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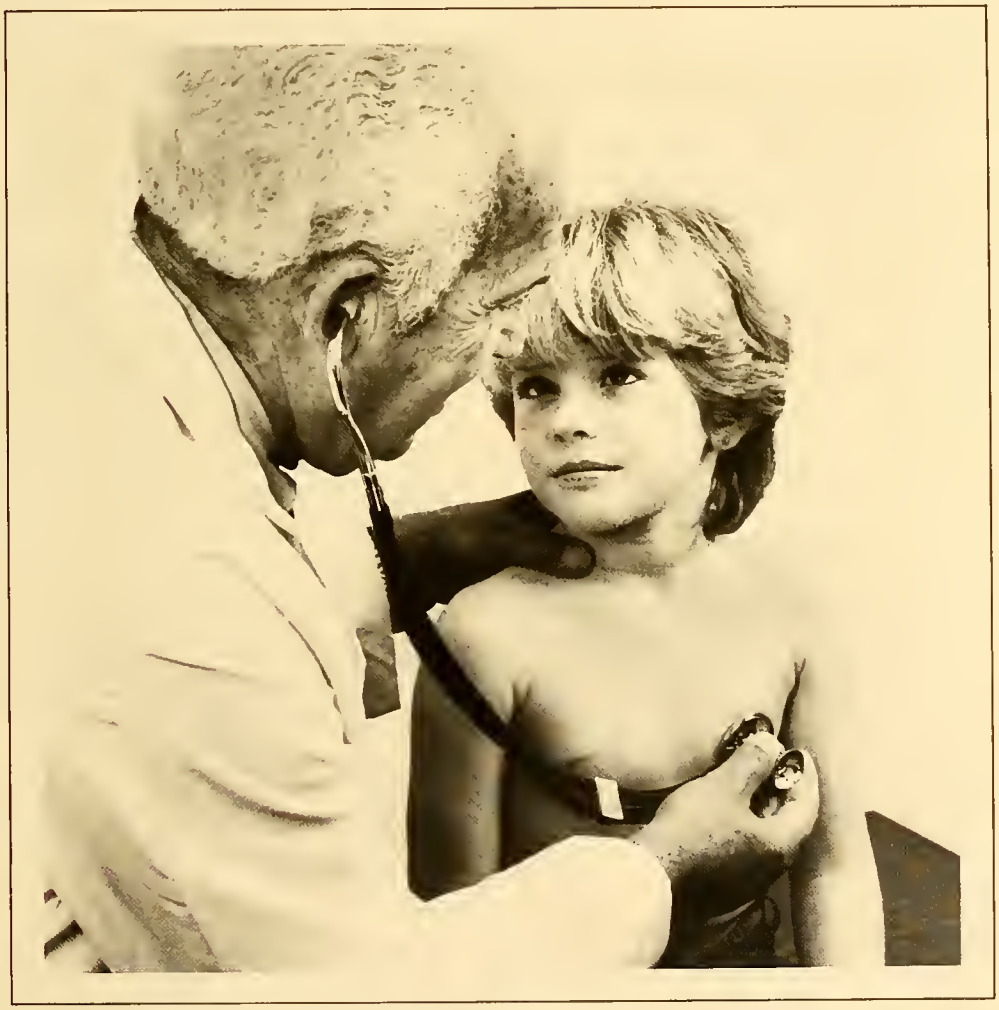
Seventh Report of the Director, National Heart, Lung, and Blood Institute



U. S. Department of Health, Education, and Welfare
Public Health Service
National Institutes of Health

Heart, lung and blood diseases affect all segments of the population—young and old, black and white, rich and poor alike. Our future hope lies with early detection and prevention of these diseases in the young, before they take their toll later in life. With this in mind, the *Seventh Report of the Director, National Heart, Lung, and Blood Institute* is dedicated to the health of the youth of America in the International Year of the Child, 1979.

In this volume, the Institute reports its accomplishments during the past year and projects future needs and goals to enhance the quality of life for the people of America—the people pictured throughout these pages, whose faces bring to life the larger mission of NHLBI.

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

U. S. Department of Health, Education, and Welfare
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DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH
BETHESDA, MARYLAND 20014

NATIONAL HEART, LUNG, AND BLOOD INSTITUTE

November 30, 1979

The Honorable Patricia Roberts Harris
Secretary of Health, Education,
and Welfare
Washington, D.C. 20201

Dear Madam Secretary:

It is with great pleasure that I submit to you the Seventh Report of the Director, National Heart, Lung, and Blood Institute. This volume provides a comprehensive overview of NHLBI activities and achievements during the past year and outlines immediate and long-range goals -- all directed toward the conquest of the Nation's most serious health problems.

As described in this report, the cost of heart, lung, and blood diseases to this country and its people is beyond measurement in dollars or lost productivity. The loss felt by the families of the nearly 1 million people who died of heart and blood vessel diseases in 1978 is a prime example of the toll that is extracted but cannot be quantified. The suffering caused by blood diseases, so frequently striking in childhood and often complicating disorders of other organs, is another compelling reason for continuation of a vigorous attack through research to prevent, control, and treat the major health threats that fall within NHLBI's purview.

Over the last 10 years, the United States has witnessed a dramatic decline in mortality from cardiovascular diseases. Mortality from respiratory diseases has also declined, but the prevalence has steadily increased since 1968; and the problems of blood diseases and maintaining the national blood resources are continuing critical concerns. The Seventh Report of the Director examines the factors that have contributed to improved death rates as well as the obstacles to progress that are yet to be overcome.

A large portion of this year's report is devoted to descriptions of important research advances; however, the Institute's specialized programs for assessing research needs, evaluating research results, and communicating emerging information and technology to the health care community are also discussed in some detail. The Institute's research efforts of the past 12 months have been very productive, and the goals set forth for the next 5 years reflect our prevailing belief that continued efforts can indeed bring about effective amelioration of the burden of heart, blood vessel, lung, and blood diseases that touches the lives of virtually every American.

Sincerely,

Robert I. Levy

Robert I. Levy, M.D.
Director

Preface

In 1972, the National Heart, Blood Vessel, Lung, and Blood Act called for a coordinated national effort to reduce the suffering, death, and disability caused by cardiovascular, pulmonary, and blood diseases. Thus the National Heart, Lung, and Blood Institute (NHLBI) was directed to plan and implement a national program of research to combat these diseases. In this volume, the Institute reports its accomplishments during the past year and projects future needs and goals to enhance the quality of life for the people of America.

The *Seventh Report of the Director, National Heart, Lung, and Blood Institute* includes descriptions of the magnitude of the problem facing the Institute and the Nation, a description of NHLBI programs directed at solving these problems, a brief overview of the Institute's planning and evaluation process, and an explanation of the strategy and range of research activities that characterize NHLBI's approach to improving knowledge of the causes, possible treatment, and prevention of heart, lung, and blood diseases. Selected accomplishments and highlights of 1979 research projects are presented, as are descriptions of the 1979 accomplishments of special NHLBI initiatives such as the Specialized Centers of Research; clinical trials; research and demonstration centers; prevention, education, and control programs; technology transfer activities; and coordinating activities. Programs of manpower development and international activities are described as well. An individual section is devoted to setting forth goals and planned activities for 1981 through 1985, and a section on resource allocations indicates the fiscal and personnel requirements to carry out activities planned for 1981 and projected through 1985.

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I. Magnitude of the Problem and Legislative Mandate

A National Concern

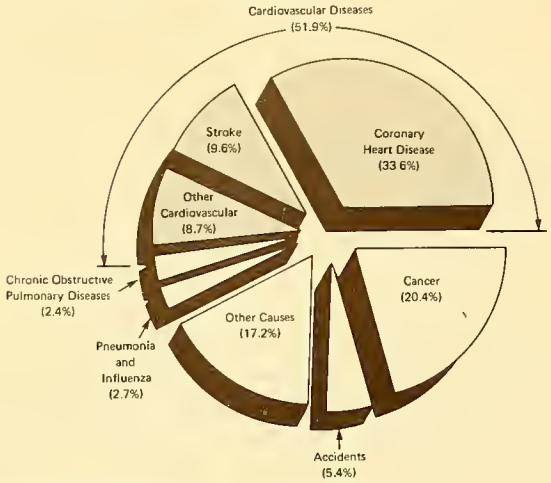
The NHLBI is responsible for the major share of U.S. research in heart, blood vessel, lung, and blood diseases, as well as for the management of American blood resources. Diseases of the heart, lungs, and blood account for an excessively large part of this Nation's sickness, death, and illness-related financial loss; the magnitude of NHLBI's responsibilities should be viewed from this perspective.

In 1977, 4 of the 10 leading causes of death in the United States were problems that fall within NHLBI's purview: diseases of the heart (ranked first), cerebrovascular diseases (third), chronic obstructive lung disease (sixth), and arteriosclerosis (eighth). In 1977, these four disease categories accounted for 1 million deaths (table 1), well over half of the year's total. Coronary heart disease alone accounted for more than one-third of all 1977 deaths; with deaths from other cardiovascular diseases added, heart and blood vessel diseases caused 51.9 percent of all 1977 deaths. (See figure 1.)

Although the problem is enormous, significant advances are being made. Life expectancy in the United States has increased, in the past three decades, by about 5 years for both men and women. (See figure 2.) A significant portion of this increase in life expectancy can be attributed to the decline in cardiovascular death rates, especially in the last 10 years. In fact, cardiovascular death rates have decreased at almost double the pace of death rates from other causes. Deaths from coronary heart disease have declined by over 22 percent during this decade, and deaths from stroke have declined even more precipitously (over 33 percent since 1968, and by an annual rate of more than 5 percent each year since 1972). (See figure 3.)

The decrease in cardiovascular death rates has been particularly steep since 1968. The effect of this decline is dramatic. If the cardiovascular death rates of 1968 had remained unchanged over the past 10 years as our population has grown larger and older, more cardiovascular

Figure 1.— Deaths by cause and percentage of total deaths, 1977



Source: National Center for Health Statistics

deaths would have been expected than the number that was observed. In 1977 alone, there would have been 300,000 more cardiovascular deaths than the number that actually occurred. (See figure 4.)

Many factors may be responsible for this decline. Although the exact contribution of particular determinants is not known, it is quite certain that recent research findings, particularly those that have to do with medical practice and cardiovascular risk factors, have already had a major impact. Improved medical practices appear to have contributed significantly to the decline. Such things as prompt emergency care, the use of hospital coronary care units, medical treatment of high blood pressure, improved surgical techniques, and improved diagnosis of diabetes, hyperlipidemia, and hypertension are all probable contributors to the improvements in death rates for cardiovascular disease. It also appears that the public has become more aware of the known cardiovascular risk factors and has adjusted behavior and lifestyles to reduce a number of important risks. For example, there has been a decrease in the use of tobacco products, a decrease in the consumption of high saturated fat-high cholesterol foods, and a greater awareness of the need to control both hypertension and obesity and of the benefits of exercise.

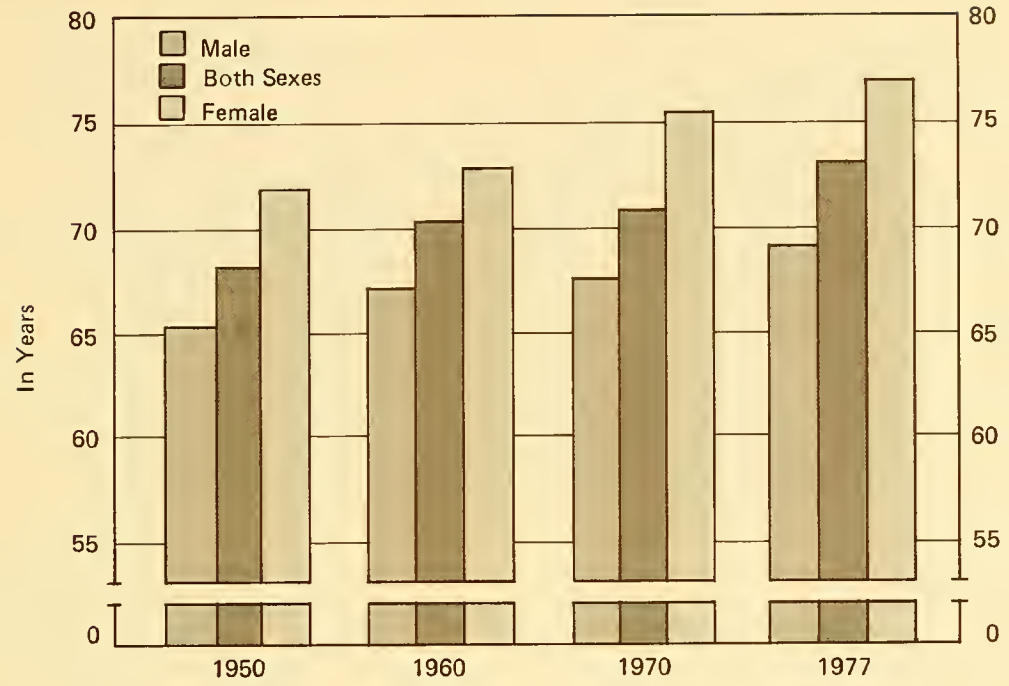
Current research, supported by NHLBI and described in part in this report, is focusing on measurement of the actual impact of individual factors such as those mentioned above. This ongoing research will help determine what

Table 1.— Death rates for 10 leading causes of death: United States, 1977

Rank*	Cause of Death	Death Rate (per 100,000 Population)	Number of Deaths	Percentage of Total Deaths
	All causes	878.1	1,899,597	100.0
1	Diseases of heart	332.3	718,850	37.8
2	Malignant neoplasms, including neoplasms of lymphatic and hematopoietic tissues	178.7	386,686	20.4
3	Cerebrovascular diseases	84.1	181,934	9.6
4	Accidents	47.7	103,202	5.4
	Motor vehicle accidents	22.9	...	...
	All other accidents	24.8	...	...
5	Influenza and pneumonia	23.7	51,193	2.7
6	Chronic obstructive lung disease	21.4	46,325	2.4
7	Diabetes mellitus	15.2	32,989	1.7
8	Cirrhosis of liver	14.3	30,840	1.6
9	Arteriosclerosis	13.3	28,754	1.5
10	Suicide	13.3	28,681	1.5

*Based on number of deaths.
Source: National Center for Health Statistics, "Monthly Vital Statistics Report," May 1979.

