The Fifteenth Report of the

National Heart, Lung, and Blood Advisory Council

Progress and Challenge

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service
National Institutes of Health

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
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The President
The White House
Washington, D.C.

Dear Mr. President:

We are pleased to submit to you our fifteenth report on the progress of the National Heart, Lung, and Blood Institute's program to control and prevent diseases of the heart, lung, and blood, as well as to ensure an adequate and a safe supply of blood resources. In submitting this report, we wish to take this opportunity to thank you, the Congress, and the Institute for the privilege of serving the people of this country.

Respectfully,

The National Heart, Lung,
and Blood Advisory Council

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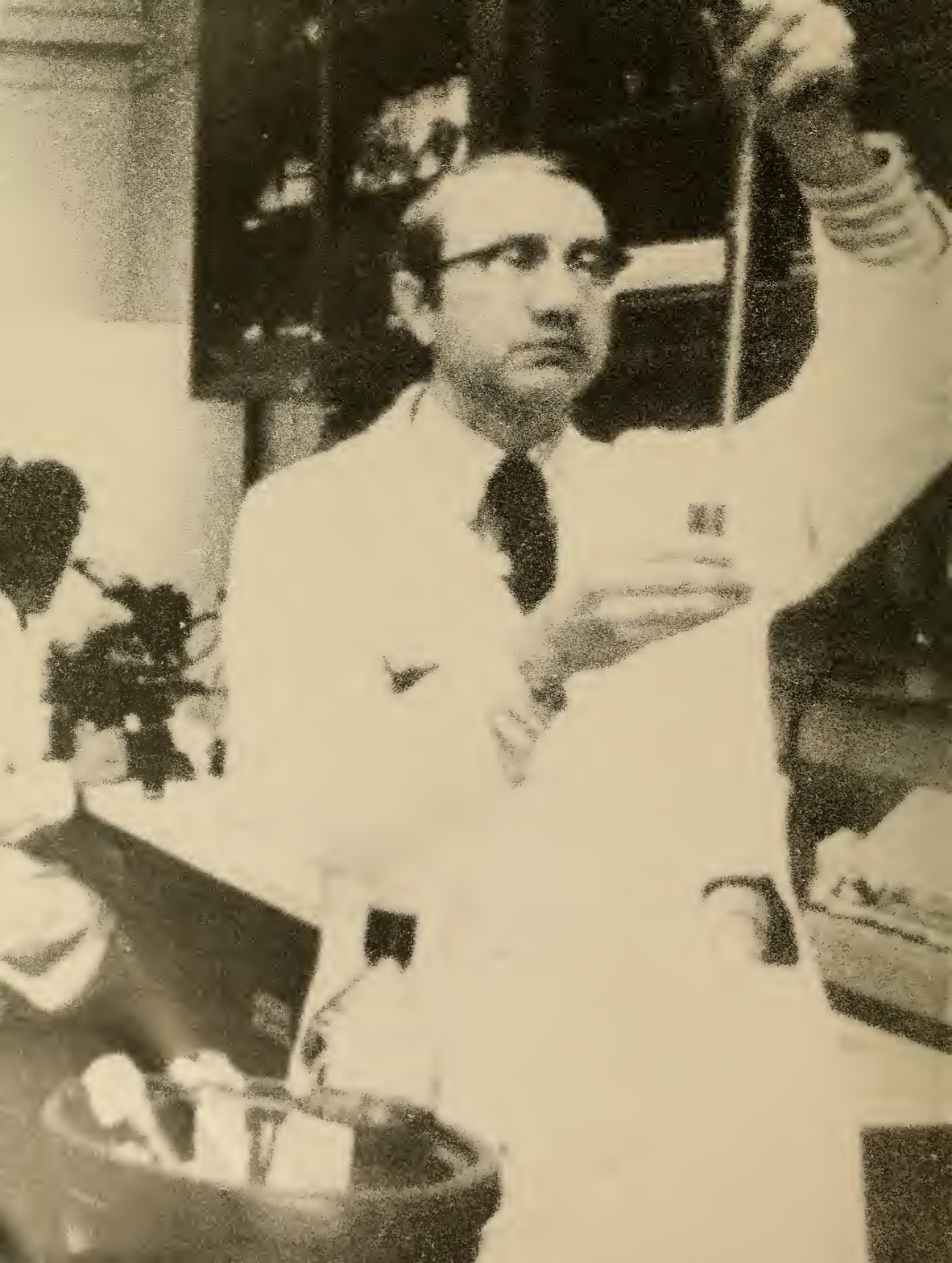


The goals of the National Heart, Lung, and Blood Institute (NHLBI) are the prevention, diagnosis, and cure of heart and blood vessel disease, lung and blood disease, and the provision for an adequate and safe blood supply for the Nation. In this fifteenth report of the National Heart, Lung, and Blood Advisory Council (NHLBAC), entitled "Progress and Challenge," we highlight a few of the many achievements made possible by NHLBI support in these areas during the 40 years of its existence and identify areas where future progress is needed. In addition to celebrating the 40th anniversary of the NHLBI, we join with the other Institutes in commemorating the 100th anniversary of the National Institutes of Health (NIH).

Heart disease is a particularly *American* problem. We have almost the highest rate of coronary heart disease in the world. In the coming year, about 1,250,000 Americans will suffer heart attacks; approximately 500,000 will die, many while in their most productive years. Painstaking research over the last several decades, supported by the NHLBI, has led to major advances in our understanding of the risk factors for heart disease, such as smoking, elevated blood cholesterol, and high blood pressure. These advances will have a major impact on the prevention of heart disease. In addition, new and more effective treatments are now available which will limit the extent of damage should a heart attack occur and otherwise improve the quality and length of life once disease is manifest. Significant recent advances in cardiac surgery are also described in this report.

In the first section of this report, we will present a brief history of cardiac surgery, including significant advances which have been supported by the National Heart, Lung, and Blood Institute. We will then explore how the identification of risk factors for heart disease has led to breakthroughs in heart disease prevention.

Cigarette smoking continues to be one of the Nation's major risk factors for pulmonary and cardiovascular disease, not to mention cancer and other adverse health consequences. In 1985, Americans spent more than $30.25 billion on cigarettes according to *Tobacco Outlook and Situation,* U.S. Department of Agriculture, (1985); while $2.1 billion was spent by the tobacco industry on cigarette advertising in 1984, as stated in the Federal Trade Commission's Annual Report to Congress. The budget for all the NHLBI programs in heart, lung, and blood research for FY 1988 will total $965.32 million.

The enormous progress that has occurred in the understanding and treatment of pulmonary diseases is illustrated in this report by a discussion of the discovery of pulmonary surfactant, and its role in the etiology of neonatal respiratory distress syndrome. A brief discussion of progress and challenges in other pediatric pulmonary diseases reveals the urgent need for continued research and improvements in clinical management of these patients.

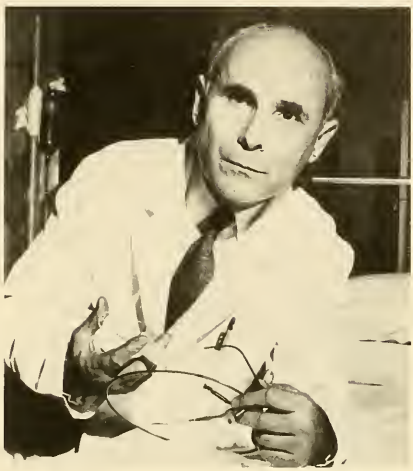
Protecting the Nation's blood supply from contamination by the AIDS virus has also been a great concern over the last several years. Even before the AIDS virus was identified, we were able to rapidly develop and implement sensitive tests to safeguard our blood supply largely as a result of research at NIH on related "obscure" viruses. This is an example of how basic research, already in progress, was applied to meet a new unanticipated challenge; it highlights the wisdom and foresight of supporting a broad range of basic scientific investigation.

In the final chapter, entitled "Priorities, Goals, and Resources," we discuss research initiatives, for which funds have been set aside, in areas identified as providing opportunity for especially rapid growth. Recommendations will be made for budget appropriations needed to carry out the Institute's programs.

This is an exciting time for biomedical research; advances in basic science are rapidly being translated into ways to prevent and treat disease. Unfortunately, we are in danger of losing this momentum because funding for basic research is becoming increasingly difficult to obtain. Only about a third of new and renewal research applications are now being funded compared to more than half funded in 1980. This fact sends a discouraging signal to young physicians and scientists just beginning their careers. Many see biomedical research as too risky a career choice because of the uncertainties of Federal funding.

In this report, we show that the American investment in biomedical research is paying dividends worth many times the original cost in terms of lives and productive years saved, not to mention improved quality of life that can be achieved. However, without continued strong support plus additional incentives to attract young scientists, we risk losing our preeminence in the biomedical research community, eroding our ability to meet the unanticipated health challenges of the future.

In honor of the 40th anniversary of the National Heart, Lung, and Blood Institute, this chapter briefly reviews the origins of cardiac surgery and summarizes the advances that have been made in this discipline since the NHLBI's founding with either direct or indirect NHLBI funding. Because of space limitations, only major historical developments are covered.



Dr. Andre Cournand holding a catheter he performed the first catheterization in man to evaluate cardiac and pulmonary physiology.

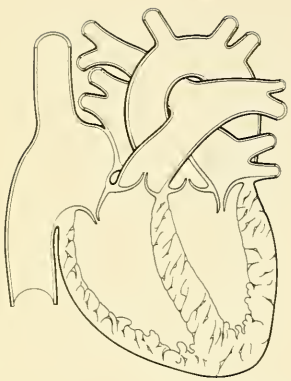
Heart Surgery Before 1948

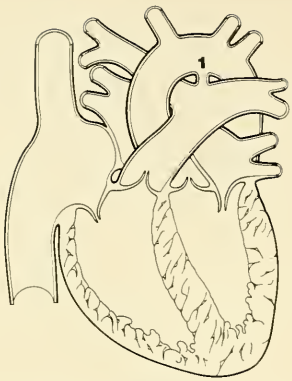
To understand why a national institute dealing with the heart was created, it is important to look at the beginning of cardiac surgery. Less than 100 years ago, many physicians were pessimistic about the feasibility of cardiac surgery. Beginning in the 1890's, however, a few surgeons performed operations on the pericardium to treat perforating injuries that would otherwise have proved fatal; by 1903, 56 successful procedures had been reported. Although this total continued to grow during the first two decades of the 20th century, further medical advances — including the improvement of anesthetic techniques, the development of blood transfusion, and the discovery of antibiotics — would be necessary before any sizeable number of heart operations could be undertaken.

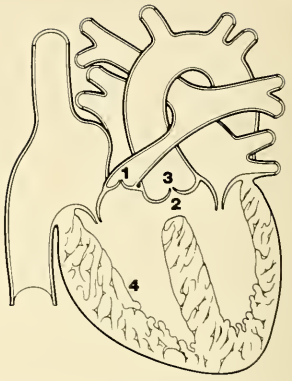
In the late 1920's, Dr. Werner Forssmann, a German surgeon, pioneered the development of cardiac catheterization, a technique that greatly furthered the evolution of heart surgery. In this diagnostic procedure, a thin tube (catheter) is inserted into a major blood vessel and is advanced through the vessels until it reaches the heart. Radio-opaque dye is then injected through the catheter so that the heart can be examined via X-ray. When Dr. Forssmann's superiors refused to let him try this technique in patients, he began a series of experiments on himself; his investigations were ridiculed by his colleagues, however, and he eventually abandoned them. Nevertheless, further research into this procedure was carried out by two American cardiologists, Drs. Andre Cournand and D.W. Richards; in 1941, Dr. Cournand finally performed the first heart catheterization in a human patient.

During World War II, cardiac trauma provided a major stimulus for the development of modern surgery, particularly in the case of Dr. Dwight Harken, an American military surgeon operating in Britain, who devised numerous ingenious techniques for removing foreign bodies from the heart and blood vessels. Dr. Harken reported application of these methods to 134 wounded soldiers, all of whom survived with normal hearts. His success in this endeavor demonstrated the heart's astonishing recuperative powers and helped establish cardiac surgery as a serious discipline.

The late 1930's and early 1940's saw the introduction of several major procedures for the surgical treatment of congenital heart defects. In 1938, Drs. Herbert Gross and John Hubbard, of Boston, carried out the first successful repair of a patent ductus arteriosus (an abnormal passage between the pulmonary artery and the aorta). The patient recovered completely, and Dr. Gross subsequently performed 1,500 more such operations. The next condition to yield to surgical treatment was coarctation of the aorta, a defect in which a portion of the aorta is abnormally constricted. The first successful operation for this condition was performed in 1944 by Dr. Gross and his colleague, Dr. Charles Hufnagel.



