FY 1982 level and the inflation index (with 1979 = 100).

Proposed Funding Levels for NHLBI FY 1984-1987
(Dollars in millions)

Fiscal Year	1979	1982	1983	1984	1985	1986	1987
To prevent decline from FY 1982 levels		$559.6	$609.9	$659.0	$711.4	$768.2	$829.7
To restore FY 1979 program level	$510.0	663.6	723.3	781.5	843.7	911.0	984.0
To adequately fund priority programs				803.5	870.5	939.2	1012.9
Inflation index (1979 = 100) 9% in FY 1982; 8% beyond FY 1982	100	130.1	141.8	153.2	165.4	178.6	192.9

Credits

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The lung cell slides appearing on page 11 were provided by Philip Pratt, Professor of Pathology, Duke University, Durham, North Carolina.

Photographs of twins born with neonatal respiratory distress syndrome, appearing on page 13, were provided by Dr. William Tooley, Cardiovascular Research Institute, Department of Pediatrics, University of California, San Francisco, California.

The electron micrograph of the platelet on page 20 was supplied by Dr. Gilbert White, University of North Carolina, Chapel Hill, North Carolina.

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