Figure 2.—Life expectancy by sex, 1950-1977



factors or combinations of factors have had the greatest impact. Such knowledge could prove invaluable in identifying yet more specific preventive methods that will further decrease cardiovascular mortality.

Despite striking improvements, however, diseases of the heart, blood vessels, lungs, and blood remain among the Nation's most serious health problems. Cardiovascular diseases constitute the leading cause of death for men beginning at age 40 and for women beginning at age 60; and at least 40 million Americans have diseases of the heart and blood vessels. Listed below are some data indicating the impact of several specific cardiovascular diseases:

- *Arteriosclerosis* is the underlying cause of an estimated 86 percent of deaths from heart and vascular diseases. Virtually all American adult males and postmenopausal females are afflicted to some degree.
- *Hypertension* is the most commonly encountered form of heart and blood vessel disease, affecting about 15 percent of the population, or almost 35 million persons.
- *Cerebrovascular disease* affects 1.8 million adults, of whom more than half are partially or completely disabled. Each year about 250,000 persons between the ages of 25 and 64 are afflicted by stroke.
- *Coronary heart disease* causes 1.25 million heart attacks a year and is responsible for chronic illness in 4 million Americans, over half of them below the age of 65.
- *Congenital heart disease* occurs in about 8 out of every 1,000 children born each year; more than half of those who die from congenital heart disease are under age 1.
- *Acute rheumatic fever and subsequent rheumatic heart disease* still occur in school-age children. About 13,000 deaths occur each year from rheumatic fever and its cardiac complications.

- *Cardiovascular illness* accounted for 17 percent of all workdays lost to productivity in 1972.
- *Cardiovascular diseases* accounted for 10 percent of all patient visits to physicians' offices and 19 percent of all short-stay hospital bed days in 1977.
- *Essential benign hypertension* is the third most frequent diagnosis rendered in physicians' offices.

Diseases of the lungs and other parts of the respiratory system constitute a major national health problem that, for some disorders, is of increasing dimensions. While the incidence of acute respiratory conditions and total respiratory mortality have declined, the National Center for Health Statistics reports a steady increase from 1968 to 1975 in total respiratory disease morbidity. This increase is specifically attributable to chronic obstructive lung disease, chronic bronchitis, and emphysema. The impact of respiratory diseases can be seen in the following examples:

- *Chronic obstructive lung diseases* afflict more than 14 million people.
- *Emphysema, bronchitis, and asthma* caused 46,325 deaths in 1977.
- *Respiratory distress syndrome of the newborn and hyaline membrane disease* claim about 3 lives for every 1,000 live births.
- *Respiratory disorders* are the leading reason for people to seek a physician's attention, accounting for 20 percent of all physician contacts and 12 percent of all short-term hospital stays.
- *Respiratory illness* accounts for more lost workdays than any other category of illness. In 1972, over 135 million workdays were lost to respiratory illness.

Figure 3.—Trends in cardiovascular disease and noncardiovascular disease: Decline by age-adjusted death rates, 1968-1978

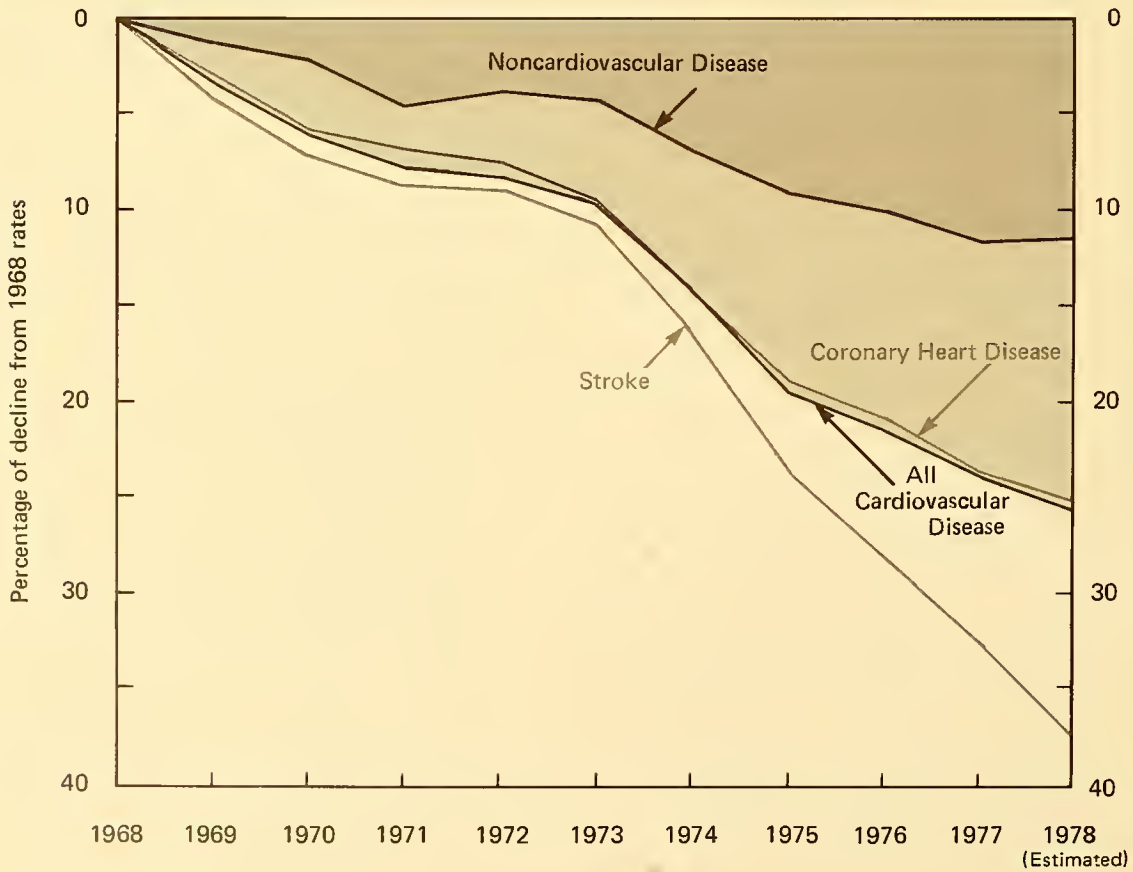
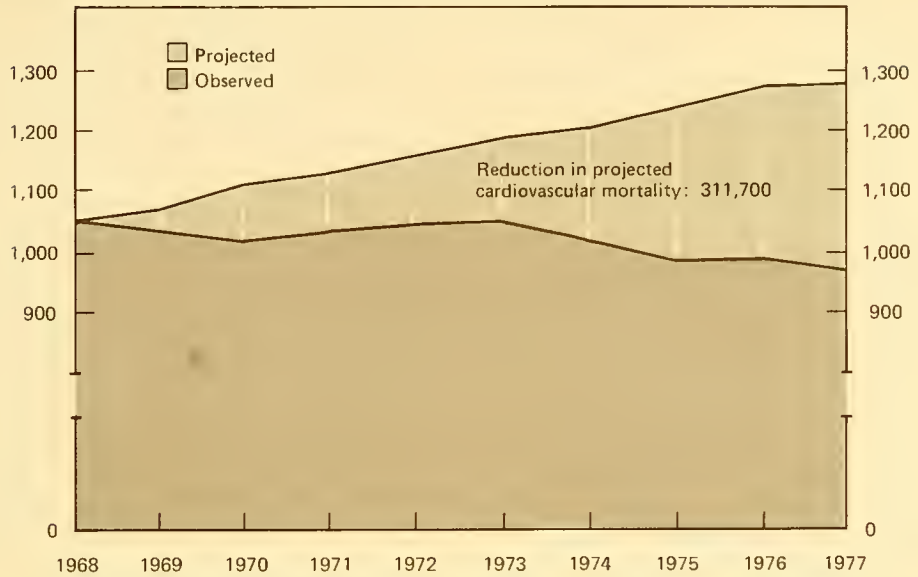


Figure 4.—Cardiovascular disease deaths, 1968 to 1977: Projected deaths based on 1968 mortality rates compared with observed deaths (numbers in thousands)



Disorders of the blood are related to many heart, blood vessel, and lung diseases. While the number of deaths specifically attributable to blood diseases is smaller than that for heart and lung disorders, abnormalities of the blood clotting system are major contributors to cardiovascular and pulmonary morbidity and mortality, as well as to other disorders in all parts of the body. Arterial thrombosis causes or complicates a great variety of diseases. For example, thrombosis involving the vessels of the kidney contributes to kidney failure, and arterial thrombosis and cerebral hemorrhage play major roles in stroke. Thrombosis in the veins may lead to pulmonary embolism; that is, clot fragments may be carried in the blood from the site of origin to the lungs. About 300,000 hospitalized persons each year are found to have pulmonary embolism, and as many as 50,000 of these patients die. Clotting in the venous circulation complicates many illnesses and surgical procedures. Autopsy studies show evidence of venous thrombosis in about 50 percent of cases examined, regardless of cause of death. Bleeding and clotting in the microcirculation are contributory or primary mechanisms in stroke, myocardial infarction, diabetes, infectious and inflammatory disease, autoimmune disease, host-graft rejection, cancer, sickle cell disease, drug toxicity, mismatched blood transfusion, hypertension, liver disease, and nephritis. Thus, the impact of blood disorders is vast even if it cannot be expressed statistically.

The following data exemplify the impact of blood disorders and the importance of the national blood resource:

- *Hemophilia* affects about 20,000 to 25,000 persons in the United States—15,000 of them severely enough to require lifelong treatment with costly preparations obtainable only from human blood plasma. Their needs constitute one of the largest single demands on the Nation's blood resource.
- *Sickle cell trait* is carried by approximately 2 million persons in the United States and about 1 in 400 black children born in this country has sickle cell disease as a result of its inheritance pattern. Nearly 50,000 individuals have sickle cell anemia and suffer this life-threatening, often crippling disorder and the painful episodes known as "crises."
- *Transfusion-transmitted hepatitis,* which remains a serious hazard for hundreds of thousands of blood recipients, results in prolonged incapacitating illness and, often, in chronic liver disease.
- *The collection, processing, distribution, and proper use* of more than 12 million units of blood annually are vital to the provision of modern health care services.

Table 2.—Economic cost of selected diseases, 1975 (dollars in millions)

Diagnosis	Direct Costs		Indirect Costs				Combined Costs	
			Morbidity		Mortality			
	$	%	$	%	$	%	$	%
Diseases of the circulatory system	15,999	16.1	8,735	15.1	25,674	29.2	50,408	20.0
Diseases of the respiratory system	7,552	7.6	8,561	14.8	3,605	4.1	19,718	8.0
Diseases of the blood and blood-forming organs	696	0.7	289	0.5	264	0.3	1,249	1.0
Circulatory, respiratory, and blood diseases combined	24,247	24.4	17,585	30.4	29,543	33.6	71,375	29.0
All diseases	99,374	100.0	57,846	100.0	87,926	100.0	244,146	100.0

Source: Dorothy P. Rice *et al.* "The Current Burden of Illness in the United States," National Academy of Sciences, Washington, D.C., October 1976.

The combined costs of medical treatment for heart, lung, and blood diseases were over $24 billion in 1975 and accounted for nearly 25 percent of all U.S. treatment costs. The combined economic loss due to sickness was over $17 billion, and losses due to early death cost Americans nearly $30 billion. Overall, the economic burden of heart, lung, and blood diseases exceeded $70 billion and accounted for approximately 29 percent of the total U.S. economic cost of illness. Table 2 summarizes data concerning the economic cost of heart, lung, and blood diseases.

The toll exacted by heart, lung, and blood diseases is an appalling one in terms of the numbers of people affected or the social and economic costs. The personal costs in suffering and grief are staggering. There is hardly a single family that will not be touched by some form of heart or blood vessel disease. There are few people in the United States who cannot count a stroke victim among their personal acquaintances. Nearly every American suffers at one time or another from respiratory problems, and the risk of more serious lung diseases is a concern to all of us. Diseases of the blood are especially tragic, particularly when one considers those bleeding disorders that so severely affect the very young. Any American may at some time have to rely on the availability of adequate blood supplies.

In addition to the measurable burdens caused by heart, lung, and blood diseases, it is certainly the personal suffering and loss they cause that continue to motivate the general public and its elected representatives, the scientific and medical communities, and the NHLBI itself to persist in the search for new and improved means to prevent and overcome heart, lung, and blood diseases.

Legislative Mandate

The National Heart, Lung, and Blood Institute is responsible for much of this Nation's research to overcome the staggering problems of heart, lung, and blood diseases. In the past three decades, the number of Institute programs and the scope of its biomedical research and professional and public education activities have grown significantly as a result of a series of legislative mandates.

The National Heart Act of 1948 (P.L. 80-655) established the National Heart Institute by adding a new section to the Public Health Service Act. Since 1948 Congress has reendorsed the Institute's authorization and expanded its mandate four times. These revisions have greatly increased NHLBI's responsibilities. The following chart indicates the evolution of the responsibilities that have resulted from particular pieces of legislation.

During the 30 years of the Institute's history, significant advances have taken place in prevention, detection, diagnosis, and treatment of heart, lung, and blood diseases. Much remains to be done to combat the disorders that fall within the Institute's mandate. These responsibilities are enormous, but the potential for improving the Nation's health is likewise immense. The Institute's programs have been designed to respond aggressively to these pressing national needs and research opportunities.

Legislative Expansion of NHLBI Mandates

1972 Legislation

Through the National Heart, Blood Vessel, Lung, and Blood Act of 1972, Congress strengthened its commitment to the Institute and to research in its disease areas. The name change from National Heart Institute to *National Heart and Lung Institute* was codified into statute and the Institute was given expanded responsibilities which added several new sections to the Public Health Service Act.

To carry out these broadened responsibilities most effectively, the Institute needed a new program strategy. Thus, the law mandated that the Director of the Institute, with the advice of the Council, develop a *national plan* within 180 days of the law's enactment. A thorough review was undertaken of the state of scientific research in heart, lung, and blood diseases, including input from hundreds of experts in these fields. The resultant plan outlined a comprehensive *National Heart, Blood Vessel, Lung, and Blood Diseases Program* based on responsibilities outlined in the law for:

- research into the *epidemiology, etiology, and prevention* of heart, blood vessel, lung, and blood diseases;
- research into *basic cardiovascular biological processes;*
- development and evaluation of *techniques, drugs, and devices* to aid diagnosis and treatment;
- programs to develop *technological devices* to assist, replace, or monitor vital organs;
- *field studies and large-scale tests* relating to those diseases;
- research into *blood diseases and the use of blood resources* in the United States, including such items as collection, preservation, fractionation, and distribution;
- *education and training* of scientists and clinicians;
- *public and professional education* programs in all aspects of those diseases;
- programs to research and study heart, lung, blood vessel and blood *diseases of children;* and
- programs to research and develop *emergency medical services*, including training of paraprofessionals and development of specialized equipment and communications.