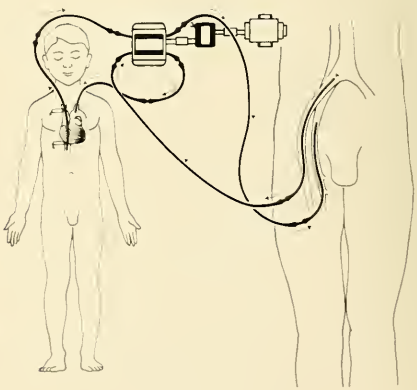




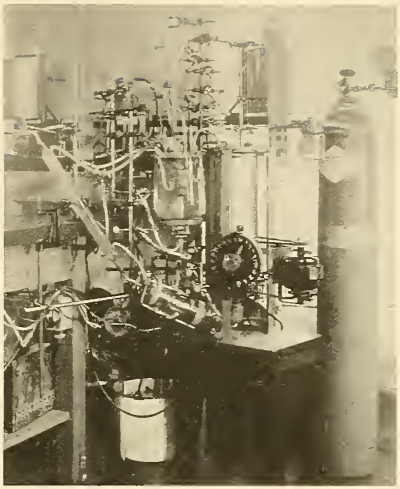
Perhaps the best-known pioneers in the treatment of congenital heart disease, however, were Drs. Alfred Blalock and Helen Taussig, of The Johns Hopkins Hospital in Baltimore. These innovators introduced a technique for palliating babies with cyanotic congenital heart disease (tetralogy of Fallot, pulmonary valvular stenosis). This technique became especially popular for tetralogy of Fallot, a complex, four-part disorder in which blood receives an inadequate supply of oxygen and the patient's skin therefore appears blue. Thanks to Drs. Blalock and Taussig, many formerly untreatable cyanotic infants ("blue babies") were given a chance to live. Dr. C. Walton Lillehei pioneered work on correction of tetralogy of Fallot; Dr. John Kirklin was successful in applying these techniques on a wider basis once Dr. John Gibbon developed satisfactory extracorporeal oxygenation techniques.

Efforts were also being devoted to the surgical correction of coronary artery disease and acquired (noncongenital) valvular disorders. In 1945, Dr. Arthur Vineberg, at Montreal's McGill University, began a series of indirect myocardial revascularization techniques designed to bring oxygen-rich blood to areas of the heart that had an inadequate blood supply. To achieve this goal, Dr. Vineberg recommended that a noncoronary vessel (preferably the internal mammary artery) be removed and used as a bridge, or bypass, around the obstructed area.

In 1948, three pioneers in cardiac surgery, Dr. Charles Bailey of Philadelphia, Dr. Dwight Harken of Boston, and Dr. Russell Brock of London, reported success in several types of valve dilatation procedures; these operations marked the transition from surgery on the outside of the heart to procedures performed, without the aid of direct vision, on structures within the heart. Despite the success of these "blind" operative maneuvers, cardiac surgery remained limited until a way could be found to keep patients alive while their hearts were opened and repaired under direct vision.



Development of Open-Heart Techniques 1948-1956



Modern cardiac surgery can be said to have originated in the early 1950's, with the development of the heart-lung (cardiopulmonary bypass) machine for open-heart operations. This breakthrough was preceded by the introduction of several methods that gave surgeons brief access to the heart's chambers.

During animal experiments, Dr. Wilfred G. Bigelow, of Toronto, had found that the heart could safely be stopped for a brief period under hypothermic conditions (i.e., if the animal's temperature was first lowered to about 86°F). In 1952, Drs. John Lewis and Richard Varco, at the University of Minnesota, used this technique to repair a hole in the atrial wall of a 5-year-old girl. Shortly thereafter, Dr. Henry Swan, of Denver, applied the principle of hypothermia in a series of successful operations. Unfortunately, however, the time allotted for intracardiac surgery by this method was extremely restricted, with an upper limit of approximately 10 minutes. For this reason, operations were frequently done in haste, and incomplete closure of relatively simple defects often resulted. More complicated lesions could not be repaired at all. Therefore, it became increasingly obvious that more sophisticated methods were needed, particularly a technique of cardiopulmonary bypass in which a machine would take over the function of the heart and lungs while the heart was stopped long enough to allow the repair of a complicated lesion.

Much credit belongs to Dr. C. Walton Lillehei and his colleagues, also of the University of Minnesota, who developed the technique of cross-circulation, a method that had been used experimentally for many years under laboratory conditions. To allow for open-heart surgery in a small child, the blood-compatible mother or father was enlisted as a "living heart-lung machine": the patient's circulatory system was linked with that of the parent, which supplied oxygen to the blood; meanwhile, a pump was used to control the volume of blood passed in and out of the patient. Owing to the success of this method, Dr. Lillehei and his associates became convinced that open-heart surgery with mechanical cardiopulmonary bypass was feasible.

For over a decade, Dr. John Gibbon, of Philadelphia, had been working on a device that would provide for the temporary oxygenation and circulation of blood within an artificial circuit. Finally, in 1953, his cardiopulmonary bypass system was tested in four patients with congenital heart disease, only one of whom survived. Although Dr. Gibbon called a halt to the clinical use of his technique, his efforts were a strong stimulus to other investigators.

Researchers continued to experiment with several designs for a mechanical oxygenator, but the one devised by Dr. Richard DeWall proved to be the most practical. With this component, as well as a pump in the circuit, the heart-lung machine finally became a practical reality. This advance paved the way for successful open-heart surgery by 1956.

The next major modification came in 1962 with the introduction of plastic disposable oxygenators, which soon replaced the permanent reusable models. During the early open-heart operations, it was customary to prime the heart-lung machine with freshly drawn, appropriately anticoagulated blood. Through the basic work of Dr. Mohamed Nazih Zuhdi in Oklahoma and clinical application by Dr. Denton Cooley in Texas, it soon became clear that a solution of 5 percent dextrose in saline could be used, instead of blood, to prime the extracorporeal circuit. This discovery relieved the heavy burden that had been placed upon blood-procurement

agencies and thereby greatly facilitated the application of open-heart techniques. In addition to causing a marked reduction in the number of complications associated with extracorporeal circulation, the use of a bloodless priming solution allowed open-heart surgery to be undertaken in patients of the Jehovah's Witness faith. Successful surgery was performed in these patients without any blood transfusion by 1963.

Advances in Open-Heart Surgery 1957-1987

Once open-heart operations became feasible, cardiac surgeons found themselves in the role of active explorers. It was almost as if they had suddenly found a key that unlocked the door to an unexplored wilderness. The pace of progress quickened, and one success followed closely after another. In addition to allowing the definitive correction of most congenital heart defects, the cardiopulmonary bypass technique paved the way for cardiac valve replacement and coronary artery bypass. As a result, many previously untreatable patients were given a chance for a normal life.

Treatment of Acquired Valvular Disease

Some of the former closed-heart techniques were now performed under direct vision with improved results. At first, surgeons attacked aortic and mitral stenosis by removing the calcium deposits responsible for the constriction and salvaging the patient's natural valve. In most cases, however, particularly those involving the aortic position, it became obvious that the natural valve should be removed and replaced with an artificial one. Credit for developing artificial heart valves belongs to many investigators of that era, but the ones who first brought such prostheses to clinical use were Drs. Albert Starr and M.L. Edwards, who described their ball-valve prosthesis in 1961. Whereas investigators had labored to create a design that imitated the anatomy of the human valve, these investigators seized upon an old principle in which a caged ball or disc was used as a valve. The results of early valve replacement operations were most encouraging and promoted great interest in the development of better prostheses. Unfortunately, many of the early

materials were subject to deterioration; until quite recently, degradation of materials has been a serious problem. Although more durable valves have become available and have yielded good long-term results, creation of the ideal prosthetic valve, entirely from synthetic materials, remains a challenge for the future.

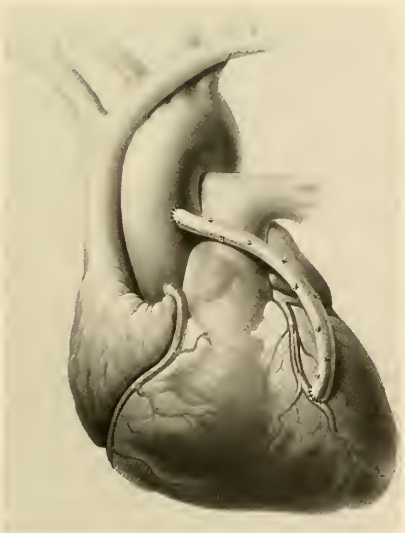
Treatment of Coronary Artery Disease

In 1956, Dr. Charles Bailey introduced the technique of coronary endarterectomy, a procedure in which the diseased vessel is opened and the obstructive lesion is peeled away like the skin of an orange. With the advent of coronary artery bypass surgery, however, endarterectomy became less popular, and interest in this procedure has continued to wax and wane.

The first coronary artery bypass operation was done by Dr. D.C. Sabiston in 1962, but the details were not published until 1974. This procedure involved the placement of a bypass graft to the right coronary artery without the use of a heart-lung machine. The patient died of a cerebrovascular accident 3 days later, and an autopsy revealed a blood clot at the origin of the graft in the aorta. Dr. Cooley and his associate Dr. Grady Hallman did the first bypasses for congenital cardiac anomalies in 1963. Finally, in 1965, the first successful coronary artery

bypass was carried out by Dr. H.E. Garrett, who encountered technical difficulties while performing an endarterectomy and was forced to bypass the left anterior descending coronary artery. Much of the pioneering work in the area of coronary artery bypass grafting was done by Drs. Rene Favaloro and Donald Effler at the Cleveland Clinic and by Drs. Dudley Johnson and Derward Lepley in Milwaukee, beginning in late 1968.

During a bypass operation, surgeons remove a healthy vessel from another part of the patient's body and use this vessel to create a bridge around the blocked artery. In most cases, a saphenous vein is obtained from the patient's leg. One end of the vein is attached to the aorta, and the other end is attached to the blocked artery at a point beyond the obstruction, thus bypassing the constricted area. This procedure is repeated for each affected artery or major branch. Long-term followup of patients with saphenous vein grafts has shown that, because these grafts undergo gradual deterioration, reoperation is necessary in a number of cases. Therefore, most surgeons now prefer to use the internal mammary artery, which is obtained from the chest, since this vessel seems less prone to degenerative changes, including atherosclerosis.



The advent of coronary artery bypass led to a boom in cardiac surgery, and the outlook for patients with coronary artery disease underwent a striking improvement. Many previously irreparable lesions began to be treated routinely. During the 1970's and 1980's, this procedure became one of the most frequently performed in the United States (202,000 in 1984).

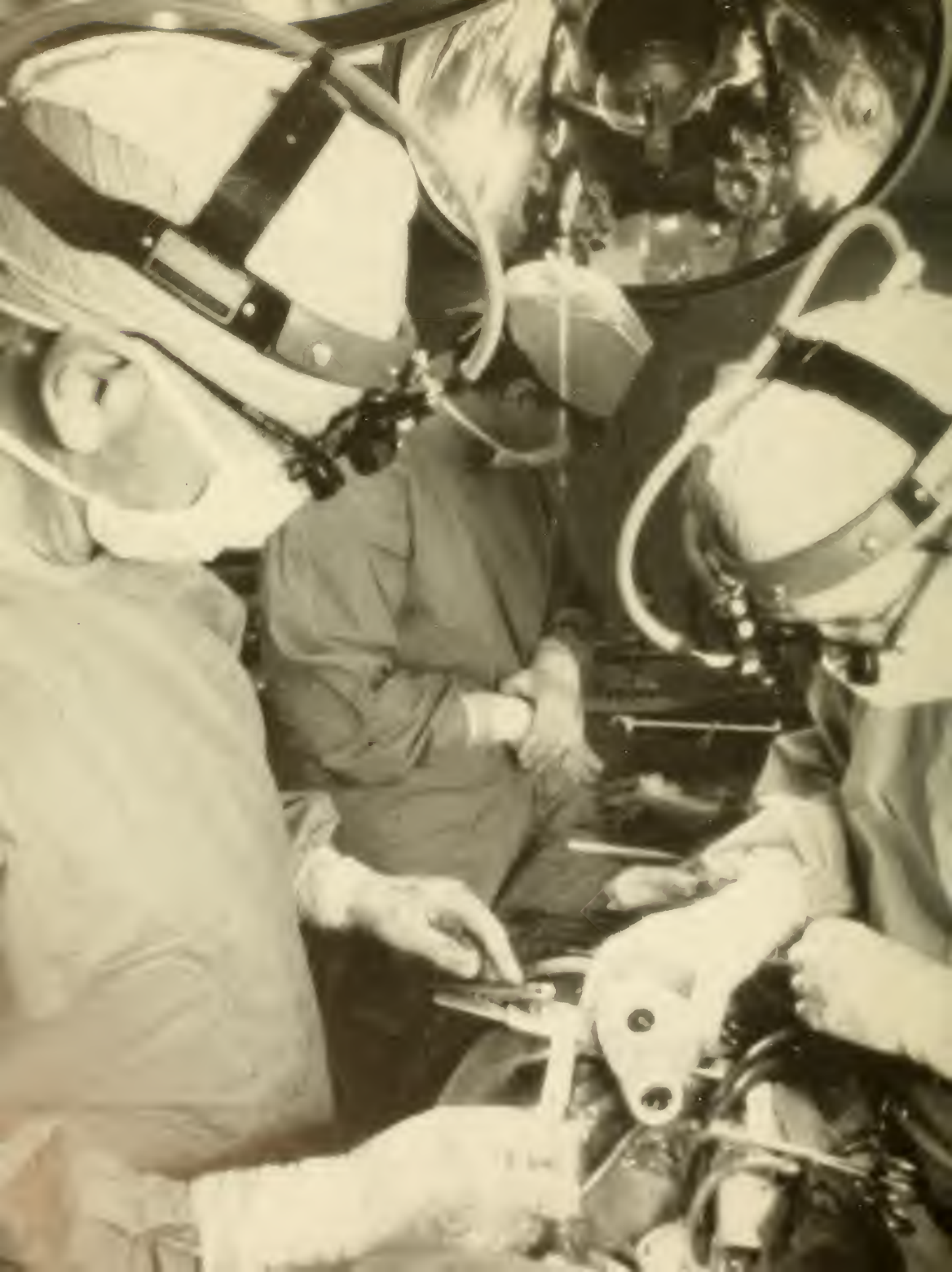
Other Advances and Future Trends

Cardiac Transplantation

Perhaps the most exciting event in the modern era of cardiac surgery occurred in December 1967, when the world's first human cardiac transplant was performed in Cape Town, South Africa, by Dr. Christiaan Barnard. The first cardiac transplant in the United States was undertaken 3 days later by Dr. Adrian Kantrowitz in Brooklyn, New York, but the patient survived for only 6-1/2 hours. Two other American surgeons, Dr. Norman Shumway of Palo Alto, California, and his colleague Dr. Richard Lower of Richmond, Virginia, had performed extensive research on this technique and were on the verge of performing transplants in humans themselves. In January 1968, Dr. Shumway undertook a series of cardiac transplants, but his first efforts in humans met with limited success. Dr. Shumway and colleagues at Stanford continued with a program of basic and clinical investigation that lead to the era of heart transplantation we know today.

The first successful heart transplant in the United States was carried out by Dr. Cooley and his associates in May 1968. The results were so encouraging that Dr. Cooley subsequently did 20 additional cardiac transplants. By December 1970, the National Heart Institute had recorded 167 such procedures, 25 percent of which had been done by only two surgical teams, Dr. Shumway's and Dr. Cooley's. Because of high mortality rates resulting from subsequent infection and rejection, the initial enthusiasm for cardiac transplantation declined during the 1970's until only two centers, Stanford University and The Medical College of Virginia, continued to be active in the United States.

A new era in heart transplantation dawned in 1980, however, with the advent of the new immunosuppressive drug, cyclosporine. Related advances included improvements in patient/donor selection, organ



procurement, and surgical methods, as well as the introduction of endomyocardial biopsy (a technique for sampling tissue from the transplanted heart in order to diagnose rejection). Therefore, cardiac transplantation, a procedure that was regarded as experimental until just a few years ago, is now considered highly acceptable for selected patients with terminal heart disease, in large part the result of NHLBI investigations. Since early basic studies of transplantation, much progress has been achieved and as a result, multiple organ transplantation has emerged.

Cardiac Assist Devices and the Total Artificial Heart

In 1984, the Health Care Financing Administration estimated that from 2,000 to 7,000 Americans per year could benefit from cardiac transplantation. Nevertheless, the estimated number of potential donor hearts is substantially more limited. Thus, despite the remarkable technologic and immunologic successes that have been achieved in transplantation, the donor shortage in this country has not been overcome. Of the patients on waiting lists for a cardiac transplant, more than 30 percent die before a suitable heart can be found. For this reason, artificial organs have been brought out of the laboratory and have become clinical realities.

Total artificial heart research has been the focus of NHLBI effort. Dr. Michael DeBakey appeared before Congress in 1964 to justify funding for research in this area. As a result, the total artificial heart program was created. This dream was shared by others such as: Drs. Kolff, Salisbury, Kusserow, and, of course, Hastings, who joined the newly created Artificial Heart Program of the National Heart Institute in 1964, come to mind immediately. In the 20 years that followed, many others in Europe, Japan and the United States have contributed and include Drs. Kwan-Gett, Bucherl, Vasku, Akutsu, Nose, Atsumi, Liotta, Pierce, Unger, and Jarvik, to name a few.

The first clinical use of the total artificial heart dates back to April 1969 when Dr. Cooley and his associate Dr. Domingo Liotta implanted the first such device as a bridge to transplantation in a 47-year-old man who would otherwise have died in the operating room. The mechanical heart functioned for 64 hours until a donor organ was obtained, but the patient ultimately succumbed to pneumonia. Nevertheless, this experience proved beyond doubt that a mechanical heart could sustain human life. In July 1981, Dr. Cooley's group implanted another artificial heart in a

The left ventricular assist device replaces the function of the ventricle by pumping blood from the left heart to the aorta.

36-year-old man who could not be weaned from cardiopulmonary bypass. The heart sustained the patient for 54 hours until he could undergo a cardiac transplant, but he died approximately 1 week later of multiple organ failure. The first such staged cardiac transplantation to result in long-term survival was performed by Dr. Jack Copeland and associates, of the University of Arizona, in a 25-year-old man.

The total artificial heart has also been used as a replacement device. One of the most successful has been the Jarvik-7 model, which captured public attention in December 1982, when it was implanted in Barney Clark in Salt Lake City and subsequently kept him alive for 112 days. The Jarvik-7 was later used as a permanent system in four other patients. Although several transplant centers have been authorized to use this device as a temporary stepping-stone to cardiac transplantation, only one center (Humana Heart Institute, Louisville, Kentucky) has been given permission to implant it on a permanent basis.

In August 1966, Dr. Michael DeBakey used a left ventricular bypass pump to support the circulation of

a 37-year-old patient who could not be weaned from the pump oxygenator. The system consisted of a valved pumping chamber, positioned on the outside of the chest. The patient recovered after 10 days and was discharged from the hospital. In February 1966, Dr. Adrian Kantrowitz implanted a U-shaped avalvular auxiliary ventricle in a 33-year-old patient whose left ventricle had failed and in May 1966, he implanted the ventricle in a 63-year-old woman. Both patients ultimately died; however, these were the first attempts at permanent implantation of an assist device.

During the 1970's and 1980's, researchers, encouraged by the earlier work and supported with NHLBI funds, worked on a series of left ventricular assist devices (LVAD's), pumps intended to assume the function of the failing left ventricle: Novacor, Nimbus, ABIOMED, Thermedics, Hershey, Gould. The first series of clinical implantations of such a device were done by Dr. John Norman at the Texas Heart Institute, and Dr. William Bernard of the Children's Hospital in Boston, using Thermo Electron Model LVAD's. The first clinical implantation of such a device as a bridge to transplantation occurred in 1978 when Dr. Norman and his team used this abdominally positioned LVAD to support a patient's circulation for 5 days until heart transplantation could be performed. Although the patient died 14 days after the transplant, investigators were spurred on to develop newer, more effective left ventricular assist systems. These pumps are now commonly used on a temporary basis, but they are not yet totally implantable; recipients must remain connected, via percutaneous tubes, to an external power source. In the future, however, LVAD's will no doubt become completely implantable, permanent forms of circulatory support, powered most likely by electrical energy.

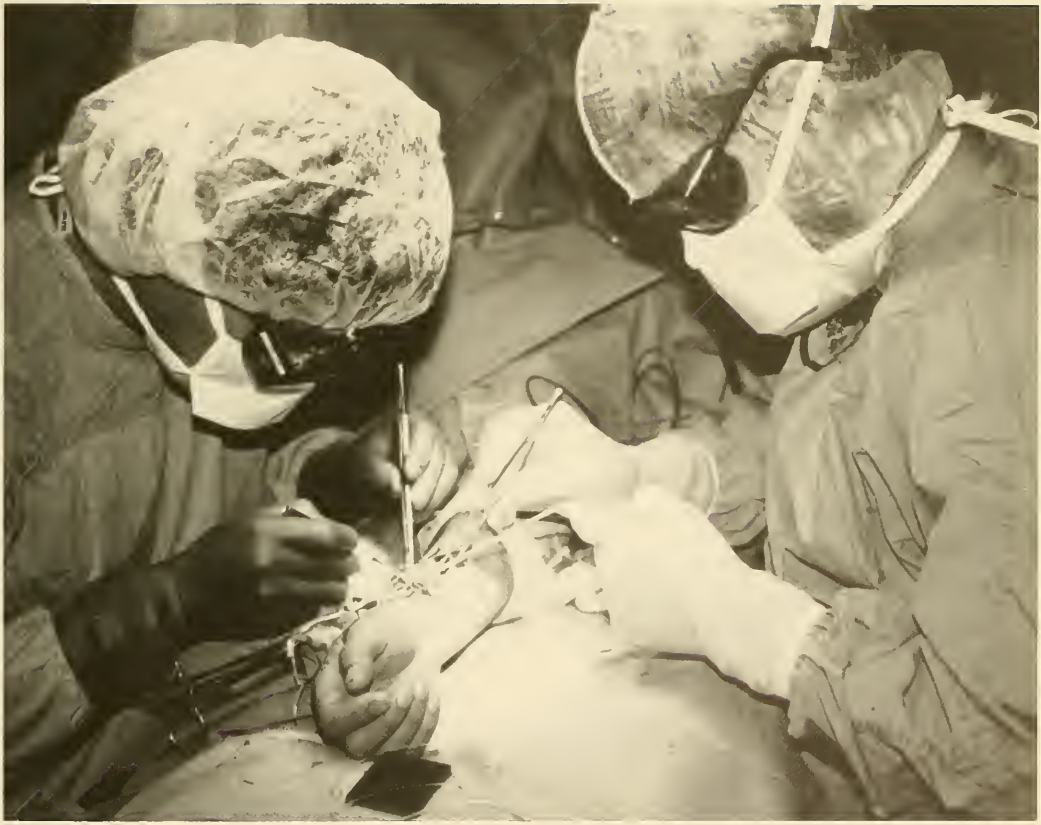
The newest type of cardiac assist system is the ventricular bypass pump, a device that can temporarily take over the work of both ventricles. Unlike the LVAD, this pump operates in a centrifugal fashion, moving the blood in the same way that a cyclone moves air. It was originally designed for use as an artificial heart but has mainly been used to provide cardiopulmonary bypass for open-heart surgery and to furnish temporary mechanical support for the failing heart. The centrifugal pump holds great potential for permanent implantation, as it significantly decreases problems of clotting and destruction of blood elements that occur in many of the "pulsed" systems.

Other Developments

Progress has also been made in diagnostic techniques. The use of ultrasound (high-frequency sound waves) to measure blood flow in the heart and great vessels has been shown to provide helpful clinical information in a number of situations. Computed tomography (CT), a technique that beams X-rays through the body and converts them into images on a television screen, is being used in several forms to evaluate pericardial disease, aortic aneurysms, cardiac tumors, cardiovascular thrombus, and, using the cine-CT, coronary bypass graft patency. Digital angiography is another new computer-assisted diagnostic technique that has been found to have dramatic clinical applications.

When the heart's electrophysiologic conduction system is abnormal, patients can suffer from incapacitating or life-threatening cardiac arrhythmias (abnormal heart beats). With certain types of unusual rhythm disturbances, infants and children, in particular, may be at high risk for sudden death. NHLBI investigators have made remarkable progress recently in the surgical treatment of intractable arrhythmias; the latest technology allows surgeons to define, locate, and remove the anatomic sources of these disorders.

The advent of laser techniques, the newest approach to the dissolution of coronary obstructions, has been viewed with a great deal of excitement. The method that is currently receiving the most attention is laser coronary endarterectomy, a technique in which atherosclerotic lesions are vaporized from vessel walls, thus restoring adequate blood flow. The first clinical trial of this technique in the United States is underway at the Texas Heart Institute, and the preliminary results are encouraging. Another approach that shows great promise is laser-assisted microvascular anastomosis, a method of welding small vessels together. Several additional cardiac procedures, including myocardial revascularization and coronary angioplasty, may eventually be accomplished with laser techniques. All are under investigation by NHLBI.



Surgeons use an argon laser to reconnect small blood vessels.

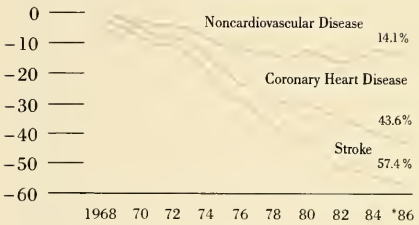
The future of cardiac surgery holds vast opportunity. Although surgeons are able to replace some portions of the heart with artificial devices, a suitable mechanical substitute for the heart itself has not yet been developed. Research efforts must be focused in two directions: (1) toward temporarily supporting the failing left ventricle, and (2) toward total, permanent replacement of the hopelessly damaged heart. The cardiac assist devices introduced during the past decade show considerable promise for the future. Moreover, as methods for preventing tissue rejection and preserving donor organs are perfected, cardiac transplantation will probably gain even greater clinical application.

The extraordinary development of cardiac surgery during the last few decades has astonished even active participants in the field. As we approach the start of a new century, the opportunities for young cardiac surgeons are even brighter than they were 40 years ago when NHLBI had its beginnings.