The National Program has continued to be the foundation of the Institute's activities, and is updated each year. As a provision of the 1972 legislation, Congress mandated that the *Director of the Institute* submit an *annual report* to the President, for transmittal to Congress, on the accomplishments of the National Program during the preceding year and plans for the next 5 years.

The Act also mandated an *annual report from the Advisory Council* to the President, for transmittal to Congress. Membership on the Council was expanded from 16 to 23 members, including for the first time representatives from the public and from medical residency training programs. Corresponding to the Institute's increased mandates, the Council's functions expanded from concern with heart diseases to concern with heart, blood vessel, lung, and blood diseases.

To complete its expansion of Institute mandates, the 1972 Act:

- establish a specific post of *Assistant Director for Health Information*, to provide the public and health professionals with information about cardiovascular and pulmonary diseases, including emphasis on the effects of lifestyle factors such as diet, smoking, exercise, and stress;
- required the Institute to establish *prevention and control programs* with other governmental and private health agencies with appropriate emphasis on children's diseases, and delineated authorization of appropriations for that purpose;
- authorized the establishment of up to 30 *national research and demonstration centers* (15 for heart, blood vessel, and blood diseases, and 15 for lung diseases, including lung diseases of children), to foster coordinated programs in basic and clinical research, training, and demonstration;
- established an *Interagency Technical Committee*, chaired by the Director of the Institute, to coordinate those aspects of all Federal health programs related to heart, blood vessel, lung, and blood diseases and blood resources; and
- specified that a minimum of *15 percent* of appropriated funds must be utilized for programs in lung diseases, and a minimum of *15 percent* for programs in blood diseases and blood resources.

From 1948 until 1972, the Institute received appropriated funds under the general research authority of Public Health Service Act Section 301, which have no specific disease category allocation or "time and dollar" limits. Beginning with the 1972 legislation, Congress designated a specific authorization level and renewal period for the Institute. (Similar action had taken place regarding the National Cancer Institute, in 1971). The 1972 Act authorized 3 years of funding; thus, the Institute required reauthorization after June 30, 1975.

1975-1976 Legislation

Reauthorization legislation for the National Heart and Lung Institute proceeded through Congress during 1975, was delayed into 1976, and was signed in April 1976. It provided for a 2-year renewal period, rather than 3 years, so that the next reauthorization would coincide with that of the National Cancer Institute and with publication of the President's Biomedical Research Panel Report. Thus, reauthorization in the Health Research and Health Services Amendments of 1976 provided funding authority for fiscal years 1976 and 1977. (Note: During this period, the fiscal year start was shifted from July 1 to October 1 through an act of Congress.)

(continued)

Legislative Expansion (continued)

The significant thrust of the 1975-1976 legislation was to emphasize, clarify, and expand the Institute's role in blood-related areas. This intention took form in several actions, including the following:

- Congress changed the Institute's name to the *National Heart, Lung, and Blood Institute* and changed the Council's name to the *National Heart, Lung, and Blood Advisory Council.*
- In the several Public Health Service Act sections where Institute responsibilities regarded "heart, blood vessel, lung, and blood diseases," Congress added language about *"the use of blood and blood products and the management of blood resources."*
- Blood diseases and blood resources were added to cardiovascular and pulmonary diseases, as areas of *information dissemination* mandated for the Institute's Office of Prevention, Education, and Control.
- The distribution of up to 30 national research and demonstration centers was reorganized into *10 centers for heart, 10 centers for lung, and 10 centers for blood.*
- Committee report language emphasized that Congress intended the Institute to function as the *locus of coordination* for blood research programs and research in the management of blood resources.

Other notable highlights of the 1975-1976 legislation included:

- a new authority for the Advisory Council, to recommend to the Secretary areas of research to be supported by *contracts*, and recommended the percentage of the Institute's budget to be expended for contracts;
- changes in the annual *Director's Report*, to be submitted after the end of each fiscal year rather than calendar year, and to include personnel and appropriations estimates for the following 5 years; and
- changes in the annual *Advisory Council Report*, to be transmitted simultaneously to the President and Congress rather than to the President for transmittal to Congress, and to be transmitted by November 30 each year rather than by January 31.

1977 Legislation

Because both Congress and a new Administration were interested in undertaking a major review of all biomedical research authorities through extensive "biomedical overview" hearings and reports, the Biomedical Research Extension Act of 1977 was a 1-year renewal.

Congressional hearings began a series of discussions on several substantive issues in the conduct and management of biomedical research, while the legislation was kept to as simple an extension as possible. In the 1977 legislation, Congress:

- *reaffirmed the need for an expanded, intensified, and coordinated National Program*, as mandated in the previous NHLBI authorization laws; and
- included a few *technical amendments* clarifying the role of research and demonstration centers for blood, adding cost-of-living increases for the centers in general, and reassigning one ex-officio Council membership space from the National Science Foundation back to the newly reestablished Office of Science and Technology Policy.

1978 Legislation

The Biomedical Research and Research Training Amendments of 1978 resulted from a compromise between two sets of concerns. From the perspective of "biomedical overview," several major issues were still being explored, and future hearings were being planned; thus, another 1-year simple extension renewal was a possibility. From the perspective of research funding stability and planning needs, however a 3-year renewal period was also proposed. The final law reauthorized the Institute for 2 years, FY 1979 and FY 1980, and included several amendments to further increase the effectiveness of the Institute's programs.

The most significant amendments affected the submission of reports and responsibilities for information dissemination.

- Transmittal requirements for the *Director's Report* were changed to correspond to the Council Report route and timing, so that the Secretary transmits both reports, by November 30 of each year, simultaneously to the President and Congress.
- Language was added to the existing information dissemination mandates, requiring that dissemination occur *"on a timely basis."*
- In the dissemination program of the Office of Prevention, Education, and Control, responsibilities were added for *"nutrition"* (in addition to "diet"), and *"environmental pollutants."*
- Research and demonstration centers were required to have programs of *continuing education* for health and allied health professionals, and *information programs* for the public.

Additional technical amendments included a reimbusement provision for *experts and consultants*.

Authorizations of appropriations in the 1978 law expire on September 30, 1980. During the winter and spring of 1980, Congressional committees will consider reauthorization bills to continue the activities and programs of the National Heart, Lung, and Blood Institute.

II. National Program Description and Future Plans

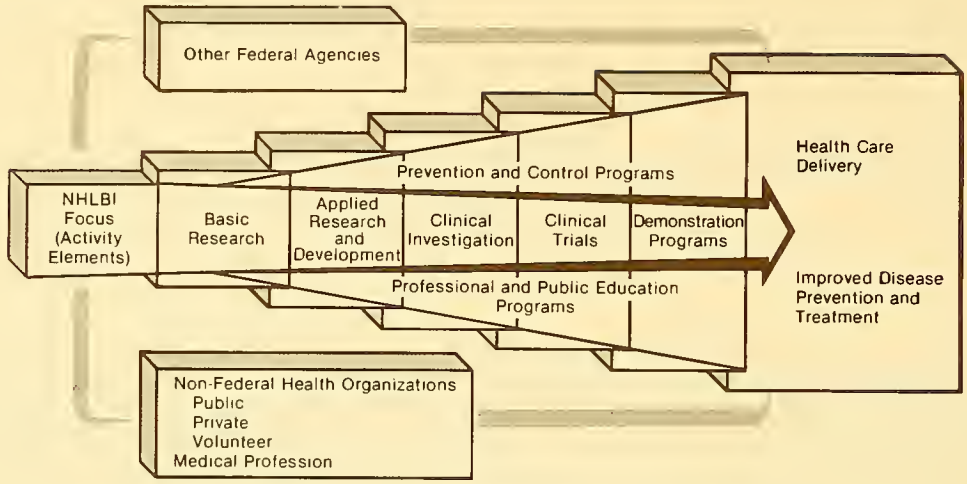
Organization and Strategy

In response to its legislative mandates, the NHLBI has developed the comprehensive National Heart, Blood Vessel, Lung, and Blood Diseases Program. This program is guided by the Five-Year National Program Plan, which is updated annually. The annual planning cycle makes use of a continuous interactive flow of information with the public, the medical community, and other Federal and non-Federal agencies and organizations. The scientific community plays a prominent role in reviewing program goals, assessing progress, and recommending future directions. Through this process the Institute fulfills its responsibilities to assimilate information from many sources and convert it into worthwhile and efficient programs. Details of the planning process and updated 1981-to-1985 program goals and planned activities are presented in the next section of this report.

While the National Program Plan addresses specific scientific goals and individual program areas, there is an overriding strategy that lends direction and momentum to the National Program as a whole. The program strategy employed for each of the disease-related mandates of the NHLBI consists of an ordered sequence: acquisition of new knowledge, testing and evaluation of promising hypotheses, and dissemination of new and existing knowledge. The Institute's strategy is aimed at maximizing the beneficial effects of research findings on clinical practice and on the health-related behavior of the American public.

The steps in the NHLBI program strategy are illustrated in figure 5, the biomedical research spectrum. This spectrum represents a logical progression of activities to identify, develop, and promote prompt adoption of approaches that are scientifically valid, socially and ethically acceptable, and economically feasible.

Figure 5.—The biomedical research spectrum



Basic research on disease etiology and pathogenesis is the keystone of the biomedical research spectrum. This stage of research seeks fundamental knowledge at the levels of molecules, cells, tissues, organs, and population groups. NHLBI devotes a major share of its resources to furthering scientific understanding of fundamental life processes as they relate to both the normal functions of the heart, lungs, and blood and the disorders related to these biological systems.

Another step in the biomedical research spectrum, **applied research,** is focused on specific knowledge concerning means of prevention, diagnosis, or treatment of a specific disease or disorder. Like basic research, applied research seeks to develop knowledge and proceeds one step further to apply this knowledge systematically to the solution of identified health problems.

Clinical investigation is the vital link between basic and applied research and clinical practice. It provides the mechanisms for translating fundamental research results into potential clinical regimens. Clinical investigations, coupled with basic and applied research, are critical to developing effective therapies to alleviate or delay the effects and progression of disease and promote new and more effective preventive measures. Furthermore, clinical research translates clinical observations into research focused on determining disease etiology.

Clinical trials are the scientific means to validate potential health care treatments and techniques. Such trials carefully test the effectiveness and safety of therapeutic approaches. Validation is critical to determining whether a given preventive measure, diagnostic technique, or therapy is ready for widespread use, whether it requires further refinement, whether it should be used only under special circumstances, or whether the approach is not workable and should be discouraged.

Demonstration programs as well as **prevention, education, and control programs** carry biomedical research into the realm of medical practice. Demonstration programs explore ways of introducing health care advances into clinical practice. Prevention, education, and control programs provide the means to encourage widespread acceptance and implementation of validated health care practices.

All of the Institute's scientific endeavors are directed at systematically advancing progress through the biomedical research spectrum—with the ultimate goal of improved health care. In marshalling its resources toward this end, the Institute has organized 3 categorical divisions concerned with the 20 disease-specific program areas represented in the National Program Plan. (See figure 6 and table 3.)

Each of the three categorical Divisions has certain responsibilities and objectives in common with the others: increasing knowledge of normal and diseased organ systems through broad programs of basic and clinical research,

clinical evaluation of research findings, and expediting the transfer of validated findings into medical practice; emphasizing programs of prevention; planning and coordinating research grant, contract, and training programs; evaluating existing activities and assessing future needs; and stimulating the health care communities to respond to identified needs. In addition, each Division promotes activities specific to its own mission. For example:

- *Division of Heart and Vascular Diseases*—application of research findings to the prevention and cure of cardiovascular disorders and diseases such as arteriosclerosis, high blood pressure, and coronary heart disease.

- *Division of Lung Diseases*—expansion of the knowledge base for diseases such as emphysema, chronic bronchitis, and pulmonary diseases of children to solve immediate national problems.

- *Division of Blood Diseases and Resources*—emphasizing bleeding and clotting disorders, sickle cell disease, Cooley's anemia, and other diseases of the red blood cell; seeking means to the optimal development and management of the Nation's blood resource.

Planning, Implementation, and Evaluation Process

The NHLBI uses an integrated, continuous process to plan, implement, and evaluate the National Program. This process was established to respond to legislative mandates, to identify and pursue the most promising opportunities, and to make effective use of resources.

The *Sixth Report of the Director* stressed the planning and implementation aspects of this process. It described the steps in the planning process and the major emphases of planned programs, updated the goals of the National Program, and described activities planned for the following year. In like manner, this report presents and updates the National Program goals and describes future planned activities (see section III), but in a slight departure from last year's format, this year's report will stress the evaluation aspects of the NHLBI planning process.

The Institute's activities are carried out under a structured management process. As discussed below, evaluation is an integral component of the Institute planning/implementation/evaluation cycle. Evaluation provides the Institute Director and his staff with the

Figure 6.—NHLBI organizational structure

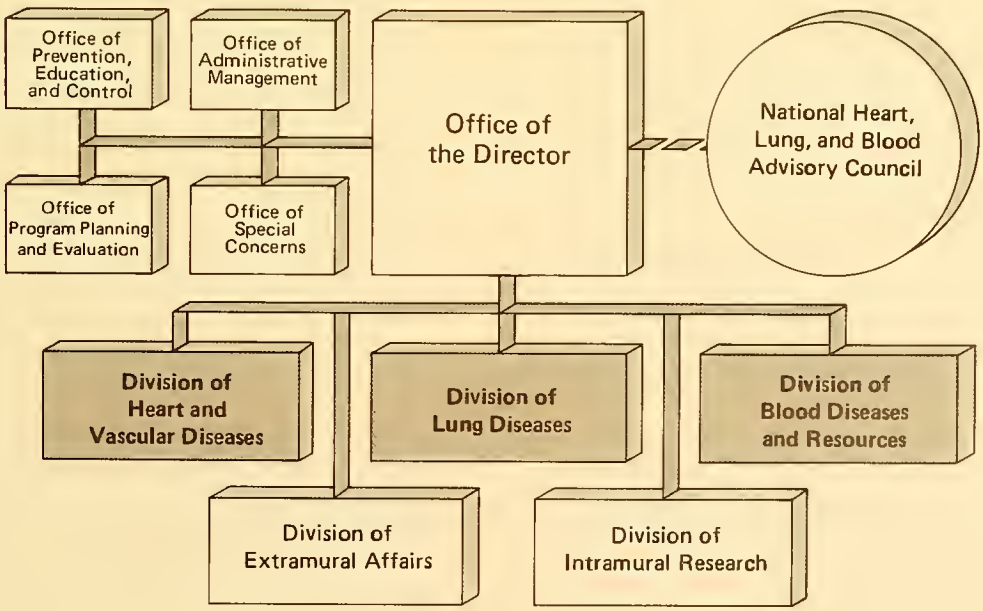


Table 3.—National Program elements by Division

	Division of Heart and Vascular Diseases	Division of Lung Diseases	Division of Blood Diseases and Resources
Program Elements	Arteriosclerosis Hypertension Cerebrovascular Disease Coronary Heart Disease Peripheral Vascular Disease Arrhythmias Heart Failure and Shock Congenital and Rheumatic Heart Diseases Cardiomyopathies and Infections of the Heart Circulatory Assistance	Structure and Function of the Lung Chronic Obstructive Lung Diseases Pediatric Pulmonary Disease Fibrotic and Immunologic Interstitial Lung Diseases Respiratory Failure Pulmonary Vascular Diseases	Bleeding and Clotting Disorders Red Blood Cell Disorders Sickle Cell Disease Blood Resources

necessary information to determine the progress of Institute programs, the need for new programs, and whether existing programs are still required. The NHLBI views evaluation as the analytic partner of planning, and it is the evaluation activity that provides a critical analysis of the Institute's program progress.

The planning, implementation, and evaluation cycle involves a continuous flow of information from the public, the medical community, other Federal agencies, and non-Federal organizations. The Institute is responsible for coordinating this process and developing required programs. The scientific community plays a prominent role in both planning and evaluation through participation on various advisory and review groups, task forces, and working groups which assess program progress and recommend future objectives and directions of the program. Scientific community participation is extremely important because of the inherent difficulties in assessing the relative values of research accomplishments and alternative future program directions.

The process is designed to ensure a thorough review of the entire program as well as the implementation of new programs and the expansion, modification, or discontinuation of existing programs.

Review, assessment, evaluation, and initial planning of programs is done through a review of the goals, objectives, and progress of the Five-Year National Program Plan with respect to the state of the science and the impact of the Program on medical care and the health of the public. This is accomplished with the participation of the NHLBI program staff, scientific advisory committees, and members of the general scientific community through workshops, task forces, and technical working groups convened to reach consensus on future directions. The results of evaluation studies are also applied. This step produces an update of the Five-Year National Program Plan and a preliminary list of program initiatives and recommended program directions for future years, together with revised objectives where appropriate.

Priority setting is the second step in the process, in which proposed new initiatives for implementation in the next year are ranked jointly by the staff of the Institute's categorical divisions and appropriate advisory committees.

Implementation planning constitutes the third step, in which the staff of the categorical divisions and the Office of the Director convert the ranked initiatives into specific program plans including programmatic justification, management and fiscal plans, and funding mechanisms.

Advisory Council review consists of a thorough review of the implementation plan by the full National Heart, Lung, and Blood Advisory Council. Council advice and recommendations are solicited in developing the final NHLBI Implementation Plan and Program Budget.

Program implementation consists of translating specific mandates and approved initiatives contained in the implementation plan into operational projects through various types of grants and contracts, intramural research, collaboration with other Federal agencies through interagency agreements, and jointly supported international activities.

The evaluative aspects of this process are carried out through a number of different mechanisms whose use depends on the objective of the given evaluation effort. Beginning at the most detailed level of the Institute program, the basic science research level, peer review serves as the primary mechanism to ensure that individual research grants are worthy of support. The Institute's ongoing advisory groups perform two evaluation-related functions. They review program progress annually over all 20 program areas and across the major categories of the biomedical research spectrum—basic science and training, applications, and transfer. This assessment of progress and needs is translated with staff assistance and judgment into the National Heart, Blood Vessel, Lung, and Blood Five-Year Program Plan. At approximately 2- to 5-year intervals, the Institute, with the aid of its advisory groups, performs a reassessment of the programs and recommends goals and actions to meet those goals. The results of the most recent of these reviews formed a major portion of the *Fifth Report of the Director.*

The Institute has found that some program areas require an effort of such detail that a special working group must be convened with staff and consultant support. These working groups focus on areas of fundamental program importance or areas that cross several program areas.

The Institute employs targeted or focused evaluation efforts for those topics where more quantifiable evaluation methods are appropriate. Such efforts tend to be most appropriate for components of the program in the applications or prevention, education, and control areas. In general, the NHLBI evaluation program seeks a balance between the use of expert judgment to assess research progress and the use of objective data to assess program impact.

In the past year, three important working groups or task forces have evaluated the Institute's scientific and educational progress in the areas of hypertension, arteriosclerosis, and respiratory diseases. The processes employed by these groups and their findings are excellent examples of NHLBI evaluative activities.

Hypertension Task Force

The Task Force on Hypertension was established to assess the current state of hypertension research. The task force consisted of 20 members, most of whom served as chairmen of 12 scientific subgroups. Each of the subgroups produced an in-depth scientific report on a discrete aspect of hypertension research. Each subgroup produced a summary report, an evaluation of the current state of knowledge, and recommendations for future research emphasis, manpower and training needs, animal models, resources, and new technology. Among the major topics covered by the task force report are the following:

- Local and systemic hemodynamics
- Neural control of the circulation
- Vascular smooth muscle: nerve terminals
- Hypertensive vascular disease
- Vascular smooth muscle: contractile apparatus
- Pediatrics
- Genetics
- Prostaglandins
- Kallikrein-kinin
- Renin-angiotensin-aldosterone
- Salt and water
- Therapy
- Pregnancy
- Obesity.

In each of these areas, the task force recommended study of specific aspects of the problem that are amenable to research and are central to improving prevention, treatment, and control approaches.

In addition, the task force recommended education and training, development of certain animal models, and specific forms of research resources such as standard reagents or central pools of chemical and pharmacologic tools. These recommendations, based on an analysis of

scientific knowledge and an evaluation of progress, will guide the Institute in its future efforts.

Working Group on Arteriosclerosis

The working group was convened to evaluate the extent to which recommendations of the 1970-71 Task Force on Arteriosclerosis have been implemented. It was charged with the following responsibilities:

- To examine the extent to which the recommendations in the 1971 task force report had been put into effect;
- To identify the progress that had been made toward the goal of prevention and control of arteriosclerosis;
- To determine whether the document is still timely as a basis for the National Program; and
- To make recommendations on the advisability of appointing a task force similar to the 1971 Task Force on Arteriosclerosis to assess the current state of understanding of atherosclerosis and its complications with respect to cause, prevention, control, and treatment, and to relate this understanding to current needs in research and health care.

In the course of its deliberations, the working group identified a variety of areas in which significant accomplishments have occurred since publication of the 1971 task force report and recommendations. Among those areas are:

- Measures which affect the diagnosis and treatment of angina pectoris and myocardial infarction;
- Advances in the surgical management of angina pectoris;
- Development of safe, sensitive, noninvasive instrumentation;
- Emergency medical and coronary care;
- Studies of the lipoproteins that carry cholesterol;
- New knowledge of the processes of arterial injury and repair;
- Molecular studies of blood coagulation processes;
- Identification of the enzyme participating in lipoprotein degradation;
- New knowledge of the biology of the cells of the artery wall; and
- New observations concerning the reversibility of atherosclerotic lesions.

On the basis of this assessment of progress, the working group identified a number of new areas for study. One very important area is that of the early stages of atherogenesis and the prevention of arteriosclerosis, beginning in the pediatric age group. Although the ultimate goal of the NHLBI atherosclerosis program is prevention, rather than management, the working group concluded that, in our present state of understanding, approaches to prevention and management have to be developed in parallel. Both require research as the basis for national intervention. In the course of its review and contact with expert witnesses, the working group identified various opportunities for accelerating the national effort in atherosclerosis. However, a number of questions also arose that could not be settled within the confines of the charge and the allotted time:

- Are the new directions in research receiving a share of national support proportional to their potential impact on current understanding of atherosclerosis and the magnitude of the problem?
- Are activities that began years ago living up to current expectations?
- Are new opportunities being recognized and actively explored?
- Is research involving problems in U.S. subpopulations (e.g., the unique problems of cardiovascular disease in the black population) receiving appropriate attention?
- Should current priorities be the same as those of 1971?
- Are there new fruits of research that are ready for clinical validation or practical application?
- Should NHLBI play a larger role in public education and in the dissemination of information concerning risk factors?
- How does the national commitment of resources for atherosclerosis relate to commitments for other health problems?
- Does public policy concerning atherosclerosis reflect the present understanding of prevention, early detection, and management of the disease?

The working group did recognize that, during the last decade, much scientific progress and advice had been successfully translated by Congress into mechanisms for coping with this major disease of mankind. However, the working group did not probe beyond its charge to determine the extent to which the 1971 program of the Task Force on Arteriosclerosis had been and was being implemented. In the course of fulfilling its assignment, the working group repeatedly encountered topics in research in atherosclerosis that merited detailed consideration. Therefore, it concluded unanimously that the time was ripe for a second task force that would help to redefine goals and priorities for research into the causes, prevention, and treatment of atherosclerosis.

In response to this recommendation for a second task force, the currently active Working Group on Arteriosclerosis was appointed in the fall of 1978. As indicated, research relating to arteriosclerosis and its complications encompasses a variety of disciplines and opportunities—basic and clinical and community-oriented—aiming to prevent disease or seek improved treatment. The new working group is in the process of soliciting information from a spectrum of expert witnesses. In meetings with members of the working group and other consultants, these experts discuss current knowledge and opinion and document their findings in summaries written for the working group. A final draft of the report is expected in the spring of 1980, and the final publication should be available in the summer.

Task Force on Prevention, Education, and Control in Respiratory Diseases

The task force was charged with providing the analytic background and assessment data required to provide the basis for a feasible, manageable program to prevent and control respiratory diseases through the education of health professionals and the public. The report of this group was to address lung diseases or disease categories that constitute national health problems and have been studied to the point where knowledge is available for translation to education and demonstration projects.

To discharge its responsibilities, the task force selected the following topics as major disease areas to be assessed:

- Pediatric pulmonary diseases
- Asthma
- Chronic obstructive lung diseases
- Fibrotic and immunologic lung diseases
- Infectious lung diseases.

These areas were chosen because they constitute major health problems, and because they are potentially preventable or controllable.

The recommendations of the task force are the outcome of selective procedures that began in task groups, continued at task force meetings, and will be further pursued as steps are taken to implement the recommended programs. All task groups as well as the full task force addressed the following basic questions to arrive at recommendations:

- What *new* knowledge or techniques are ready to be used in community settings?
- What available knowledge or techniques are being utilized ineffectively? Need to be reinforced? Need to be replaced or updated?
- What procedures or regimens are being used in community settings even though evidence is lacking that they are effective?
- What types of educational programs are needed for wider and more effective use of available knowledge and techniques?
- What evidence is there to support the impression that health professionals and the public are utilizing—or are incorrectly utilizing, or do not know how to utilize—knowledge that is available to prevent or control respiratory diseases?
- What components of the health care system, as presently constituted, are not being used effectively to facilitate utilization of health-related knowledge and techniques?

Recommendations based on the answers to these questions specify educational programs for physicians, patients and the public, and staff development activities directed at applying known scientific and behavioral findings to the control of the major disease categories mentioned earlier. These recommendations will guide the Institute in its future undertakings.

As noted earlier, the Institute's planning, implementation, and evaluation process is the

mainstay of the Institute's management plan. Evaluation is stressed in this process through NHLBI advisory committees, the National Advisory Council, and specially convened scientific task forces such as those just described.

Other evaluation-related efforts under way include a number of working groups. Of major importance is the Working Group on Prevention and Education Relating to Heart Disease. This group will establish goals, assess opportunities and needs for research regarding the prevention of cardiovascular disease and the education of health care professionals, patients, and the general public regarding cardiovascular disease.

The Task Force on Epidemiology of Respiratory Diseases will review ongoing activity in the epidemiology of respiratory diseases at the National Institutes of Health and other Federal agencies. It will also identify needs and recommended approaches by which the Institute's Division of Lung Diseases can meet these needs.

Also under way is an examination of the Institute's progress, needs, and planning with respect to heart diseases in childhood. This effort is emphasizing the study of the precursors of heart disease, their identification in children, and the potential for their early control.

Other ongoing activities include program reviews of the national research and development centers as well as the periodic assessment of the Institute's Specialized Centers of Research.

III. Program Goals and Planned Activities: 1981-1985

The scientific staff of the NHLBI, with extensive input from NHLBI advisory committees and task forces, develops program goals and planned research activities. Other leading research experts are called upon to contribute their specialized knowledge in reviewing proposed goals and activities. After agreement is reached, the program goals and activity plans are presented to the National Heart, Lung, and Blood Advisory Council for its consideration.

The general program goals for 1981-1985 indicate areas of research priority. The activity listings indicate major areas of emphasis but are not all-inclusive. New areas are continually being evaluated, as the Institute seeks to maintain the flexibility to fund research in new areas that show promise.

Heart and Blood Vessel Diseases

Arteriosclerosis

Program Goals

The Institute's mission is to improve the diagnosis, treatment, cure, and prevention of arteriosclerosis and arteriosclerotic disease beyond that which is possible at present. The following goals have been developed to serve as guidelines for research activities during the next 5 years:

- Gain a better understanding of the pathogenesis of arteriosclerosis.
- Further specify the causes, correlates, and associated risk factors for arteriosclerosis.
- Define those circumstances that may promote the regression of arteriosclerosis.
- Develop preventive measures against arteriosclerosis.
- Improve the diagnosis of arteriosclerosis and its risk factors.

Planned Activities

Fundamental research on the etiology and pathogenesis of arteriosclerosis, the biology of blood vessels, regression and development of arteriosclerotic lesions, new risk factors; research in basic, clinical, and population aspects

of arteriosclerosis; continuation of the Multiple Risk Factor Intervention Trial and the Lipid Research Clinics Coronary Primary Prevention Trial; and development and testing of noninvasive methods of detection and monitoring of arteriosclerosis.