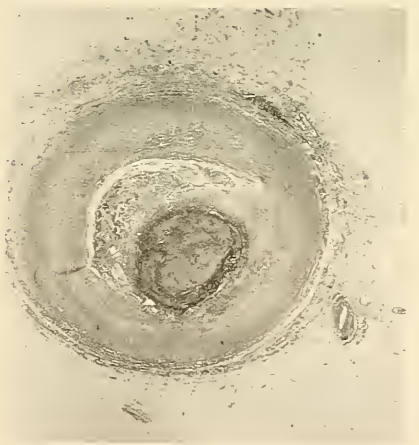
Coronary heart disease affects about 5 million Americans and remains the leading cause of death in the United States, even though there has been an approximate 40 percent decline in coronary heart disease mortality since 1968. Coronary heart disease still results in the death of about 500,000 Americans annually and contributes very substantially to human suffering, loss of productivity, and medical costs. The declining incidence in the United States is somewhat unique when compared with trends in some Western European countries and the Soviet Union. Despite the decline, the incidence is still shockingly high compared to Japan and other countries. It is the goal of the heart and vascular diseases program to increase knowledge of causes, treatment, and prevention in order to ameliorate the impact of cardiovascular disease on the Nation's health.

Coronary atherosclerosis is the result of deposition of cholesterol in the blood vessels supplying the heart, ultimately leading to obstruction of blood flow. Partial obstructions, when severe, result in diminished blood flow and oxygen delivery to heart muscle producing the symptom angina pectoris (chest pain) and sometimes fatal rhythm disturbances. Complete blockage results in death of the cardiac muscle. This usually produces symptoms and signs recognizable as a heart attack. Dr. James Herrick, the same physician who described "peculiar elongated and sickle-shaped red blood corpuscles" in a patient with sickle cell anemia, was also the first to attribute the symptoms of heart attack to coronary thrombosis, or blood clots in the coronary arteries. Because of the enormous morbidity and mortality attributable to coronary atherosclerosis, the National Heart, Lung, and Blood Institute has placed a very large emphasis on the identification of risk factors which accelerate atherogenesis; basic investigations into the processes leading to atherosclerotic plaque formation; and the development of treatment for individuals at risk or who are afflicted with coronary heart disease.

Decline in Age-Adjusted Death Rates; U.S., 1968-1986



*Provisional rates/NHLBI estimates
Source: Mortality statistics from NCHS and NHLBI estimates



Risk Factors for Coronary Heart Disease:
An Opportunity for Prevention

Extensive epidemiologic studies have identified and quantified high blood pressure, high blood cholesterol, and cigarette smoking as modifiable coronary risk factors. The longest and most productive program in this assessment has been the NHLBI-sponsored Framingham Study, now in its 41st year. Observations in which one-half of the men and women of Framingham, Massachusetts, have participated, have clearly defined the risks of high blood pressure, elevated cholesterol, cigarette smoking, and diabetes in the development of coronary heart disease. The work of the Framingham group has also led to a much better understanding of the risks attributable to specific fractions of serum cholesterol and goals for their management. A special tribute was held on its 40th anniversary to honor the people of Framingham for their unique contribution to the Nation's knowledge of coronary heart disease risks.

Hypertension

Hypertensive vascular disease, which afflicts about 58 million American adults, has been shown to substantially increase the risk of heart attack, stroke, and heart and kidney failure. During the past 40 years, high blood pressure has passed from being a largely untreatable silent killer to a commonly recognized problem for which many effective therapies are available. Because the disease produces few symptoms prior to an often catastrophic and ultimately irreversible event such as stroke, heart attack, or kidney failure, it has deserved the designation of "silent killer." Forty years ago, only those who had unfortunately already suffered a catastrophic episode were being treated, and therapy was largely limited to salt restriction and rest. During the 1950's, medications were introduced, but because of common severe side effects, and because the clinical benefits of blood pressure control were recognized only in those with very severe hypertension, efforts at hypertension control were quite limited.

Large epidemiological studies further identified the specific risks of blood pressure elevation, and more effective and better tolerated medications were developed. A large clinical trial by the Veterans Administration demonstrated the effectiveness of treating moderate and severe blood pressure elevations in reducing stroke and cardiac and renal failure. A very large NHLBI-sponsored study subsequently demonstrated that reductions in these problems and increased longevity could be achieved by treating the very large population which has only modest diastolic blood pressure elevation.

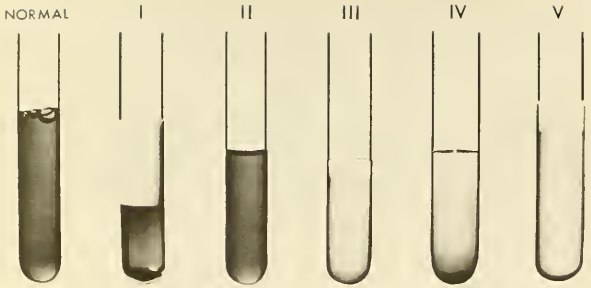
Due to the lack of public awareness of the importance of high blood pressure control during its period of silence and the demonstrated ability to reduce the severe complications of this disease, the NHLBI-sponsored National High Blood Pressure Education

Program was initiated in 1972 to inform the public of these findings. This program extensively used all public media and achieved cooperation with over 2,000 Federal, state, and community agencies and organizations. Prior to this program, only 50 percent of those with high blood pressure were aware of their problem, and only half of that number were being treated. Half of those were adequately controlled. Subsequent to this effort, the awareness of blood pressure elevation had risen to 73 percent of those affected and the percentage of people with high blood pressure being treated had increased from 37 to 56 percent by 1980. The National High Blood Pressure Education Program was also notable for its effectiveness in improving awareness and treatment of high blood pressure in all racial and socioeconomic groups. Many individuals who were at especially high risk have been identified and are now receiving treatment.

Currently, a detectable cause can be found in less than 5 percent of hypertensive patients. An understanding of the cause and prevention of hypertensive vascular disease in this very large number of people is likely to come from basic research into many factors and systems which are known to affect blood pressure. This will require investigations into the role of the central nervous system and endocrine function, genetics, emotional responsiveness, and the basic physiology and pharmacology of vascular smooth muscle. Such studies are currently supported by NHLBI.

It is known that systolic blood pressure, which is represented by the larger of the two numbers on a blood pressure reading, increases with age and that there are more frequent cardiovascular problems in individuals with systolic blood pressure elevation. There has been a tendency for some to accept systolic blood pressure elevation as a consequence of aging and a result of existing atherosclerosis rather than a cause. Limited studies have shown a reduction in cardiovascular events as a result of treatment. Because medications tend to be less well tolerated in this older population, and the benefits have not been clearly defined, a large problem exists as to who should receive treatment. An NHLBI-supported multicenter trial is currently ongoing which will provide insights into this problem.

A participant in the NHLBI-supported Systolic Hypertension in the Elderly Program receives periodic high blood pressure monitoring.



High Blood Cholesterol

During the early 1960's, scientists working in the intramural program of the then National Heart Institute continued earlier research that found that cholesterol is carried in the blood on particles called lipoproteins. Their investigations did much to improve the clinical recognition and treatment of diseases involving excess blood cholesterol. Their observations and the resultant classification of hypercholesterolemic patients emphasized the importance of the variations in the lipoproteins with which cholesterol is combined. This classification permitted the prediction of genetic transmission, likely associated diseases, risk of development of coronary disease, and responsiveness to different forms of management. The recognition that coronary heart disease was related to low density lipoprotein cholesterol (LDL) and that high density lipoprotein cholesterol (HDL) is actually protective, gave added emphasis to basic studies in LDL metabolism and control. Public interest was stimulated in 1984 by the findings of the NHLBI-sponsored Lipid Research Clinics Coronary Primary Prevention Trial, in which it was shown that a 2 percent reduction in coronary heart disease was achievable with each 1 percent reduction in serum cholesterol. This finding, along with new target values for serum cholesterol set by the NHLBI-sponsored National Cholesterol Consensus Conference in 1984, formed a basis for a national program to reduce coronary risk. A National Cholesterol Education Program supported by NHLBI and many voluntary and professional organizations is currently working to further this goal.

Basic investigations in familial hypercholesterolemia have detected a deficiency of LDL receptors on the tissue cells of individuals with this disease. The reduced number of LDL receptors on liver cells of these patients results in reduced LDL cholesterol uptake, very high serum cholesterol levels, severe coronary heart disease, and premature death. Important studies on LDL receptors by Drs. Michael Brown and Joseph Goldstein led to their receiving the Nobel Prize in 1985.

Basic research that identified HMG CoA reductase as an important enzyme in cholesterol synthesis has led to the development of a recently released HMG CoA reductase inhibitor, mevinolin, which has been shown to reduce serum cholesterol by about 33 percent. These very important basic research findings, along with the identification of the gene responsible for control of LDL receptors, offer opportunities for much improved treatment of this disease and perhaps its ultimate elimination.

Methods for modifying behavior to reduce coronary risk are being extensively studied in NHLBI-sponsored investigations. Educational programs to improve the awareness of all risk factors and methods for their control are being studied in both children and adults in an attempt to reduce cigarette consumption, improve diet and physical fitness, and control blood pressure.

Improved Medical Treatment for Existing Coronary Heart Disease

During the past four decades major improvements have been made in the treatment of angina pectoris allowing a more active and productive lifestyle for affected individuals. These improvements are attributable to advances in both medical and surgical therapy. A class of agents, termed the "beta blockers," has been developed which is very effective in improving the exercise tolerance of patients with angina pectoris. This result is largely achieved through a reduced heart rate and blood pressure response to exercise.

Angiographic and physiologic observations have confirmed the contribution of coronary arterial spasm to angina pectoris in patients with and without

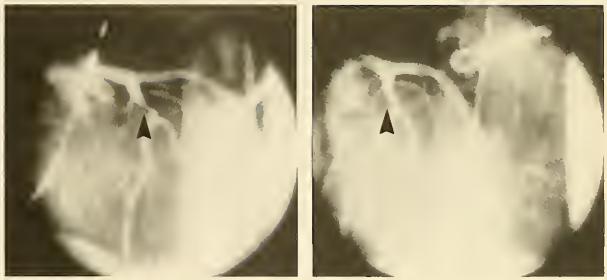
coronary atherosclerosis. A new class of compounds which block calcium entry into smooth muscle cells was found effective in reducing coronary spasm, increasing exercise tolerance and relieving angina in these patients.

During the early 1960's, it became possible to safely perform coronary angiograms in large numbers of individuals and to identify the obstructions responsible for chest pain. Saphenous vein bypass of these obstructions became a very popular and effective operation for the control of angina pectoris and possible prolongation of life. Considerable controversy arose regarding the indications and the influences of this procedure in improving exercise tolerance and longevity. The NHLBI-sponsored Coronary Artery Surgery Study did much to define the benefits and complications of this operation in various categories of patients and to provide an improved basis for recommending this procedure.

There has been subsequent development of technology which permits the dilation of obstructed coronary arteries with an inflatable balloon, a procedure known as percutaneous transluminal coronary angioplasty. This technique, which satisfactorily relieves angina in about 85 percent of patients, has the advantage of being performed without opening the chest or requiring general anesthesia. It can be repeated since it is not limited by the availability of veins. As with bypass surgery, there are still many questions regarding efficacy in improving exercise tolerance and life expectancy, as well as the frequency and nature of complications. The NHLBI-supported research in both intramural and extramural programs has contributed very substantially to these advances.