Hypertension

Program Goals

A better understanding of the physiological systems that control blood pressure, and of the means by which these systems can initiate and/or exacerbate the developmental process of hypertension, could result in a significant reduction in the incidence of hypertension. More effective therapy for those already afflicted is another potential benefit. The following basic goals have been established by the Institute as guidelines for research during the next 5 years:

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

Planned Activities

Fundamental research on inhibitors of kinins, kallikreins, and prostaglandins to understand more fully the physiological actions of these hormones; basic and clinical activities focused on the role of salt and weight control; fundamental investigations toward improved diagnosis, treatment, and prevention of hypertension; and a broadly focused hypertension education program directed toward the general and medical public.

Cerebrovascular Disease

Program Goals

The mission of the NHLBI in the area of cerebrovascular disease is to elucidate the etiology and pathogenesis of the vascular component of cerebrovascular disease and to enhance programs that will accomplish this goal. Thus, the major goals of the program are to:

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

Planned Activities

Intensive study of the etiology and pathogenesis of cerebrovascular disease; and development of animal models.

Coronary Heart Disease

Program Goals

The ultimate objective directing the Institute's choice of program goals for the next 5 years is to decrease even further the mortality from coronary heart disease. The essential thrust of already established programs will be continued together with ongoing assessment procedures. The specific goals through which the Institute plans to enhance the reduction in death and disability from coronary heart disease are the following:

- Improve the recognition and assessment of latent coronary artery disease and overt coronary heart disease.
- Improve the therapy of patients with acute myocardial infarction and patients with chronic ischemic heart disease.
- Assess the proper role of coronary artery bypass surgery in the management of ischemic heart disease.
- Assess possible methods for the reduction of the incidence of sudden cardiac death.
- Develop techniques for reducing the amount of heart muscle irreversibly damaged during the course of myocardial infarction.

- Develop methods of reducing the incidence of recurrent myocardial infarction.
- Improve rehabilitation of patients with coronary heart disease.
- Assess the proper role of percutaneous transluminal angioplasty (a method for compressing plaque by threading a balloon catheter through the blood vessel, inflating the balloon to compress the obstruction, and then removing the catheter) in the management of ischemic heart disease.

Planned Activities

Studies to limit the myocardial damage due to coronary events; development and testing of new techniques of emergency cardiovascular diagnosis and therapy; investigation of the mechanisms and factors which precipitate acute coronary events; and major clinical trials including the Beta-Blocker Heart Attack Trial (BHAT), Multicenter Investigation of Limitation of Infarct Size (MILIS), Aspirin Myocardial Infarction Study (AMIS), and Coronary Artery Surgery Study (CASS), a coordinated attack to improve the management of coronary heart disease.

Peripheral Vascular Diseases

Program Goals

The Institute's broad goal in the area of peripheral vascular disease for the next 5 years is to improve techniques for the diagnosis and treatment of peripheral arterial and venous diseases. Specific goals over the next 5-year period are to:

- Develop more effective noninvasive methods of evaluating the severity of peripheral arterial diseases, suitable for the assessment of symptomatic patients, for the recognition of latent arterial diseases, and for research assessment of new modes of therapy designed to retard or reverse atherogenesis.
- Improve management of patients with peripheral arterial diseases, with particular attention to the long-term effects of arterial grafts and the improvement of graft techniques for smaller arterial vessels.
- Encourage greater research effort on the causes and treatment of peripheral venous diseases.

Planned Activities

Studies to improve the diagnosis, therapy, and rehabilitation of peripheral arterial, venous, and lymphatic diseases; studies of the natural history of occlusive venous disease with and without surgery; studies of the effectiveness of various therapeutic procedures and drugs; and noninvasive techniques for diagnosis and monitoring.

Arrhythmias

Program Goals

Now that sophisticated monitoring systems routinely provide data on the variety and characteristics of arrhythmias, the focus of NHLBI research is on improving the understanding of lethal arrhythmias and the means to prevent them. Consequently, the broad goals of the Institute now are to defiine the fundamental processes of electrical rhythm and conduction disorders and to develop methods of acute and chronic preventive therapy. Specific goals of the Institute over the next 5 years are the following:

- Develop improved understanding of the mechanisms whereby arrhythmias arise.
- Develop methods of chronic prophylactic therapy, using pharmacological agents, to prevent sudden cardiac death.
- Assess the role of pacemakers in the management of various conduction disturbances and define the indications for their use.
- Achieve a better understanding of the significance of rhythm disturbances commonly found in long-term, ambulatory monitoring of electrocardiographic rhythm to permit clinical management.
- Develop more effective methods for the recognition of those at heightened risk of sudden cardiac death.

Planned Activities

Investigation directed at fundamental understanding and prevention of arrhythmias; and studies of sudden death and improvement of methods to prevent, diagnose, and manage arrhythmias and other electrical disturbances of the heart.

Heart Failure and Shock

Program Goals

In the next 5 years the Institute plans to define mechanisms more fully, improve diagnostic techniques, and develop methods for the prevention and treatment of heart failure and shock of cardiogenic origin. Specific Institute goals are to:

- Elucidate the fundamental, biochemical, and cellular mechanisms involved in myocardial ischemia and gain a better understanding of the systemic effects of cardiogenic shock.
- Develop methods for protecting ischemic myocardium and for preventing the conversion of reversible ischemic tissue to irreversibly infarcted and scarred myocardium.
- Develop methods for quantifying the extent of ischemic myocardium to aid the assessment of therapeutic efficacy and patient management.
- Encourage greater research effort on the development and evaluation of new drugs with a positive inotropic action.

Planned Activities

Laboratory and clinical studies that focus on the cellular factors leading to death of heart muscle; efforts to quantify the extent of heart muscle inadequately perfused or irreversibly damaged following a heart attack; and development of methods to minimize the extent of heart muscle damage in heart attack.

Congenital and Rheumatic Heart Diseases

Program Goals

Congenital and rheumatic heart diseases typically become manifest in childhood or young adulthood. Diagnostic and surgical techniques have brought about great advances in the saving of life and improving the quality of life for afflicted individuals. Prevention efforts have made great strides against rheumatic heart disease, but only a few causes of congenital heart diseases are understood, and few cases can be prevented. This difference brings into focus the value and importance of prevention, and the key is the elucidation of fundamental causes and mechanisms. Thus, during the next 5 years, the Institute's research program will be directed toward achieving the following goals:

- To understand more fully the etiology of congenital heart defects.
- To improve surgical techniques for repair of defects and noninvasive techniques for diagnosis and treatment of patients with congenital and rheumatic heart defects.
- To seek better understanding of the developmental biology of the heart and the causes of, and/or susceptibility to, congenital and rheumatic heart disease.

Planned Activities

Studies on etiology of congenital heart diseases; research on animal models; and study of the immunological problems in heart disease and their management, specifically in relation to rheumatic heart disease.

Cardiomyopathies and Infections of the Heart

Program Goals

The goals of this program area over the next 5 years are:

- To encourage greater research effort on the causes and treatment of cardiomyopathies and infections of the heart.
- To develop more effective methods for diagnosis and treatment.

Planned Activities

Experimental work to study this disease; and investigation of animal models of several types of cardiomyopathy.

Circulatory Assistance

Program Goals

Depending on the extent to which cardiac function is compromised, circulatory assist devices may be required to relieve, in varying degrees, the workload of the heart or to perform the entire pumping function in place of the heart. The kinds of devices that may be suitable depend not only on the degree of cardiac function which must be restored but also on the time span during which such lifesaving support is required. Thus, the broad goal of the Institute in this program area is to develop and test short-, intermediate-, and long-term circulatory assist devices for clinical use. Specific goals include:

- Investigate and assess components for circulatory-assist systems, such as blood pumps, engines, and control systems.
- Investigate and assess biocompatible materials suitable for circulatory-assist and other cardiovascular device applications.
- Extensively bench and animal test circulatory-assist devices, particularly of the left ventricular assist type.
- Conduct clinical evaluations for assessing the efficacy of, and defining the clinical indications for, left ventricular assist devices.

Planned Activities

Research, development, and evaluation of short- and extended-term implantable heart devices and power sources; clinical evaluation of temporary left ventricular assist devices directed at the short-term management of heart failure and shock.

Lung Diseases

Structure and Function of the Lung

Program Goals

The overall goals for the Institute in this area are to increase knowledge and understanding of the biochemical, physiological, immunological, and cell biological events that occur in the developing and adult normal respiratory system, and to determine how these are altered prior to clinical onset and during the course of pulmonary disease. The specific goals by which this mission will be accomplished are as follows:

Respiratory Function

- Improved understanding of gas exchange and transport, and of alterations associated with exercise, high altitude hyperbaria, and disease states.
- Elucidation of respiratory mechanics in normal breathing, physiological adjustments to exercise and altered environments, and disease states.
- Increased knowledge of the roles of chemical, mechanical, and neural factors in the control of ventilation, and of adjustments during exercise, sojourn at high altitude, in sleep, and in the course of pulmonary disease.

Nonrespiratory Function

- Elucidation of the roles of lung cells, enzymes, hormones, and immunological reactions in the defense of the lung against insults, both exogenous and endogenous, and disease.
- Improved understanding of the synthesis, secretion, and degradation of pulmonary surface active material and its role in respiratory function of the normal and diseased lung.

Lung Structure

- Characterization of structural and functional features of various types of lung cells, interrelationships among different cell types, and modifications associated with lung injury and disease.
- Characterization of chemical and structural features of lung connective tissue components and alterations in the course of pulmonary disease.

Lung Growth and Development

- Increased knowledge of structural and functional changes during pre- and postnatal lung growth and development, and of the effects of endogenous and exogenous factors.

Planned Activities

Development of methods to separate major types of lung cells and to determine the ultrastructural and biochemical characteristics of individual lung cells; studies of the mechanisms of lung tissue damage and repair; studies of intermediary metabolism of lung; and studies of basic lung physiology, the role of chemical, mechanical, and neural mechanisms in the control of ventilation, and the processes of gas exchange in the immature and the mature lung in health and disease.

Chronic Obstructive Lung Diseases (Emphysema and Chronic Bronchitis)

Program Goals

The Institute's program seeks means to prevent diseases through improved understanding of their causes; to delay or reverse disease progression through greater knowledge of pathogenesis; and to ameliorate disease effects through improved techniques for early diagnosis and more effective management. Specific goals to be achieved during the next 5-year period are:

Chronic Obstructive Lung Diseases

- Elucidation of basic mechanisms involved in structural and functional derangements associated with onset and progression of chronic bronchitis and emphysema.
- Improved management of chronic obstructive lung diseases through identification of presymptomatic stages, critical assessment of current therapeutic measures, and development of more effective regimens.
- Prevention of chronic obstructive lung diseases through understanding of individual risk factors, and their interactions and roles in the etiology and pathogenesis of these disorders.

Asthma

- Elucidation of underlying mechanisms in bronchoconstriction and development of more effective measures to ameliorate or prevent the bronchostrictor response.

Planned Activities

Longitudinal studies of the natural history of chronic bronchitis and emphysema; studies to correlate biochemical and physiological alterations in early stages of chronic obstructive lung diseases; and clinical trials to study the efficacy of nocturnal oxygen therapy and the use of intermittent positive pressure breathing for treatment of chronic obstructive lung disease.

Pediatric Pulmonary Diseases

Program Goals

Working toward the prevention of pediatric pulmonary diseases through increased knowledge of the underlying disease process, the Institute plans to achieve the following specific goals during the next 5-year period:

Neonatal Respiratory Distress Syndrome

- Improved detection, management, and prevention of neonatal respiratory distress syndrome.

Bronchiolitis

- Increased understanding of the relationship between bronchiolitis in childhood and subsequent disorders of the respiratory system.

Cystic Fibrosis

- Improved identification of the basic defect and early pathogenetic changes through study of structural and functional derangements.
- Improved management of cystic fibrosis through critical assessment of current modes of therapy and development of new regimens.

Planned Activities

Investigations to characterize the clinical, pathological, physiological, biochemical, and molecular events associated with normal lung development and with the onset and course of hyaline membrane disease; and clinical trials of the efficacy of antenatal administration of steroids in prevention of hyaline membrane disease.

Fibrotic and Immunologic Interstitial Lung Diseases

Program Goals

The overall goals of the Institute in this category of lung diseases are to prevent interstitial lung diseases through better understanding of their causes and pathogenesis and to ameliorate their effects through improved diagnosis and management. Specific goals during the next 5 years are as follows:

- Elucidation of the roles of immunologic and other basic mechanisms in the onset of interstitial lung diseases and the progressive changes that lead to pulmonary fibrosis and granulomatous lesions.
- Prevention and improved management of interstitial lung diseases through identification of risk factors, detection of early disease, and development of regimens to arrest their progression.

Planned Activities

Investigations of specific agents responsible for fibrotic lung diseases in occupational environments, with specific attention to dose-response relationships; and investigations relative to the immunological and biochemical responses to organic and inorganic dusts that lead to fibrotic lung diseases and hypersensitivity pneumonitis.

Respiratory Failure

Program Goals

To reduce death and disability from respiratory failure, the Institute's overall goal is to improve the diagnosis, management, and prevention of adult respiratory failure through better understanding of the structural, biochemical, immunologic, and physiologic mechanisms of acute lung injury and repair. Specific goals directing the Institute's program during the next 5 years are as follows:

- Elucidation of mechanisms involved in lung injury and the progressive changes that result in respiratory failure.
- Improved management of respiratory failure through development of measures that arrest or reverse degenerative changes following lung injury.

Planned Activities

Studies to elucidate the basic mechanisms of the adult respiratory distress syndrome; and studies to determine how degenerative changes in the lung can be arrested or reversed.

Pulmonary Vascular Diseases

Program Goals

In pulmonary vascular diseases, early detection of disease is the key to effective patient management, as increased fundamental knowledge of pulmonary circulation is to effective disease prevention. The overall goals of the Institute with respect to these diseases are to elucidate mechanisms regulating both normal and diseased pulmonary circulation to improve understanding of the pathogenesis of pulmonary edema, pulmonary hypertension, cor pulmonale, and pulmonary embolism and to bring this knowledge to bear on improving the diagnosis and treatment of these disorders. Specific goals for the next 5 years are as follows:

- Prevention of pulmonary edema through understanding of mechanisms involved in the hydrostatic and permeability changes that affect fluid and electrolyte exchange in the lung.
- Elucidation of fundamental mechanisms involved in development of pulmonary hypertension.
- Improved management of pulmonary vascular diseases through development of noninvasive diagnostic techniques and more effective therapeutic regimens.

Planned Activities

Development of noninvasive techniques for early detection and continuous monitoring of pulmonary hypertension and pulmonary edema; and investigation of the structural, biochemical, and physiological characteristics of pulmonary vascular smooth muscle.

Blood Diseases and Blood Resources

Bleeding and Clotting Disorders

Program Goals

Advances in basic understanding of the coagulation system are critical to reduction of the incidence of disability and death from occlusive arterial and venous thrombosis, to the alleviation of symptoms of hemophilia and other bleeding syndromes, and to the development of effective therapies for congenital and acquired platelet disorders. To make these therapeutic improvements a practical clinical reality, the Institute has established six basic goals to guide its research activities for the next 5 years:

- Improve the diagnosis of, and therapy for, arterial thrombosis and the various clinical sequelae of this disease process; increase our understanding of the pathophysiology of arterial thrombosis to bring about its ultimate prevention.
- Enhance the knowledge of the basic mechanisms of venous thrombosis so as to provide improved patient care.
- Develop better understanding of the genetic and pathological mechanisms underlying hemophilia and other bleeding disorders to develop improved diagnostic techniques and specific treatments.
- Develop better methods for identifying and detecting individuals at risk for acquired coagulation disorders.
- Increase the general understanding of the role of platelets in the mechanisms of bleeding and clotting and develop more effective therapy for individuals suffering from congenital and acquired platelet disorders.
- Explore the pharmacology of agents such as the prostaglandins, aspirin, and oral contraceptives, which affect platelet

interactions, endothelial function, and cellular reactivity to a variety of stresses.

Planned Activities

Investigations of the structure and function of coagulation factors and their *in vivo* regulators or inhibitors; further study of prostaglandins and thromboxanes to determine how platelet function is controlled; a broad range of studies to understand the thrombotic process and improve ability to prevent and treat thrombotic disorders.

Red Blood Cell Disorders

Program Goals

The overall goal of the program for the next 5 years is the development of new knowledge leading to reduced morbidity and mortality for those afflicted with thalassemia, aplastic anemia, and refractory anemia as well as various hemolytic anemias. Specific goals are to:

- Devise improved treatment for those afflicted with thalassemia. Major effort will be devoted to identification of carriers through effective screening.
- Develop an understanding of factors controlling bone marrow proliferation and differentiation; develop knowledge of the underlying causes of aplastic and refractory anemias to permit prevention and improved treatment; and develop information concerning the natural history of these diseases.
- Further elucidate red cell membrane structure and function as well as intracellular metabolism to provide information which may be utilized to improve the health status of patients afflicted with various hemolytic anemias.
- Improve overall knowledge of the crucial role of the red blood cell in oxygen transport through studies of the mechanisms that control oxygen exchange.
- Develop erythropoietin preparations suitable for use in controlling human diseases.

Planned Activities

Studies of the molecular and clinical aspects of thalassemia; purification of erythropoietin; and studies of the red blood cell membranes.

Sickle Cell Disease

Program Goals

To fulfill its mission to reduce morbidity and mortality due to sickle cell disease, the NHLBI has established the following goals:

- Continue basic research into the pathophysiology of the disease process at the molecular, cellular, and clinical levels.
- Develop improved methods of clinical care.
- Develop a more rational approach to patient management based on the latest scientific advances.
- Provide accurate, up-to-date information to health care providers and consumers.
- Evaluate the effectiveness of education, testing, and counseling programs.

Planned Activities

Studies of the conversion of fetal hemoglobin synthesis to adult hemoglobin production; molecular studies of globin gene expression at the alpha, beta, and gamma loci; studies on the metabolism of sickled cells and the role of coagulation in vaso-occlusive crises; collaborative studies to identify and evaluate the factors which determine the clinical course of sickle cell disease and the presence or absence of complications; activities in educational, diagnostic, and counseling services in sickle cell disease, training, and community demonstrations.

Blood Resources

Program Goals

The mission of the NHLBI in the area of blood resources is directly related to the National Blood Policy objective of an adequate supply of high quality blood and blood products. In pursuit of this objective, the Blood Resources and Transplantation Branch supports research in the areas of donor and recipient safety, blood substitutes, blood component therapy, transplantation biology, and all aspects of the management of blood resources, including collection, preservation, fractionation, and distribution.

Blood Resource Management

- Foster the efficient use and assure an adequate supply of high-quality blood products for everyone in need.
- Promote more effective planning in the management of the national blood resource

through the collection and analysis of national blood resource data.
- Encourage improved blood resources sharing both regionally and nationally.

Blood Safety Program
- Prevent morbidity and mortality from post-transfusion hepatitis and other transfusion-transmitted infections.
- Promote basic investigations centering on immunohematologic problems related to safety of blood therapy, particularly on different aspects of blood group antigens and antibodies, the Rh complex, and red cell antibody and complement interactions.
- Promote studies that will lead to greater safety for donors of blood and blood components.

Blood Substitutes Program
- Pursue further development of newly synthesized fluorocarbon compounds for use as blood substitutes in transfusion therapy, organ perfusion, and other promising areas of application through screening and biological testing with the goal of clinical investigations into their usefulness in human medicine.

Blood Component Therapy Program
- Develop definitive guidelines for the clinical use of blood components, including packed red cells, granulocytes, and platelet concentrates, for transfusion.
- Determine and clarify parameters for collection and storage of leukocytes as related to effective transfusion therapy; explore use of buffy coat as a source of human interferon.
- Develop new methods of plasma fractionation including the preparation of clinically useful trace components. Support clinical trials to establish the effects and role of these new components and methods.

Transplantation Biology Program
- Support fundamental research in immunology, immunogenetics, and other aspects of transplantation biology.

Planned Activities

Study of national trends in transfusion practices; development of a program for evaluation and recognition of regional blood service systems; implementation of a national blood data center; evaluation of the impact of adenine on blood banking; development of specific and sensitive serological tests for the detection of non-A, non-B hepatitis carriers; support of studies to elucidate the immunopathogenesis of the hepatitis chronic carrier state; prospective analysis of trends in the incidence and etiology of transfusion-transmitted hepatitis; support of facilities for breeding and maintaining chimpanzees for use in hepatitis research; formulation and biological study of new fluorochemicals that have been previously screened for toxicity and suitability for blood substitution; research on the isolation and characterization of plasma proteins that have potential for new therapeutic uses; and support of various research and demonstration projects at regional blood centers.

IV. Highlights and Accomplishments

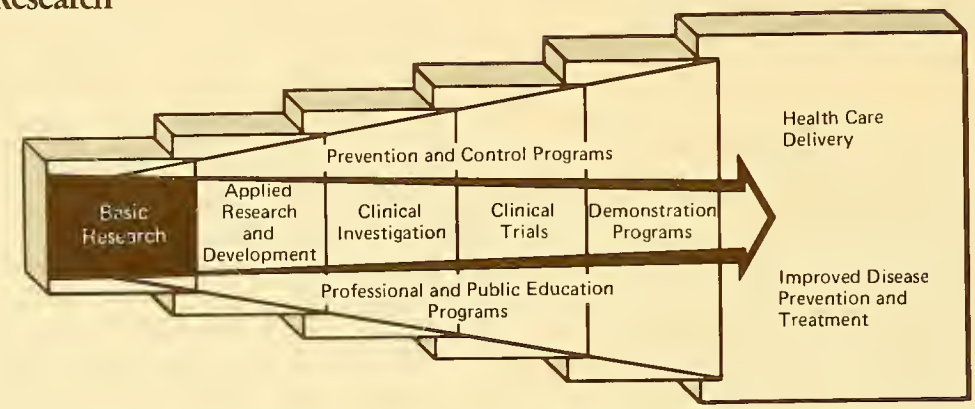
The past 30 years have seen major advances in the diagnosis, treatment, and prevention of heart, lung, and blood diseases. Though well-publicized surgical breakthroughs have provided some of the impetus and indeed much of the necessary anatomical information, it has been a strong program of basic, applied, and clinical studies that has allowed less obvious but crucial accomplishments such as the near-conquest of rheumatic fever through the use of antibiotics, the development of various technologies for noninvasive diagnosis, the use of artificial heart and lung machines, and the development of drugs to control both high blood pressure and blood clotting.

Even such accomplishments as these depended on the quiet accumulation of thousands of bits of knowledge about how antibiotics work, how the blood carries oxygen, and how vascular resistance is controlled. The research findings that allowed advances came from scientists working on fundamental and clinical studies in nearly every conceivable discipline from physics to pharmacology, from biochemistry to epidemiology. Their work has encompassed every stage of the biomedical research spectrum from basic research to prevention, education, and control programs and the transfer of findings to clinical practice. It would be impossible to chronicle every one of the myriad studies and discoveries that have led to today's improved health care practices, and it is difficult even to choose the most important accomplishments among the many breakthroughs of the past year. The following section, however, describes a few examples of the cumulative process, basic nature, and diverse origins of the research that has led to some of the many accomplishments of the past year.

While the activities described in this section are grouped according to their most appropriate segment in the biomedical research spectrum, it should be noted that the categorical allocations among them are not always clear-cut. Often an important research finding or technological achievement will overlap with and

contribute to the progress of activities in other areas. It is hoped that the examples that follow will provide the reader with insight into the complicated way in which different kinds of research relate to each other, seemingly disparate findings are combined and resynthesized, and new knowledge is added to older understanding. The result of this process is an ever-growing arsenal of methods to prevent or combat disease and improve the Nation's health.

Basic Research



Basic research is a systematic, intensive effort directed toward greater knowledge or understanding of the subject studied.

Within biomedicine, basic research deals with the structure and function of molecules, organelles, cells, tissues, organisms, and populations of man—or of suitable nonhuman models—in health and disease.

As the foundation of the Institute's program, basic research on disease etiology and pathogenesis receives the major portion of Institute resources. This research has resulted in a number of significant concepts, theories, and discoveries which, in turn, have become the foundation for further research, refinement, development, evaluation, and dissemination to the medical community and the public.

Hypertension
. . . Prostaglandin Antagonists Development

Although research on prostaglandins in the cardiovascular area has increased significantly in recent years, the role of the prostaglandins in hypertension and blood pressure regulation remains unknown. Research findings thus far seem to indicate that, among the prostaglandins and related substances, PGA_2, PGE_2, PGF_2 alpha, and PGI_2 (prostacyclin) act as vasodilators, whereas PGH_2 and thromboxane A_2 (TA_2) act as vasoconstrictors. In their action, the prostaglandins seem to affect the circulation by serving as local mediators of hormone systems which are vasoactive, for example, the bradykinin or angiotensin II systems. The complex nature of prostaglandin chemistry and the lack of specific prostaglandin antagonists make it virtually impossible to define the role of specific prostaglandin compounds in hypertension and blood pressure regulation.

A thromboxane A_2 antagonist has been synthesized, and its activity independently confirmed. The antagonist manifests greater activity in thromboxane A_2 receptor blocking than in inhibiting thromboxane synthetase enzyme. Moreover, this antagonist, unlike the enzyme inhibitors, does not affect the prostacyclin systems. The antagonist has been named pinane-thromboxane A_2 (PTA_2) since its chemical structure incorporates pinane, a six-carbon ring with a hydrocarbon bridge.

Hypertension
. . . Clues to Understanding the Process of Blood Pressure Regulation

Renin is a proteolytic enzyme that releases the angiotensin I peptide that is the precursor of angiotensin II, a potent vasopressor that raises blood pressure. Inactive renin (prorenin) can be converted to active enzyme in the laboratory by acidification or storage at low temperature.

The finding that kallikrein, another proteolytic enzyme, activates renin is key because it may be yet another chemical link between the renin/angiotensin and the kallikrein/kinin systems that are involved in the regulation of blood pressure. (The mechanism whereby kallikrein activates renin is not known, but proteolytic cleavage of peptide bonds is probably involved.) This finding is also timely in that the antihypertensive drug captopril affects both of these systems. Conceivably, this activation process may shed light on the chemical structure of renin and the mechanism by which captopril controls blood pressure.

Atherosclerosis
. . . A Mechanism for the Origin of Atherosclerotic Plaques

Using isoenzyme markers, investigators have demonstrated the close relationship among blood clots that adhere to blood vessel walls, plaque (the fatty or fibrous deposits that obstruct blood vessels), and atheromatous lesions. In fact, there is a point in the process of plaque formation at which organizing blood clots cannot be distinguished from plaque itself. It has been shown that stationary blood clots associated with atheromatous lesions become increasingly uniform with respect to the marker as the lesion matures. In the late stages of organization or replacement by smooth muscle cells and fibroblasts, the clots resemble fibrous plaques in nature. The important implication of this finding is that blood clots may become indistinguishable from plaque and, in fact, that blood clots may give rise to plaques.

Atherosclerosis
. . . Endothelial Cell-Platelet Interactions in Atherogenesis

Atherosclerosis is the thickening and deposition of a fatty substance in the inner layer of blood vessel walls. The deposits, called plaque or atheroma, project above the surface of the blood vessel lining and can obstruct blood flow. One possible explanation of how this comes about is aggregation of platelets (disk-shaped components of the blood which can stick together, forming clots at the site of an atheromatous lesion). Normally, platelets do not aggregate on endothelial (blood vessel lining) surfaces, and it has been suggested that the blood vessels produce a protective substance that inhibits aggregation.

Experiments using cultured endothelial cells indicate that endothelial cells do indeed produce a substance that inhibits the action of adenosine diphosphate (ADP) and collagen in the induction of platelet aggregation and prostaglandin production. However, the addition of low density lipoprotein (LDL), the major lipoprotein thought to be responsible for atherogenesis, blocks production of this protective substance by the endothelial cells. This work suggests that LDL contributes to atherogenesis in part by interfering in the normal endothelial cell-platelet interaction.

Coronary Artery Disease
. . . Possible Role of Prostaglandins in Regulation of Coronary Circulation

Prostaglandins are widely distributed compounds synthesized in the body from polyunsaturated fatty acids. They play many roles in human physiology, but their biological significance is not entirely clear. Studies have shown that prostaglandin synthesis in veins is significantly different from that in arteries. Prostaglandins have been shown to have both vasodilatory and vasoconstrictive properties in veins and arteries, and arterial tissue has been shown to produce large amounts of a vasodilatory prostaglandin, prostacyclin, whereas veins produce very little, if any, prostacyclin. It is well established that clotting processes in arteries and veins arise from different mechanisms. Recent findings indicate that prostacyclin production in the arteries may be important in preventing the formation of clots in response to damage to the intimal lining. Any process that interferes with arterial production of prostacyclin could increase an artery's susceptibility to clotting or spasm and thus increase the risk of coronary artery disease.