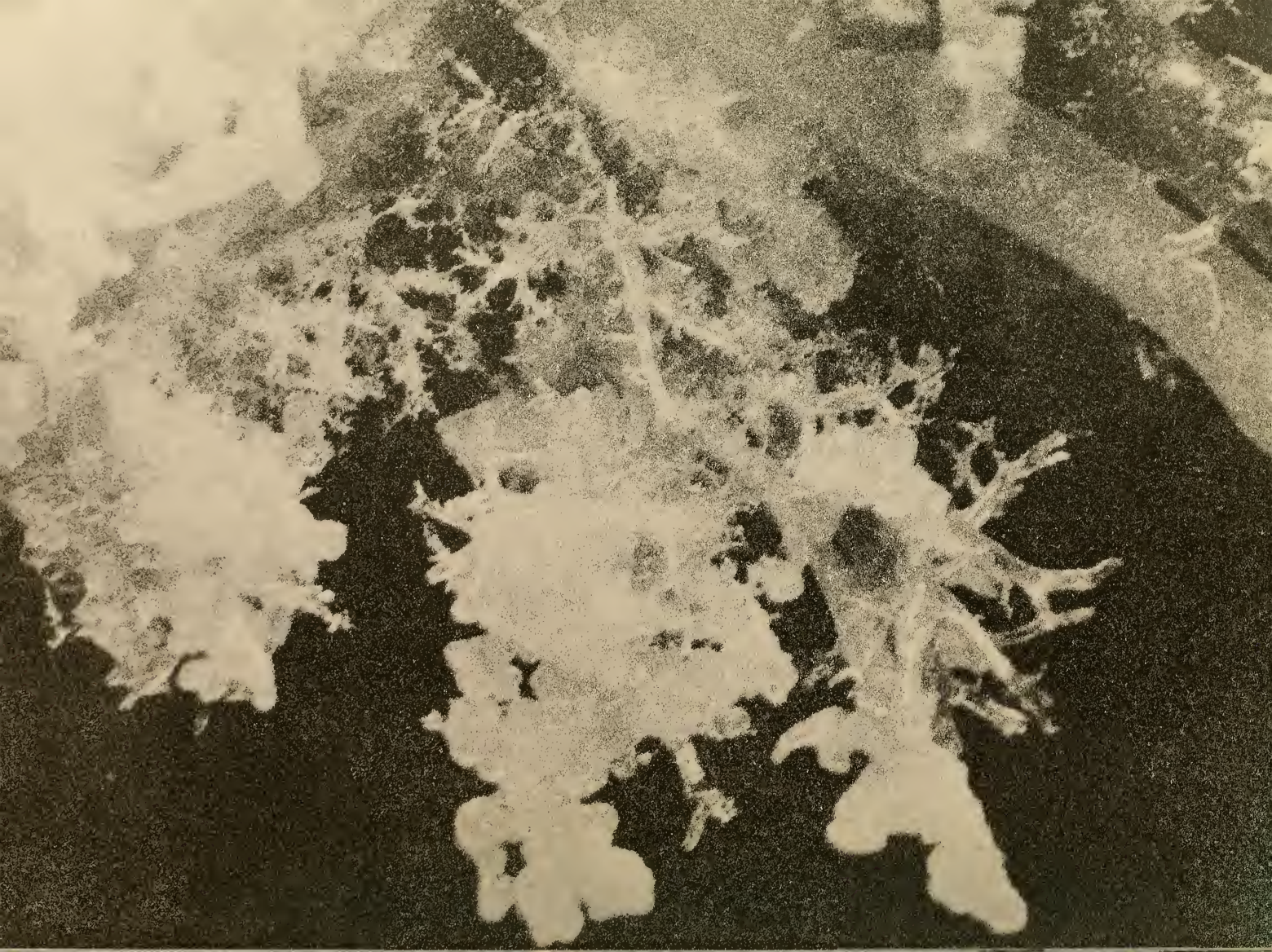
Lessening the Severity of Heart Attack

Since clot formation has been identified as the immediate event leading to myocardial infarction in many patients, extensive studies in the alteration of blood coagulation and clot dissolution have received NHLBI support. The use of thrombolytic drugs has been shown to reduce the size of the damaged heart muscle and reduce mortality. The dissolution of coronary clots was first demonstrated with streptokinase, a substance derived from streptococcus bacteria. Clot dissolution has been more effectively achieved by the administration into the blood of a naturally occurring substance which activates plasminogen, and begins the normal system of clot dissolution. This tissue plasminogen activator has been produced through genetic engineering and continues to be extensively studied for benefits and complications by NHLBI-supported studies including a large multicenter trial of Thrombolysis in Myocardial Infarction. This trial also seeks to define the role of coronary angioplasty when combined with thrombolysis.



Sudden coronary death remains a common problem. Extensive studies have defined major risk factors. A reduction in postmyocardial infarction sudden death by treatment with beta blockers was demonstrated by a NHLBI trial which provided the basis for their administration to most patients following myocardial infarction. In this Beta Blocker Heart Attack Trial, in which 3,787 postmyocardial infarction patients participated, there was a 26 percent reduction in mortality and a 16 percent decline in nonfatal infarction during an average 25-month followup period. Progress continues to be made in studies which define the risk of serious rhythm disturbance and methods for prevention.

This report only touches upon the enormous progress that is being made in the prevention and control of cardiovascular diseases. Continued progress can be expected from efforts in basic and clinical investigation.



The lung diseases program supports fundamental research concerned with lung cell biology and respiratory physiology, and both basic and clinically oriented studies of respiratory diseases including chronic obstructive pulmonary diseases (emphysema, asthma, chronic bronchitis), occupational and immunologic lung diseases, pulmonary vascular diseases, respiratory failure, and pediatric pulmonary diseases. The past 40 years have been a time of enormous progress in research concerned with lung biology and pulmonary medicine. Significant areas of accomplishment in the lung diseases program have resulted in substantial improvements in the detection, clinical management, and prevention of respiratory disorders.

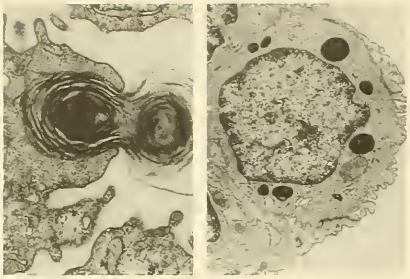
This report focuses primarily on neonatal respiratory distress syndrome (RDS), a condition that affects approximately 40,000 infants per year in the United States. Progress made in the prevention and treatment of RDS illustrates just how far we have come. A brief discussion of bronchopulmonary dysplasia, a chronic lung disease of infants first recognized about 20 years ago, and cystic fibrosis, an inherited disease that affects the pulmonary system, points out just how far we still must go.

Neonatal Respiratory Distress Syndrome

Neonatal RDS, which develops almost exclusively in premature infants, usually begins within an hour or so after birth. The dominant feature of the disorder is atelectasis: collapse of the tiny air sacs (alveoli) in the lungs, which rapidly leads to respiratory failure. Typically, the infant shows many signs of a great struggle for oxygen. Recovery, when it happens, usually occurs within a week. Until recent years, however, half of afflicted infants died.

We now know that atelectasis is caused by the inability of the immature newborn to produce pulmonary surfactant, a unique substance that lines the alveoli and prevents lung collapse by lowering surface tension. Key studies in the early 1960's helped to clarify the pathogenesis of neonatal RDS and to define the physiologic role of surfactant in normal breathing. Suddenly, the problem had become clear: newborns with RDS suffer alveolar collapse because they lack the surfactant necessary to reduce surface tension at low lung volumes thereby keeping their lungs open.

This new awareness of pulmonary surfactant and its role in RDS attracted the interest of researchers from a variety of disciplines. Many exciting challenges became apparent: to characterize surfactant, to identify its source, to find a method to hasten its arrival or replace it in immature infants, and discover ways to keep babies alive until they develop their own surfactant. Fortunately, these questions came at a time when new disciplines and techniques were becoming available to answer them. These included modern lipid and protein chemistry, high resolution electron microscopy, cell biology, amniocentesis, and sophisticated bioengineering, which made the concept of neonatal intensive care a reality.



Basic Research Leads the Way

In 1954, a particular cell type found in the lining of the lung alveoli, the type II alveolar epithelial cell, was first recognized to be the possible source of surfactant. Researchers used the electron microscope to examine this cell that we now know to be unique to the lung. They found unusual structures within the cells that had a lamellar form (i.e., they appeared to be composed of many concentric layers, much like an onion). Other investigators observed that these lamellar bodies were absent from the lungs of very premature animals, and that they did not appear until the time in gestation when the surfactant was present. We now know that the lamellar bodies are the intracellular storage sites for the surfactant.

The NHLBI took an active role in supporting the anatomical, physiological, and biochemical studies that took place in the late 1960's and throughout the 1970's aimed at discovering the chemical nature and regulation of surfactant. By 1972, pulmonary surfactant had been isolated and the lipid portion of surfactant had been almost completely described. A substance called dipalmitoyl lecithin was identified as the active ingredient responsible for its highly surface active properties. In the following year, investigators identified a surfactant-associated protein that was unique to the lung.

The Institute launched a new program in 1973 to encourage the isolation and characterization of lung cells. By this time there was much evidence from sophisticated biochemical and anatomical experiments that the type II cell was the cell that manufactures and stores surfactant. Studies were undertaken to isolate type II cells and grow them in the laboratory. For the first time, direct evidence was obtained that these cells were indeed the source of the surfactant.

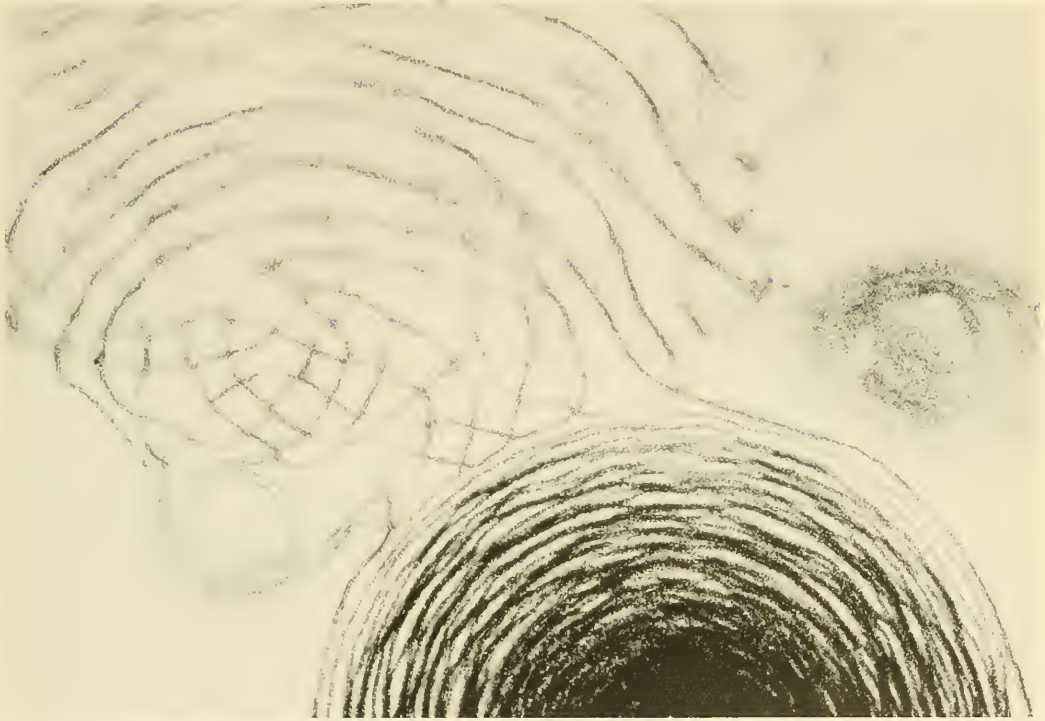
The realization that surfactant is made by cells found only in the lung sparked a virtual explosion of research activity and marked the beginning of an exciting new field of lung research. The lung was viewed not only as a respiratory organ, but also as an organ that had active metabolic functions that were vital for life. A major new effort to elucidate the metabolic, or nonrespiratory, lung functions had begun. Many different groups of scientists provided important new insights and valuable clues to the metabolic pathways of surfactant synthesis and regulation of its secretion.

The studies with isolated cells, in conjunction with biochemical analyses of surfactant, and investigations into the physiologic role of surfactant in the living organism laid the groundwork for the dramatic improvements that have occurred in the detection, treatment, and prevention of neonatal RDS.

The excitement and sense of accomplishment resulting from the work of the last 20 years continues to this day. New opportunities made possible by the recent advances in molecular biology and genetics have already resulted in major contributions to understanding of surfactant biology. This work has great promise for new advances in the care of infants with RDS. The findings from the basic sciences have already contributed in a number of important ways to the favorable outlook for infants at risk of RDS.

Prenatal Testing and Prevention of RDS

An important advance that resulted from the characterization of the lipid components of the lung surfactant was the development of the first clinical prenatal test to diagnose immature lungs in 1971. The test involved measuring the ratio of lecithin (L) (a major component of surfactant) to sphingomyelin (S) (a nonsurfactant lipid found in the lung) in the amniotic fluid. A high L/S ratio indicated sufficient surfactant; whereas, a low ratio meant that the baby was at high risk of RDS. Knowing this before delivery permitted physicians to postpone the delivery, if possible, or to transfer the mother to a hospital with intensive care capabilities before the baby was born.



Now that it was possible to predict immature lungs prenatally, the question arose: Is there any way to hasten the arrival of surfactant before the baby is delivered? In 1969, it was discovered that lambs delivered prematurely after infusions of corticosteroids had mature lungs. The suggestion that corticosteroids accelerate the appearance of surfactant was soon confirmed and extended by morphologists and biochemists studying surfactant production.

A multicentered, randomized, double-blind, collaborative clinical trial was initiated by the NHLBI in 1976 to determine the efficacy of the treatment and to identify any short- or long-term adverse effects on the mother and infant. The results of the trial confirmed earlier work and demonstrated that prenatal administration of corticosteroids is effective in reducing the overall incidence of RDS. However, they indicated that the magnitude of the treatment benefit may depend upon the sex, race, and other characteristics of the infant and mother. Followup studies revealed that no detectable adverse effects of the steroid treatment were apparent in the first 3 years of life.

These findings gave physicians an important tool to use in the prevention of RDS. They also stimulated further work on the role that hormones play in the production of surfactant. Studies in a number of mammalian species have shown delayed appearance of surfactant in male fetuses. The lack of effect of dexamethasone on male fetuses, observed in the clinical trial, reinforced the point that sex differences exist in surfactant production. Currently, the lag in male fetal surfactant production is believed to be due to the presence of male hormones (androgens) which inhibit surfactant synthesis.

If androgens prove to be important inhibitors of fetal lung maturation, hormonal therapies may be effective in preventing RDS. Investigators are also looking at the role of thyroid hormone in the stimulation of surfactant production, and the possibility that thyroid hormones and corticosteroids act synergistically to stimulate synthesis of surfactant lipid and be an effective means to prevent RDS. If studies in

humans bear this out, it is possible that a thyroid hormone-dexamethasone combination may prove efficacious in preventing RDS in both male and female babies.

Progress in Treatment: Intensive Care and Replacement Therapy

While advances in prevention have spared many newborns the problems of RDS, it still develops in thousands of babies. The great improvements in survival that have occurred during the past 25 years are attributable to the backbone of RDS treatment: neonatal intensive care. Before 1965 there were no intensive care facilities for newborns, but technological innovations occurring around that time spurred their development at major medical centers. Since the mid-1970's, the regionalization of perinatal health care has become standard; today, mothers in premature labor and their newborns are routinely transported to tertiary care facilities equipped to handle their special problems.