Ischemic Heart Disease
. . . Determination of Microvascular Pressures

Blood pressure in the small blood vessels of the heart cannot be measured in the beating heart by conventional microscopy techniques. Therefore, the hypothesis that heart compression

plays a significant role in modulating blood flow to the heart muscle can be tested only indirectly. Investigators are addressing this problem by developing a technique that allows them to measure such pressures directly in the *in situ* rabbit heart. The technique uses a conventional micropipette in a computer-controlled electromechanical manipulator. The computer is programmed to use a synchronized strobe light, allowing the investigators to produce stationary visual images of the heart at any selected point in the cardiac cycle. By tracking cardiac motion and directly measuring coronary microvascular pressures, investigators can address several functional problems of both normal and ischemic heart tissue. Among the areas that could be investigated with this technique are the role of vascular compression in producing resistance changes, the location and size of resistance vessels, and the functional role of the coronary collateral circulation, particularly as it relates to the development of myocardial ischemia.

Heart Valve Disorders

. . . Functional Role of Valve Muscles

In valvular heart disease, the heart valves open or close improperly. In the latter case, the valves allow blood flow back in the wrong direction. Though surgical techniques can correct most valvular disorders, the way in which the valves become dysfunctional is understood for some, but not all, types of disorders.

Muscles associated with the mitral and tricuspid valves of the heart have been studied extensively *in vitro*. These muscles are innervated by both divisions of the involuntary nervous system and exhibit intracellular action potentials and the ability to contract. Recently, investigators have demonstrated that the valve muscles are also electrically and mechanically active under *in situ* conditions. Now, investigators have extended their experiments to determine the function of these valve muscles in the normal heart. By measuring displacement of the valve leaflets at various atrial (upper heart) chamber pressures and determining the extent of neural modulation by the involuntary nervous system, researchers are determining whether the atrioventricular valves are passive flaps of tissue responding to pressure differences between the heart chambers or whether active muscle contraction aids in closing the valves. By determining whether the muscles play an active or a passive role, investigators are gaining significant insight into valvular heart disease.

Arrhythmia

. . . Fluorescent Dyes for Determining Membrane Potentials

Arrhythmias are irregularities in heart rhythms, sometimes life-threatening. These rhythms are controlled by electrical activity of the heart muscle, but the electrophysiologic processes are not wholly understood. Electrical potential differences develop across many biological membranes because these membranes are able to segregate certain ions such as sodium and potassium. Up to this time, many cells were either inaccessible or too small to allow measurement of these membrane potentials and other electrophysiological events by conventional techniques. However, the use of fluorescent dyes now permits the study of electrical events in these membranes by optical methods.

Researchers are using cyanine and merocyanine dyes to develop a method that will permit the quantitative photometric measurement of membrane potentials in either single cells or networks of cells. Such study can elucidate changes in ion permeability produced by the dyes in lipid bilayer membranes. Using spectroscopic studies of these membranes, investigators have examined the effect of variations in membrane composition and aqueous ion concentration on the fluorescent response of these dyes when membrane potential changes. These studies, along with appropriate scanning techniques, are leading the way to monitoring the pathway of electrical excitation in the heart and to analyzing the electrical interactions between cells in neuronal networks. Such information has widespread relevance in furthering our knowledge of the origin and progression of cardiac arrhythmias.

Lung Disease Detection

. . . Ventilation-Perfusion Ratios Determined

In various lung diseases, ventilation-perfusion ratios (the ratio of air entering to blood flow) are not uniform throughout the lung. These ratios change, for example, in conditions such as asthma, respiratory distress syndrome, and interstitial lung disease.

With the development of a method to determine continuous distributions of ventilation-perfusion ratios, a notable advance has been made in understanding lung gas exchange in healthy and diseased lungs. The complex method includes infusion of six inert gases followed by simultaneous collection of blood samples and mixed expired gas. The technique measures the amount of blood flow to unventilated lung (shunt) and also indicates the approximate amount of blood flow to lung units having specific ventilation-perfusion ratios. Since this technique can determine the continuous distribution of ventilation-perfusion ratios, its potential for detecting the subtle signs of early lung disease is promising.

Pulmonary Vascular Diseases
. . . Active Component of Streptococcal Bacteria Identified

Group B streptococcal sepsis, an increasingly serious clinical problem in the newborn, is characterized by early-onset apnea and cardiopulmonary collapse. Its effects on the pulmonary vasculature closely resemble that of gram negative endotoxin shock. Group B streptococci, type III, isolated from human babies are being used to examine the effects on the chronic sheep lung lymph preparation, an animal model widely used to study pulmonary vasculature by increasing microvascular pressure without increasing permeability. The different components of the bacteria have been fractionated and tested in the sheep model to identify which component produces the pulmonary response. The active component has been identified as an extracellular polysaccharide and has been immunologically characterized as a type III antigen. If the target organs can be identified by radioactive tagging of the active component, it might be possible to identify pharmacologic blockers, e.g., indomethacin, diphenhydramine, and methysergide, to block the physiologic response of increased fluid filtration.

Pulmonary Hypertension
. . . Hypoxia-Induced Hypertension Related to Sex and Age

Pulmonary hypertension is a serious complication in patients suffering from chronic lung disease and heart disease. A correlation between hemodynamics and structural changes has been made in animal models of hypoxia-induced pulmonary hypertension. The maximum structural and functional changes occur within 2 weeks following the onset of exposure to the low oxygen; the functional response appears to be both sex- and age-related. Adult female animals show less elevation in pulmonary artery pressure and less right ventricular hypertrophy than shown in males. However, the same degree of increased muscularization of arteries is seen. The pulmonary artery pressure returns to normal, and the increased muscularization of arteries shows partial regression when adults are returned to normal oxygen levels. More severe functional and structural responses are seen in the newborn than in adult animals. These findings are important in helping to understand the pathogenesis of pulmonary hypertension and in designing therapeutic regimens.

Oxygen Toxicity
. . . Prevention by Endotoxin

It is widely recognized that prolonged exposure to high concentrations of oxygen is toxic, yet there are many situations in which such exposure is mandatory, particularly in the treatment of the neonate. Although oxygen has been linked to the development of two neonatal diseases, retrolental fibroplasia and bronchopulmonary dysplasia, there are no effective therapeutic techniques (other than avoidance) available to prevent or remedy the toxicity. It was reported previously that daily treatment with endotoxin markedly reduces the toxicity associated with hyperoxic exposure. New findings indicate that a single dose of endotoxin (1/50th of LD_{50}) protects rats from acute hyperoxic lung damage and death. In addition, after a month's recovery period, the untreated animals that survive oxygen exposure show marked pulmonary fibrosis, whereas endotoxin-treated animals show only slight diffuse lung damage. Thus endotoxin treatment just prior to hyperoxic exposure appears to offer protection from both the acute and the chronic manifestations of pulmonary oxygen toxicity.

The basis for endotoxin's protective effect is believed to be related to increased activity of the pulmonary antioxidant enzyme defense system, as activities of superoxide dismutase and other enzymes were increased after endotoxin exposure.

Further knowledge about the role of endotoxin in stimulating lung antioxidant defense mechanisms may have important implications in the pursuit of the etiology of neonatal and adult respiratory disease and in the identification of agents that may minimize pulmonary toxicity associated with oxygen therapy.

High Altitude Breathing Problems
. . . *How Birds Can Fly at High Altitudes*

Physiologists have been intrigued for decades by the ability of birds to survive, even to thrive, at altitudes that are harmful to other species. At high altitudes, all animals hyperventilate—an involuntary mechanism of fast breathing in which carbon dioxide is expelled in large amounts. This loss of carbon dioxide causes the pH of blood to become alkaline and constricts blood vessels. This condition, in turn, reduces the flow of blood to the brain and brain cells become starved for oxygen, eventually dying. An alkaline pH in the blood can also produce other fatal effects; but this does not appear to occur with birds.

A recent study examined the blood flow to the brain in a species of duck which can readily tolerate altitudes to 9,000 meters or more. With a technique called xenon clearance, a radioactive gas was injected into an artery leading to the duck's brain, and then the rate at which the xenon moves out of the brain tissues was monitored. The results showed that blood flow through the duck's brain during hyperventilation was close to the rate observed when the animal was breathing normally. Under similar conditions, brain blood flow in mammals would be 50 to 75 percent below normal and they would experience severe pain.

It is clear, then, that birds have some mechanism that prevents constriction of blood vessels when carbon dioxide is expelled, and it is this mechanism which permits them, but not man, to survive at high altitudes. By clarifying the mechanisms by which birds maintain adequate cerebral blood flow during hypoxia, we may gain valuable information on how to maintain blood flow to the brains of humans exposed to hypoxia not only as a result of altitude exposure but, more importantly, as a result of certain lung diseases or injury that markedly decrease lung surface area or diffusion capacity.

Chronic Obstructive Lung Disease
. . . *Role of Alpha-2-Macroglobulin in Emphysema*

Being healthy can be defined in one sense as maintaining proper balances between opposing forces within the body. It is generally believed that emphysema is the result of a disruption in one such balance, that between elastase, an enzyme that destroys structural protein, and the antiproteases, proteins that inhibit elastase. Until now, much of the attention has been focused upon alpha-1-antitrypsin (AAT), an antiprotease that is deficient in some individuals genetically predisposed to emphysema. However, recent evidence indicates that alpha-2-macroglobulin (A_2M), an antiprotease found in serum, may also be vitally important in this delicate balance.

In normal individuals, serum AAT binds five times as much elastase as A_2M, but in people genetically deficient in AAT, this ratio drops to 2:1. This increased reliance upon A_2M has profound effects because, in contrast to the AAT-elastase complex—which is inactive—the A_2M-elastase complex is still capable of breaking down protein. Furthermore, while in this form the enzyme is protected from inactivation by other protease inhibitors. It has been shown by use of radiolabeled elastase that there is still elastolytic activity in these complexes 4 days after introduction of the labeled enzyme. Thus, it now appears that A_2M cannot be disregarded when considering the disruptive effect that AAT deficiency may have on the delicate balance between elastase and antiprotease.

Chronic Obstructive Lung Disease
. . . *Three-Methylindole in Cattle*

Bacteria present in the large intestine of all animals and in the rumen of cattle, sheep, and goats appear to be able to convert tryptophan (an amino acid present in protein that is required in the diet of most animals) to a product called three-methylindole. In cattle and horses, three-methylindole is actively metabolized by the lung to a more toxic intermediate, causing selective destruction of secretory cells lining the small airways and the cells lining the lung alveoli (air sacs). The animals develop small airways disease and alveolar emphysema with similarities to some forms of human lung disease.

Metabolism of three-methylindole resulting in lung toxicity serves as an important model of chemically induced lung disease. The specific effects of this chemical on the lungs of horses and ruminants provide an outstanding opportunity for further research on the relationship between the biochemical mechanism and the physiological and pathological effects of the disease process.

Fibrotic Lung Disease

. . . Immunologic Role in Idiopathic Pulmonary Fibrosis

Idiopathic pulmonary fibrosis is a disease of unknown etiology which results in scarring of the lung with ultimate loss of lung function and debilitation of the patient. For many years both cause and treatment have been enigmas; search for etiologic agents has been in vain. Recently, evidence has been uncovered which may prove to be the first step toward unraveling the etiology and pathogenesis of this disease. Quantities of immunoglobulin G, one of the major classes of human antibodies, are significantly increased in bronchoalveolar lavage fluids of fibrotic patients when compared to fluids from normal individuals. Furthermore, immune complexes have been found in both lungs and blood of patients with the disease. Since the agent that stimulates the formation of these antibodies is still unknown, it is not clear whether they represent a response to some extrinsic agent, such as a virus, or an autoimmune reaction against the patient's own tissue. The findings are important because they provide a first clue toward mechanisms underlying this disease and provide beginnings of scientific rationale for treatment. They also provide a stimulus for attempting to identify the specificity of the antibody and thus determining the inciting agent.

Control of Breathing

. . . New Techniques for Study of Neuronal Pathways

The neural control of breathing, a highly complex process, remains a technically difficult subject to study. A new technique that will help to trace the neural pathways involved in controlling respiration has been developed. The technique is based on the injection of an enzyme, horseradish peroxidase, into nerves via a microelectrode. The nerve then transports the material, which allows microscopic viewing of brain sections. The chief advantage of this method is that it does not interfere with the normal neural pathway in any way, unlike a classical lesion experiment. The technique has been used for the first time to study how the pulmonary receptors are connected to the nerve centers in the brain. With this technique, it appears that a specific nerve center in the brain (the pontine pneumotaxic center) seems to be strategically connected to all the major groups of respiratory nuclei that have been implicated so far in the regulation of respiration. The technique is now being used to study the reflexes originating from pulmonary receptors during edema and pulmonary congestion, and it has the potential for application to the problem of abnormalities in the respiratory rhythm, malfunction of the respiratory reflexes, and even the possible underlying neural mechanism in sudden infant death syndrome.

Pulmonary Hypertension

. . . Neural Pathway—Identification of a Reflex Mechanism

In an animal model, distension of the pulmonary artery with an inflated balloon causes excessive neural discharge and a constriction of the pulmonary artery downstream from the distension site, resulting in an increase in pulmonary artery pressure and pulmonary vascular resistance. Studies in awake newborn lambs, 3-month-old sheep, and adult sheep show the response is significantly greater in the newborns than in the older animals. This neural reflex pathway could play a significant role in the control of the normal circulation, particularly in the fetus and newborn. The possibility exists that in severe fetal hypoxemia or asphyxia, the resultant pulmonary hypertension will induce a distension of the pulmonary artery, excessive neural stimulation, and, finally, hypertrophy of vascular smooth muscle. It is also possible that fetuses *in utero* with partial constriction of the ductus have increased artery pressure and distension of the pulmonary artery. The distension stimulates the reflex mechanism, thus augmenting the normally high pulmonary vascular resistance. Elucidation of this reflex pathway may lead to an understanding of the mechanisms responsible for the persistent pulmonary hypertension or persistent fetal circulation syndrome seen in some newborns exposed to hypoxia.