In the 1960's, many types of assisted or mechanical ventilation used in adults were tried in newborns with RDS, but mortality remained high. Most babies were treated with some form of intermittent positive pressure (i.e., pressure only during inspiration), and their lungs almost invariably collapsed on expiration. This alveolar collapse placed a severe strain on the newborn's respiratory muscles and also impaired the infant's already limited capacity to produce adequate amounts of surfactant.

In 1969, investigators supported by the NHLBI developed continuous positive airway pressure (CPAP), a new method that involved maintaining a steady pressure throughout the entire respiratory cycle. The results were dramatic: the alveoli remained open on expiration, and survival was greatly improved. An added benefit was that CPAP enabled the use of lower concentrations of oxygen than other methods, thereby reducing the toxic effect of oxygen on the lungs.

Concurrently, great advances were made in the technology used to monitor blood gases in newborns. The "miniaturization" of equipment and techniques used for adults permitted frequent, safe, and accurate monitoring of the oxygen level in arterial blood. Knowledge of nutritional support for premature infants has also advanced in recent years. The typical baby with RDS is born without adequate energy stores and is usually too ill to nurse. Moreover, a tremendous amount of energy must be expended just to breathe and to maintain body temperature. Recent work has identified key nutrients and improved methods of providing them to prevent loss of protein and meet the caloric requirements of the infant with RDS.

Ever since it was discovered that RDS results from a deficiency of surfactant, the development of an effective, safe replacement therapy has been a dream of clinicians and basic researchers. Attempts were made in the 1960's to introduce surfactant into the lungs of animals and infants with respiratory distress, but the results were inconsistent. The first report of successful treatment of human infants with RDS with surfactant isolated from animal lung came from Japan in 1980.

Since that time, several different preparations have been developed. Surfactant from natural or animal sources is available from cows and pigs, and a human surfactant can now be obtained from amniotic fluid. Other preparations are natural surfactants supplemented with additional chemical compounds, and synthetic surfactants that are made in the laboratory. These various surfactants are now being tested in clinical trials throughout the United States, Canada, Europe. The NHLBI plays an active role in the support of many of these investigations. Results from several studies suggest that surfactant therapy works to provide immediate benefits in pulmonary function, and that multiple doses of surfactant given to babies as early as possible after birth produce a sustained positive response and improve survival. It is encouraging that several studies published to date suggest that the therapy is safe and without significant toxicity. Clearly, further careful study is needed before the effectiveness and long-term safety of surfactant therapy can be determined.

Molecular Biology

In 1985, NHLBI-supported investigators announced the isolation and characterization of the gene that encodes the major surfactant-associated protein. Several surfactant apoproteins have been isolated and characterized, and their role in facilitating the functions of surfactant are being elucidated. The genetic regulation of surfactant is beginning to be explored.

For example, the gene for the major surfactant protein has been localized to a particular human chromosome.

A new avenue of research is the development of a bioengineered surfactant replacement therapy that would eliminate the concern of possible allergic reactions resulting from introducing a foreign surfactant protein into immature infants. Whether such a preparation can be devised that will be as effective as the natural surfactants remains to be seen. Other questions for future study include whether abnormalities of the surfactant gene play a role in neonatal RDS. If so, a more accurate and specific screening test could be devised to detect and better treat infants at risk for RDS. Scientists also speculate whether surfactant therapy might prove beneficial in certain lung diseases of adults that are associated with surfactant deficiency.

The truly remarkable advances in surfactant research that have occurred in the past few decades have saved the lives of many babies and resulted in a new understanding of a complex and unique biological system. Clearly, surfactant research has been driven by the desire to eradicate RDS in newborns, yet it promises to yield exciting progress in the treatment of adult lung diseases as well.

Bronchopulmonary Dysplasia and Cystic Fibrosis

Bronchopulmonary Dysplasia

Modern intensive therapy has assured that most babies will survive RDS. However, it has been estimated that more than half of neonates with RDS will manifest some complication of intensive therapy. A major respiratory complication is bronchopulmonary dysplasia (BPD), a chronic lung disorder that was first recognized in 1967. The condition involves abnormalities in the architecture of the lung that lead to poor gas exchange and, in many instances, progressive respiratory failure. Much research is now being done on bronchopulmonary dysplasia, but many questions remain to be answered.

There is evidence to suggest that the etiology of BPD is related to both the pulmonary problems associated with prematurity and treatment of the respiratory disease with oxygen and mechanical ventilation. With the increasing number of preterm infants surviving mechanical ventilation, BPD has become one of the most common sequelae of neonatal intensive care. It is associated with increased morbidity and mortality, and is a frequent cause for prolonged hospitalization. The majority of infants who develop BPD are born prematurely, and most, but not all of these cases follow neonatal RDS. The

incidence of BPD in infants who receive mechanical ventilation and survive varies between 10 and 20 percent. One third of extremely premature babies will manifest a chronic lung disease and will require supplemental oxygen for several months. Approximately 1,300 infants will survive with BPD each year in the United States; the number of infants with milder forms of the chronic lung damage is much higher, and may approach 8,000 cases per year.

The majority of infants with BPD recover without any further complications. However, BPD extends the need for costly intensive care, impedes an infant's feeding and growth, and is associated with more lung infections in the first few years of life. Little is known about the long-term sequelae of the pulmonary lesions in BPD; followup studies of children who have survived are currently in progress.

The Institute, primarily through the Specialized Centers of Research Program on Respiratory Disorders of Neonates and Children, is supporting basic and clinical research into the etiology, treatment, and prevention of BPD. A recent study of incidence and care of infants with BPD at several institutions revealed that less intrusive care for premature babies with breathing problems at birth may prevent BPD. These encouraging findings suggest several new approaches that may prove beneficial. For example, at the first sign that a newborn is having respiratory difficulty, often right in the delivery room, short plastic prongs are inserted into each nostril to deliver warm, humid air at a steady low pressure. This is in contrast to the usual practice of inserting a tube into the infant's trachea and using a ventilator to administer high concentrations of oxygen. The study suggests that extra oxygen should be applied only to the sickest babies and for shorter periods of time than currently used at most hospitals. Further research is needed to determine whether these approaches will offer new opportunities for reducing the incidence of BPD.

Other recent work approached the problem of BPD from the assumption that its pathogenesis originates, not from injury to the lung, but during the lung repair process. It has been known for some time that vitamin A augments epithelial cell repair following injury, and that very low birthweight neonates are often deficient in vitamin A. A recent clinical study has demonstrated that vitamin A supplementation in premature infants who are dependent on mechanical ventilation and oxygen promotes lung healing and reduces the incidence and severity of BPD. The efficacy and safety of treating premature neonates with vitamin A has yet to be established. This study is a first step in the evaluation of vitamin A supplementation as a means of reducing the incidence of chronic lung disease in premature infants.

Whether other nutritional interventions would also help to reduce lung injury and promote healing in premature infants is not known; indeed, the optimal nutritional requirements for premature infants are not yet completely understood. There are many other important questions concerning bronchopulmonary dysplasia that urgently need to be addressed, including very basic research issues related to the immune functions of the developing lung, the regulation of alveolar development, and the long-term effects of BPD on pulmonary health of children and adults. Of course, the prevention of premature births remains a most critical need. It is clear that much more needs to be done.

Cystic Fibrosis

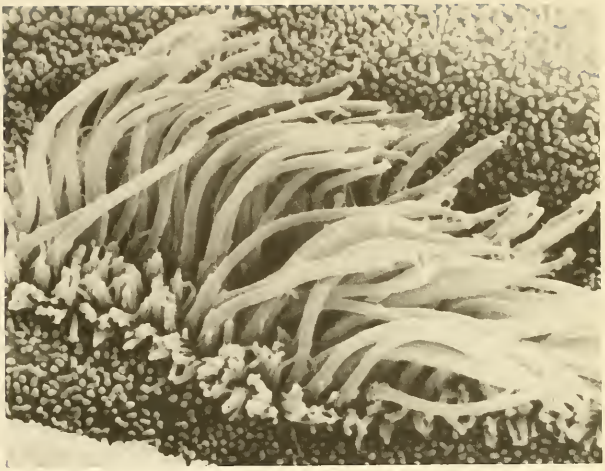
Cystic fibrosis is the most common lethal genetic disease of Caucasians; approximately 1 in 2,000 Caucasian newborns are affected. Its characteristic symptoms of obstructed breathing, pulmonary infections, and malnutrition result from the abnormal production of thickened and highly viscous secretions.

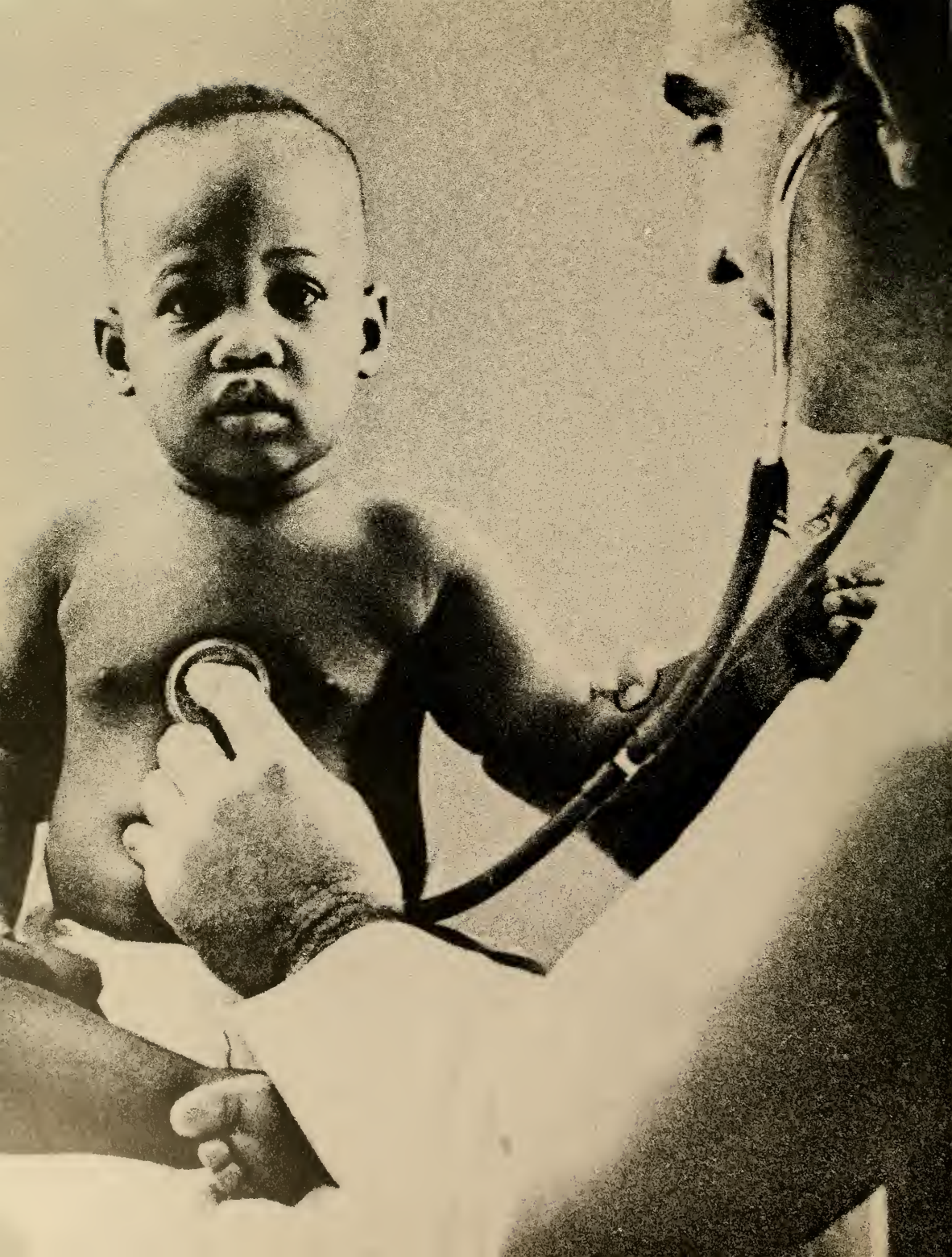
Although the life expectancy of patients with cystic fibrosis has improved significantly over the past several decades, current therapy is essentially palliative. Scientists are coming closer to discovering the basic defect in cystic fibrosis.

Progress made in recent years points to an inability of the cells lining the lung airways to properly transport sodium and chloride ions across cell membranes. This derangement of ion transport results in dehydration of the airway surface fluid and leads to thickened mucus and impairment of lung mucociliary function, the lungs' major defense against foreign particles and bacteria. Researchers are investigating whether agents that inhibit sodium absorption may help to correct abnormal ion transport in cystic fibrosis.

Molecular biological approaches have provided new impetus to investigations of the abnormalities associated with cystic fibrosis. Molecular genetic studies of tissue and blood samples from members of families with a history of cystic fibrosis have indicated that the genetic defect might be associated with a specific chromosome. Several biochemical and genetic markers of the diseases are closely linked to this chromosome. Investigators are actively cloning DNA segments in an attempt to identify the specific region responsible for the disease. Once the gene has been identified and cloned, it should be possible to characterize the precise metabolic defect. These studies have the potential to lead to development of a gene replacement therapy for cystic fibrosis.

Another avenue of research being explored is the development of cystic fibrosis cell lines that have an indefinite life span, so-called "immortalized cells." The Institute has recently initiated a program aimed at providing a steady supply of these cells. Initiation of the Specialized Centers of Research Programs in Cystic Fibrosis will encourage a multidisciplinary approach to research efforts to combat the disease. Another Institute program is designed to develop and evaluate educational programs to assist patients and their families in coping with the rigorous treatment requirements and the psychosocial difficulties of cystic fibrosis. It is hoped that these efforts will offer new approaches to improve the quality of life of the patients and their families.





The blood diseases and resources program supports and plans research relating to the causes, prevention, diagnosis, and treatment of genetic and acquired diseases of the blood as well as research that will help ensure a safe and adequate blood supply for the Nation. The program is organized into four main areas: hemostasis and thrombosis (clotting and bleeding disorders), red cell disorders, sickle cell disease, and blood resources (transfusion medicine). In this chapter, a few of the recent advances that have occurred largely through the support of the National Heart, Lung, and Blood Institute are highlighted.

Blood Diseases

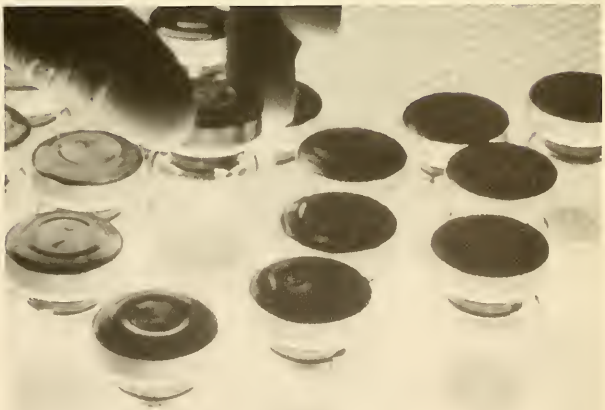
Clotting and Bleeding Disorders

A basic understanding of the mechanisms of coagulation and hemostasis is essential for the management and prevention of many diseases. The complex interactions of proteins in the clotting cascade have been unraveled through basic research supported by the Institute. The application of biochemistry and molecular biology has allowed elegant studies of chemical structure/function relationships and of the interaction between protein and cellular factors during clotting and hemostasis. Abnormal clotting in the blood vessels of vital organs results in disability and death for millions. When clots plug coronary arteries, myocardial infarction (heart attack) occurs; clots in blood vessels of the brain produce stroke. Deep venous thrombosis is very common, especially after surgery. Such venous thrombosis often results in pulmonary embolism which adds to postoperative morbidity and can be fatal.

The genes for a number of coagulation proteins have been cloned, paving the way for basic biochemical studies and for the pharmaceutical production of therapeutic quantities without the use of human or animal sources. Basic research on thrombolytic agents and their mode of action, supported by the NHLBI, laid the groundwork for the production and successful clinical application of genetically engineered tissue plasminogen activator (TPA). TPA effectively dissolves clots by converting plasminogen to plasmin, a lytic enzyme which acts on the insoluble meshwork of fibrin in clots. Pharmaceutical TPA has recently been approved for general clinical use (November 1987) and shows promise of greatly reducing mortality and morbidity for millions who suffer from acute blockage of arteries and veins.

Hemophilia

Hemophilia is a sex-linked bleeding disorder which plagued the descendants of Queen Victoria and was made notorious by the antics of Rasputin. The classic form, hemophilia A, is caused by an inherited deficiency of antihemophilic factor (factor VIII) and another, less common form results from an inherited factor IX deficiency. Advances in the management of hemophilia have resulted not only from advances in treatment modalities but also in a teamwork approach by hematologists, orthopedic surgeons, social workers, nurse clinicians, and rehabilitation counselors. These patients now grow to adulthood without the crippling orthopedic disabilities caused by repeated hemorrhages into major joints.



A major problem for patients with hemophilia is the transmission of hepatitis virus infections, and more recently acquired immune deficiency syndrome (AIDS) virus (human immunodeficiency virus or HIV-1), by factor VIII concentrates. Replacement therapy with large amounts of these concentrates is needed by about two-thirds of the 17,000 hemophilia A patients in this country. Heat or chemical treatment of these concentrates has nearly eliminated HIV-1 transmission, but probably not all hepatitis virus infection. Basic research on factor VIII supported by NHLBI was largely responsible for the recent cloning and sequencing of the gene for factor VIII. Not only is this a major technological achievement, given the large size of the gene, but it paves the way for the production of factor VIII. This production will be independent of the blood supply and, henceforth, free of transfusion-transmitted diseases.

Hemostasis

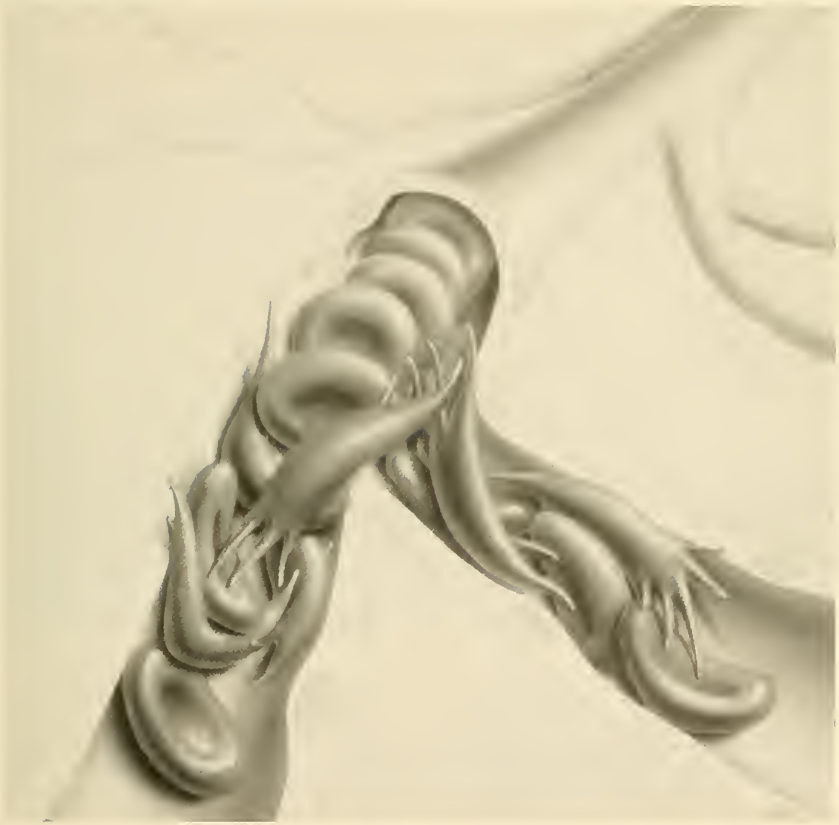
The hypercoagulable state is believed to be of profound importance in myocardial infarction and terminal vessel occlusion in atherosclerosis. Studies in this area, previously very difficult, have been given a considerable boost by Institute-supported studies of platelets, megakaryocytes and of proteins C and S. The dynamic role of the endothelium in abnormal thrombosis is now being elucidated. The genes for platelet surface glycoproteins have been cloned and sequenced, allowing examination of their specific roles in hemostasis at the molecular level. These platelet surface glycoproteins (or similar molecules), which have now been found in a number of other cells, are believed to be involved in interaction and communication between cells.

Workshops supported by the NHLBI furnish an excellent mechanism to focus the knowledge of experts on areas not receiving sufficient attention. A workshop on neonatal hematology resulted in a research initiative to explore the nature of coagulation disorders in premature infants. This has become a major issue because of the frequency of infant prematurity in teenage pregnancies. Eight percent of hemophiliacs are unresponsive to factor VIII therapy. A workshop on inhibitors of factor VIII generated a research initiative to study ways to handle this important problem. Workshops on deep vein thrombosis and thrombosis associated with lupus anticoagulant(s) stimulated further activities to elucidate these problems.

Sickle Cell Disease

For at least 20 years, it has been known that children with sickle cell anemia have an increased susceptibility to severe bacterial infection, particularly due to the organism *Streptococcus pneumoniae.* The risk of major infection with this organism is greatest in the first 3 years of life and can occur as early as 4 months of age. The first clinical manifestation can be fulminant, progressing from the onset of fever to shock and death in less than 9 hours. This complication carries a fatality rate as high as 35 percent, a statistic that has remained unchanged in the past 20 years, despite the widespread availability of pneumococcal vaccines and improved programs of care for children with sickle cell disease. Therefore, the NHLBI initiated a multicenter trial to investigate the effectiveness of daily oral penicillin given prophylactically to reduce the incidence of proven bacterial infection. The trial was terminated 8 months early when the compelling results showed an 84 percent reduction in the incidence of infection in the group treated with penicillin, as compared with the group not given the antibiotic. There were no deaths in the group given penicillin.

On the basis of these results, it is now being widely recommended that newborns be screened for sickle



cell anemia, and those affected be placed on daily oral penicillin by 4 months of age to decrease the morbidity and mortality associated with severe pneumococcal infection.

Although the technology to screen infants for sickle cell anemia in the newborn period has been available for many years, widespread adoption of screening has not occurred. Therefore, the National Heart, Lung, and Blood Institute, the National Institute of Child Health and Human Development, the Bureau of Health Care Delivery and Assistance of the Health Resources and Services Administration, and the NIH Office of Medical Applications of Research convened an NIH Consensus Development Conference to address this issue. The panel, experts in genetics, biochemistry, pediatrics, obstetrics, public health, law, and ethics, strongly recommended that all babies should be screened, and state laws should mandate

the availability of these services while permitting parental refusal. As a result of these recommendations, many states are in the process of developing legislation to fund and implement statewide screening programs for sickle cell disease as a part of existing programs presently testing newborns for inborn errors of metabolism.

Blood Resources

The most critical area in transfusion medicine today is the problem of the transmission of viral diseases (for example, AIDS) by blood transfusion. The Institute has supported and continues to sponsor considerable research in this area. In the past, a vaccine was developed to prevent hepatitis B infection by a virus that not only causes liver inflammation but also liver cancer. Blood banks have just recently implemented two tests, derived from Institute-supported research, to reduce the transmission of non-A, non-B hepatitis by blood transfusion.

The Institute supports many studies concerning AIDS and the Nation's blood resource. The Transfusion Safety Study (TSS) established a repository of sera from more than 200,000 donors in anticipation of the routine screening of blood donors for HIV

antibodies. Followup of donors and recipients has shown that 91 percent of those who received blood components from anti-HIV positive donors had become anti-HIV positive. This confirmed the infectivity of blood containing such antibodies and the value of the screening tests. The TSS also has provided data to improve further the safety of clotting factor concentrates, now heated or chemically treated, using methods developed by Institute-supported research to prevent the transmission of viral infections including hepatitis and HIV. The TSS has also confirmed that HIV infection is not spread within households except by sexual contact.

The Institute supports major efforts in prevention of infection by transfusion. In one area, investigators are working to develop more sensitive means for earlier detection of HIV infection to increase the safety of transfusion. In another approach, an anti-HIV hyperimmune gamma globulin has been prepared and after suitable safety studies, now nearing completion, a multicenter trial to test the clinical benefits of this preparation may be launched. Such a preparation could be useful for preventing infection at the time of an inadvertent exposure.

The rapid advances in transfusion medicine have made it imperative that more attention to this subject be included in the curricula of schools of medicine, osteopathy, and veterinary medicine. The Institute-supported Transfusion Medicine Academic Awards have resulted in the development of such educational programs. The influence of education in the use of blood components is already being felt and promises to lead to improvement of blood usage by professionals throughout the country.

Two recent consensus development conferences, one on fresh frozen plasma and one on platelet transfusions, along with other developments, have underlined the need to educate professionals and the public about blood transfusions. Accordingly, a general educational program addressed to both the public and the professions that order blood products for their patients was believed to be urgently needed. The Institute, with the assistance of many voluntary and professional organizations, is leading this educational effort through the newly-developed National Blood Resource Education Program.

National Blood Resource Education Program

As stated in the introduction of this report, the National Heart, Lung, and Blood Institute's primary goal is to discover the unknown about diseases of the heart, lungs, and blood and thereby to treat, cure, and prevent these diseases. To achieve this goal, 20 national program areas were identified in 1972. They have been slightly modified since then to meet changing needs and emerging concepts. All new and continuing initiatives are incorporated into these national program areas, ten of which are concerned with heart and vascular diseases, six with lung diseases, and four with blood diseases and resources.

The highest funding priority continues to be given to investigator-initiated research programs. Research training and research career development programs continued as priorities in order to maintain and to expand the development of young scientists who will become the researchers of the future. Included is a sustained emphasis on minority investigators, clinical investigators, and physician-scientist awardees.

Heart and Vascular Diseases Program

Specific efforts were made this year to identify priority areas for initiatives or workshops that would enhance knowledge in the ten national program areas that represent the major heart and vascular diseases responsible for mortality and morbidity in the United States. Both the Division of Heart and Vascular Diseases and the Division of Epidemiology and Clinical Applications support the basic, clinical, epidemiologic and behavioral research in these areas:

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

Areas of special need and opportunity were considered from among recommendations put forth by NHLBI scientific workshops, outside scientific organizations, professional staff, and the working groups of the Cardiology Advisory Committee and the Arteriosclerosis, Hypertension, and Lipid Metabolism Advisory Committee and the Clinical Applications and Prevention Advisory Committee.

Specialized Centers of Research (SCOR's) are centers of excellence in basic and clinical research. The competitive renewal of SCOR's in arteriosclerosis this year demonstrated that these centers have the strong scientific capability to advance knowledge of the fundamental causes of atherogenesis through the application of molecular biology, molecular genetics, and cell biology. Demonstration and education research emanating from the centers provides knowledge of direct value for disease prevention and health practices.

During the year the following 20 recommendations for new solicitations were approved by the Advisory Council:

- To support research which applies modern cellular and molecular technologies to the structure, function, and regulation of receptors, ion channels, and pumps in the myocardial sarcolemma and sarcoplasmic reticulum

- In cooperation with the Blood Diseases and Resources Program to encourage the development of basic and clinical research addressing the effect of omega-3 polyunsaturated fatty acids, such as those found in fish oils, on thrombosis and atherogenesis

- To encourage well-controlled studies in human subjects of the long-term effects of alterations in dietary fat, fatty acids, and fiber on the structure, function, and metabolism of lipoproteins

- To examine the biological and behavioral effects of smoking cessation contributing to relapse

- To identify the knowledge, beliefs, and behaviors among blacks concerning symptoms of coronary heart disease, as well as those environmental factors (including barriers), that influence their seeking and obtaining appropriate medical care for acute coronary heart disease or its symptoms

To conduct research to develop and validate a potentially accurate method, using isotope washout, of estimating usual dietary intake of sodium

To conduct research to increase the base of knowledge about hypertension in pregnancy

To determine which estrogen/progestin preparations convey the most desirable effects on cardiovascular disease risk factors

To encourage multidisciplinary research on the molecular and cellular endothelial events leading to acute myocardial infarction due to the formation of occlusive coronary thrombosis in patients with coronary heart disease

To elucidate the underlying mechanism(s) of obesity-associated hypertension and identify ways to improve its control and prevention

To select a central lipid and apolipoprotein laboratory to conduct accurate and precise measurements of cholesterol, HDL cholesterol, apolipoprotein A-1 and B, HDL-2 and HDL-3 cholesterol, and triglycerides, and to provide these data to the National Center for Health Statistics for use in the Health and Nutrition Examination Survey III (HANES); to monitor national trends in cholesterol and other lipid values by comparing data gathered in previous surveys

To establish a data center to collect, edit, store, and analyze baseline and outcome data on patients with severe valvular stenosis treated with balloon valvuloplasty

To determine whether totally-implantable, electrically-activated left ventricular assist systems are safe in the clinical environment, and to determine the physiological effects of these implantable systems in patients with end-stage heart disease

To study the interactions of behavioral factors with sodium administration, ingestion, sensitivity, and excretion in blood pressure regulation

To identify potentially modifiable characteristics associated with recruitment and refusal problems in the Cardiac Arrhythmia Treatment Study to be tested and applied by nursing staff in other hospital-based clinical trials

To test the acceptability of interventions in school-based cardiovascular health trials by parents, food service, and curriculum components, behavioral changes likely or possible, and information needed to complete the study design for a full-scale field trial in the school-based setting

To conduct research on ways to improve and maintain physicians' strategies in monitoring their patients to initiate, achieve, and maintain dietary changes for lipid lowering

To develop a variety of aids to strengthen the teaching of cardiovascular disease nutrition by physicians, nurses, and other health professionals in medical schools

To determine whether known cardiovascular disease and stroke risk factors lose their predictive value with increasing age; to determine the short-term precipitants and long-term determinants of new heart attacks, other coronary events, and stroke; and to determine the predictors of mortality, disability, functional impairment, institutionalization, and survival among elderly patients with clinical cardiovascular disease and stroke

By the use of ambulatory blood pressure monitoring, it is expected that important data relevant to the diagnosis, treatment, and long-term management of hypertension may become newly available. This program announcement included efforts to refine the use of the instrumentation and methods for data collection and analysis.

Lung Diseases Program

A high priority continued to be basic research related to the structure and function of the respiratory system and processes involved in lung injury and repair. With the concurrence of the Pulmonary Diseases Advisory Committee, some resources were set aside to create incentives for the exploration of new research avenues, an action considered a priority by experts in the field. All priorities identified by professional staff, scientific workshop participants, outside organizations, the Pulmonary Diseases Advisory Committee, and expert members of the National Heart, Lung, and Blood Advisory Council fall within the Division of Lung Diseases national program areas:

Structure and Function of the Respiratory System
Chronic Obstructive Pulmonary Diseases
Pulmonary Vascular Diseases
Occupational and Immunological Lung Diseases
Respiratory Failure
Pediatric Pulmonary Diseases

During the year, the Advisory Council concurred with the recommendation that five special solicitations for grants be announced and eight workshops be held, one of which was a major conference on primary pulmonary hypertension where data from a 5-year patient registry sponsored by the NHLBI were presented.

The five special solicitations announced were designed to stimulate new research in the following areas:

- To develop genetic probes for antioxidant enzyme genes and the use of such probes to identify the subcellular sites of synthesis and regulation of antioxidant enzyme production in normal and diseased lungs
- To apply sophisticated neurobiological techniques to the study of respiratory control, including the identification of natural neurochemicals and cellular networks that regulate breathing
- To identify and characterize heterogeneous subpopulations of lung fibroblasts that contribute to fibrotic lung disease
- To develop a viral vector for somatic gene therapy to correct the gene deficiency for alpha-1-protease inhibitor, a primary risk factor for familial emphysema
- To isolate and characterize selected ion channels from pulmonary epithelial and other cells in order to elucidate the processes regulating their biosynthesis and function and to correlate their structure and function in health and disease.

Blood Disease and Resources Program

In fiscal year (FY) 1987-88, the Advisory Council recommended approval of ten new and renewal programs in this area as recommended by professional staff, an Ad Hoc AIDS Working Group, the Blood Diseases and Resources and the Sickle Cell Disease Advisory Committees, individual scientists, other ad hoc working groups, workshops, and conferences. The Division of Blood Diseases and Resources national program areas are:

Bleeding and Clotting Disorders
Disorders of the Red Blood Cell
Sickle Cell Disease
Blood Resources

These and other activities continued the program's strong commitment to the support of creative investigator-initiated research and to its efforts to assure that sufficient and appropriately trained research personnel will be available to study productively those research areas already identified and others where careful examination has identified gaps that should be filled.

The Advisory Council recommended for approval three programs that were recommended for renewal:

- To continue to maintain collections of blood specimens from NHLBI-sponsored studies: to make appropriate specimens available to the scientific community for use in research related to transfusion medicine, particularly transmission of diseases by blood or blood components, and to research on blood diseases
- To maintain a colony of chimpanzees that is available for research on posttransfusion viral hepatitis or AIDS
- To evaluate the possible hazards of daily oral penicillin prophylaxis in children with sickle cell disease, and of cessation of prophylaxis at age five; to continue assessing compliance patterns, splenic function, and colonization by *Streptococcus pneumoniae* of inpatients treated prophylactically with oral penicillin.

Approval was voted for seven new programs regarded by experts as vital to progress in the challenge presented by blood diseases:

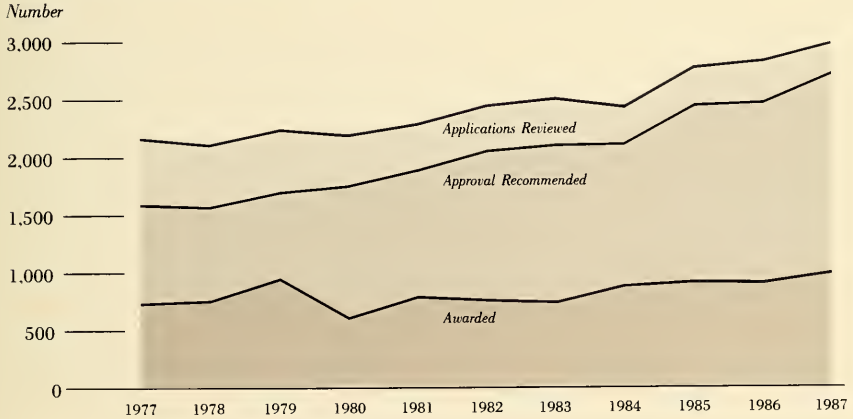
- To encourage research on the development of the hemostatic system of the newborn, with a particular focus on interpreting the molecular biology of the processes that regulate the coagulation proteins
- To determine the optimum dose schedule of hydroxyurea for achieving maximum activity with minimum risk and to determine short-term toxicities in treating sickle cell disease
- In cooperation with the Heart and Vascular Diseases Program, to encourage the development of basic and clinical research addressing the effect of omega-3 polyunsaturated fatty acids on thrombosis and atherogenesis
- To encourage basic and clinical research on the role of nutrition in sickle cell disease
- To foster research on the development and evaluation of techniques to detect venous obstructions, including deep vein thrombosis; to quantitate obstructions, detect and quantify blood flow in peripheral veins; and to estimate the age of clots in veins, using methods that are equally accurate but less invasive than venography
- To determine the natural history of the clinical, biochemical, and histological outcome of chronic non-A, non-B hepatitis
- To conduct a preclinical evaluation of AIDS immunoglobulin directed to *in vitro* efficacy, including pre- and post-exposure prophylaxis in chimpanzees or other animal models, if the current contract for the development of the AIDS immune globulin finds it safe and efficacious in the preliminary studies.

Resources

In recommending the Institute's budgets for FY's 1989-1993, the Council adhered to the following principles for the determination of appropriate funding levels:

- Budgets must increase to keep pace with increased costs of research
- A reasonable percentage of uncommitted funds must be used each year for centers, contracts, training, career awards, and other mechanisms that contribute to a balanced program while adequate funds are also provided for research project and program project grants
- Resources must be sufficient to fund as many approved research grant applications as possible to secure important potential investigators
- Administrative flexibility must be provided the NHLBI to allow effective deployment of its allocated resources.

NHLBI Competing Research Project Grants: Applications Reviewed, Approval Recommended, and Awarded, Fiscal Years 1977-1987*



Number of Grants

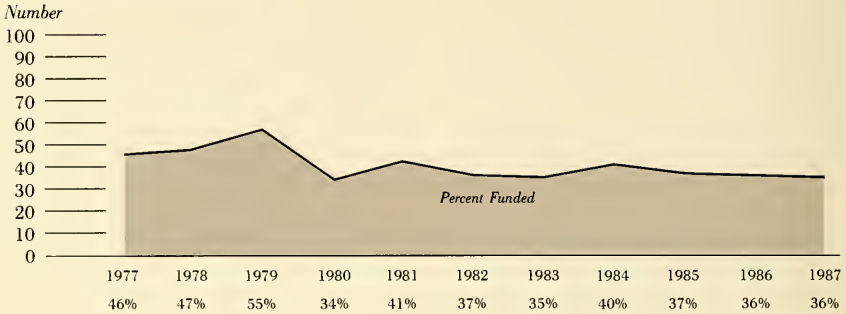
Fiscal Year	1977	1978	1979	1980	1981	1982	1983	1984	1985	1986	1987
Current Year Applications Reviewed	2,180	2,129	2,239	2,190	2,289	2,455	2,519	2,445	2,778	2,822	2,964
Current Year Approvals Recommended	1,600	1,595	1,679	1,735	1,890	2,054	2,110	2,115	2,441	2,467	2,699
Total Eligible†	1,602	1,625	1,699	1,741	1,897	2,055	2,114	2,119	2,448	2,481	2,706
Awarded	729	759	942	589	774	765	748	852	901	886	966

**Includes R01, R23, P01, R43 (beginning in fiscal year 1983), R44 (beginning in fiscal year 1984), U01 (beginning in fiscal year 1985), R37 (beginning in fiscal year 1986), and R29 grants (beginning in fiscal year 1987).*

†Includes unfunded approvals carried over from previous years that were funded within a specific year.

Source: Division of Research Grants, NIH.

NHLBI Competing Research Project Grants: Percent Funded, Fiscal Years 1977-1987



In FY 1987, the Council recommended 2,699 high quality applications for funding; however, only 963 applications or 35.7 percent were funded because of a restrictive budget and rising costs. This number of funded applications in FY 1987 was the greatest funded by NHLBI to date, but the high percentage of unsuccessful applicants may have deleterious effects on future research. Early in their careers, scientists are being discouraged by the difficulty of obtaining funding. The consequence can be seen by the declining percentage of physicians pursuing careers in biomedical research.

The Council strongly recommends the following budgets to award an adequate number of meritorious grants and to fully develop its initiatives (in millions of dollars):

FY 1990	FY 1991	FY 1992	FY 1993	FY 1994
$1,400	$1,540	$1,700	$1,870	$2,050

Conclusion

The National Heart, Lung, and Blood Advisory Council expresses its special commendation to the Institute's Director, Dr. Claude Lenfant, and the entire NHLBI staff for the high quality of their work. They are truly dedicated individuals. Their commitment to the Council, the scientists and health professionals whose research support they administer, and the general public goes well beyond the requirements of their individual jobs.

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