Cardiopulmonary Toxicity from Plant Alkaloids

. . . Effect on Lung Cell Function

Pyrrolizidine alkaloid poisoning is a problem in many areas of the world. The pyrrolizidine alkaloid monocrotaline is found in a large number of plants distributed throughout the world, including the southwestern United States. Ingestion of the alkaloid by humans leads to the impairment of the lung's ability to regulate certain vasoactive substances involved in the maintenance of systemic blood pressure. Human pyrrolizidine poisoning has been found in many third-world countries and particularly in Jamaica, where the disease is endemic. It has also been reported in Afghanistan, India, and Arizona. Pyrrolizidine has been reported as a contaminant in dairy products, honey, and herbal teas. A single injection of monocrotaline in rats produces pulmonary hypertension, inflammation of the lung blood vessels, and right ventricular hypertrophy. Enzymatic functions have been studied in isolated, perfused rat lungs to test the hypothesis that the cardiopulmonary changes produced by monocrotaline are the result of pyrrole metabolites reacting with the cells lining the pulmonary vessels. It was found that the lung could no longer remove serotonin, a vasoactive substance, from the circulation. The toxic metabolite of monocrotaline has been found to prevent right ventricular hypertrophy. Because of the widespread distribution of pyrrolizidine-containing plants, further studies will include determining the actual exposures people are receiving and the potential effects on cardiopulmonary function.

Intravascular Thrombosis

. . . Role of Lung Endothelial Cells in Preventing Platelet Aggregation and in Prostaglandin Release

The lung is capable of altering the biological activity of many substances brought to it via the blood. The pulmonary circulation acts as a filter, allowing substances like epinephrine or histamine to pass through, but inactivating serotonin or bradykinin and converting angiotensin I to angiotensin II. The lung is also capable of acting as an endocrine organ, releasing a variety of active substances into the blood. These metabolic functions of the lung seem to reflect chiefly the metabolic activities of the endothelial cells of the pulmonary vasculature. Endothelial cells may also play a role in preventing the formation of intravascular thrombi, since it has been shown that endothelial cells in culture can synthesize prostacyclin (PGI_2), a substance that can prevent platelet aggregation and can disaggregate platelet clumps. Pulmonary artery endothelial cells have an unusually large capacity for synthesizing prostaglandin E_2, a vasodilator thought to prevent or lessen hypoxic pulmonary vasoconstriction. These findings indicate that pulmonary endothelial cells can account for part of the efflux of prostaglandin-like substances into the systemic arterial circulation that may occur, for example, during anaphylactic shock. The results of these studies may have bearing on the pathogenesis of anaphylaxis and embolic diseases.

Clotting Disorders

. . . Aspirin and Prevention of Thrombosis

Aspirin is known to affect the clotting system by inhibiting the aggregation of platelets, an important early step in the formation of a clot. Aspirin works by inactivating an enzyme (cyclooxygenase) which is involved in the production of thromboxane A_2, a potent aggregating agent. The endothelial cells lining the blood vessels also have a cyclooxygenase system, but it leads to the production of prostacyclin, a protective substance.

Half an aspirin tablet once a day has been shown to be effective in eliminating platelet cyclooxygenase activity. In tissue culture experiments, the endothelial cell cyclooxygenase system was shown to be far less sensitive to aspirin than was the platelet system. It appears that doses of aspirin can be established that inactivate the platelet *aggregating* system but have no significant effect on the *protective* system in the vessel wall. Clinical studies are currently being conducted to test the effectiveness of the low-dose aspirin regimen.

Hemoglobinemia

. . . High Altitude Effects

Hemoglobin, the oxygen-carrying red pigment of blood, is normally encased within the red blood cells. Hemoglobinemia is an abnormal

condition in which hemoglobin is present outside the red blood cells in the blood plasma; it usually indicates that the destruction of red cells is occurring at an abnormal rate. The hemoglobin, and the iron which it contains, is removed from the blood and excreted in the urine. This can lead to an anemic (iron-deficient) condition if it persists too long.

Despite the years of research on the effects of high altitude and intense national interest in the space program, the adverse effect of high altitude hemoglobinemia appears to have escaped notice until it was recently reported in rats, mice, and cats exposed to a simulated altitude of 18,000 feet for 10 days. After ruling out intravascular hemolysis and an overloading of hemoglobin catabolic pathways, preliminary evidence suggests that the hemoglobinemia is secondary to production of red blood cells which lyse readily and release their hemoglobin. If this hypothesis can be proved, it may serve as a useful model for the study of factors limiting erythropoiesis (production of red cells) and hemoglobin catabolism (the process by which hemoglobin is broken down).

Fibronectin

. . . New Insights into Function of a Plasma Protein

Fibronectin is a major protein of vertebrate blood and cell surfaces. The form found in plasma is also known as cold-insoluble globulin because in some instances it may coprecipitate with fibrinogen to form cryofibrinogen. While it has been known for some time that the protein exists, its functions have not been understood. Recent work has advanced knowledge of several important properties of this protein. It appears that fibronectin may be the "scaffolding" for collagen, and the chemical cross-linking of collagen and fibronectin mediated by the coagulation enzyme, Factor XIIIa, may be the mechanism for insolubilization of fibronectin in tissues and cell matrices. This process may be involved in wound healing: Persons deficient in Factor XIII have problems with poor wound healing and excessive scarring, possibly caused by failure of this fibronectin-collagen interaction to occur.

Another recent finding is that plasma fibronectin has all the characteristics of human alpha-2-globulin opsonic protein, which has a key function in helping the reticuloendothelial system to destroy bacteria. Fibronectin levels have also been shown to decrease with sepsis and other diseases. This depletion, which may contribute to organ failure in severely ill patients, has been corrected in a group of surgical trauma patients who had developed postoperative infections. They were treated with infusions of cryoprecipitate, a blood plasma fraction rich in fibronectin. This infusion of fibronectin in the form of an easily obtainable plasma fraction may offer a new approach to treatment and prevention of multiple organ failure, especially in septic-injured patients.

Formation of a Stabilized Fibrin Clot

. . . Identification of Structures Required for Polymerization

"Stabilization" of a fibrin clot involves both noncovalent association and covalent cross-links catalyzed by Factor XIIIa. Certain structures are responsible for endowing the assembly mechanism with a specificity which leads to characteristic structures in the final fibrin clot.

Evidence shows that a set of complementary domains are exposed on fibrin after thrombin-mediated release of fibrinopeptide A and these are responsible for end-to-end polymerization. Another set exposed after release of fibrinopeptide B are responsible for side-to-side alignment. Together the two produce a branched, compact fiber.

One application of understanding the structural and functional relationships of fibrin(ogen) has been the synthesis of peptides mimicking specific portions of the molecule and the demonstration that they function *in vitro* as potent agents which prevent or inhibit blood clot formation. This may be the first step in the development of new antithrombotic agents for clinical use.

Hemoglobinopathies

. . . Genetic Control of Hemoglobin Synthesis

The normal hemoglobin molecule is a protein containing four polypeptide chains, two alpha and two beta chains. In certain

hemoglobinopathies, the beta chain is either not synthesized, as in Cooley's anemia, or is abnormal, as in sickle cell disease. The genes for producing a third globin chain, the gamma chain, are active in the red blood cells of the fetus or newborn, but become dormant soon thereafter. Gamma chains in combination with alpha chains form fetal hemoglobin. Theoretically, two gamma chains could replace the two beta chains, thus yielding the fetal hemoglobin molecule which is sufficient for sustaining the oxygen transport requirements of the red cell. The method for "switching-on" the genes for producing fetal hemoglobin remains to be discovered, but such a finding could lead to effective treatment for these hemoglobinopathies.

As a result of treatment with phenylhydrazine, a previously undescribed chicken alpha-globin gene has "turned-on." This exciting finding may provide an especially useful system in which to study the molecular events involved in globin gene switching.

Macroprotease
. . . *An Enzyme Inhibitor Complex with Unique Functional Properties*

Alpha-2-macroglobulin is a major plasma protease inhibitor. It can complex with trypsin, and the alpha-2-macroglobulin-trypsin complex, which is normally inactive, can be modified by acid treatment in such a way that the properties of the treated complex seem to be intermediate between those of the untreated complex and those of free trypsin. The complex is modified at acid pH so that a macroprotease—a modified inhibitor complex capable of hydrolyzing protein substrates to which it was refractory prior to alteration—is produced. There is a possibility that such alpha-2-macroglobulin-enzyme complexes may be modified *in vivo* by an acid environment at sites of inflammation or within cells so that the proteolytic activity of the enzyme is expressed. Although the full significance of this observation is not yet known, the fact that the enzyme is part of a macromolecular complex may mean that it stays in inflammatory exudates longer. The proteolytic activity could then be expressed in the breakdown of proteins such as fibrin in the exudate or possibly against viruses on bacteria. It has also been shown that the complex can get into cells. Since some portions of cells are more acid than others, the proteolytic activity may be expressed only in those parts.

Metabolism and Cell Regulation
. . . *Thermodynamic Control of Protein Turnover*

In spite of their essentially equal importance in metabolism, much more is understood about protein synthesis than about the control of protein degradation. The fundamental mechanisms which operate at the molecular level to control protein turnover are unknown. Our current understanding is that turnover is a proteolytic event whose rate depends on proteolytic susceptibilities of individual proteins.

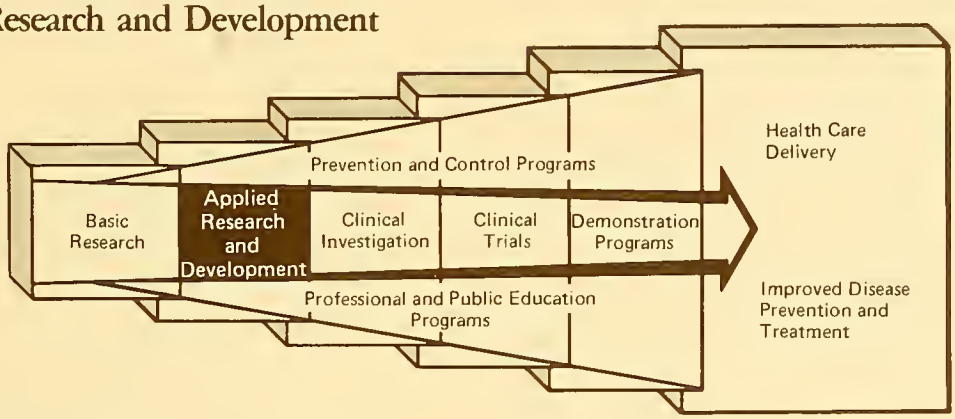
An alternative hypothesis has recently been proposed and is based on the belief that native protein conformation is a dynamic equilibrium between a number of other structures which may be partially or completely unfolded. Accordingly, conformational equilibria between folded and unfolded states may be more important than native protein conformation in determining proteolytic susceptibility. Since an unfolded protein is potentially a very reactive substrate for proteolytic enzymes, the equilibrium concentration of unfolded forms, determined by the unfolding equilibrium constant, might govern the overall rate of protein turnover. In other words, protein degradation may be thermodynamically controlled, and proof of this hypothesis would be a significant advance in understanding cell regulation.

Nutrition
. . . *Effects of Iron Deficiency on Brain Function*

It has been suggested that iron deficiency may adversely affect behavior and learning in animals and man. Because changes in mental function may result from altered metabolism due to decreased amounts of iron-containing enzymes in brain tissue, a study was undertaken to determine the effects of iron deficiency on the concentrations and activities of important iron-containing enzymes in brain and to elucidate the changes in metabolism which may result.

Studies were performed to determine the effects of iron deficiency on brain metabolism in rats. Oxidative phosphorylation, concentrations of cytochrome pigments, and activities of catalase and monoamine oxidase in brain tissue were unaffected by iron deficiency. However, activities of aldehyde oxidase, a key enzyme in the pathway of serotonin degradation, were significantly reduced, and concentrations of serotonin and total 5-hydroxyindole compounds were elevated in brain tissue of iron-deficient animals. Aldehyde oxidase activities and concentrations of 5-hydroxyindole compounds in brain tissues of iron-deficient animals returned to approximately normal values 1 week after treatment with iron dextran. This suggests that states of iron deficiency may result in reduction of important iron-containing enzymes in brain tissues and lead to altered brain metabolism.

Applied Research and Development



Applied research is a systematic study directed toward applying new knowledge to meet a recognized need. In both the laboratory and clinical settings, applied research is aimed first at obtaining specific knowledge that will enable the investigator to judge whether it is feasible to produce a new or improved means of preventing, diagnosing, or treating a particular disease. Subsequently, new approaches and technologies can be developed. To accomplish these goals, applied research is dependent on the existence of a relevant scientific base of knowledge. From this foundation, applied researchers create a means to accomplish a specific practical goal.

Development is the systematic application of available knowledge which is directed toward the production of useful materials, devices, agents, and methods to meet a recognized need. It is a subset of applied research, sharing common goals. Developmental processes to achieve these goals include design, development, and improvement of prototypes and new processes to meet functional or economic requirements.

Congestive Heart Failure

. . . Studies Indicate Therapeutic Value of Amrinone

Depression of ventricular function is the principal cause of heart failure. The use of digitalis glycosides to improve the heart's ability to contract has been the key to managing congestive heart failure; however, the digitalis glycosides exert only a modest effect. Other drugs, such as the catecholamines and sympathomimetics, are more potent heart stimulants, but, for the most part, they are effective only when administered intravenously and they may be associated with serious adverse effects. Discovery of a potent, orally effective drug that increases myocardial contractility without adverse effects would be a major advance in the medical treatment of congestive heart failure.

Recently, a bipyridine derivative, amrinone, was found to exert a strongly positive inotropic action in a variety of *in vitro* and *in vivo* preparations. When administered orally in experimental models of congestive heart failure, it consistently raised cardiac output and lowered ventricular filling pressures. Additionally, when amrinone was administered to eight patients whose severe congestive heart failure

was being treated with full doses of digitalis, major increases in inotropic effects were achieved without demonstrable toxicity. More clinical and animal studies are needed to discover amrinone's mechanism of action and to demonstrate that when administered orally it has lasting beneficial effects without adverse side effects.

Diagnosis and Evaluation
. . . New Imaging Device Developed

A great part of the study and diagnosis of heart and lung pathology is associated with the distribution of blood flow to tissues and the way in which tissues interact with blood circulation. Thus, the availability of devices that can provide three-dimensional pictures of the anatomy and perfusion of blood is invaluable. Recently, a device has been developed which promises vast improvements in the understanding of heart and other organ function in health and disease, and potentially in the diagnosis of disorders of these organs.

Scheduled for investigative use in man in 1980, the dynamic spatial reconstructor (DSR) will provide the first stop-action, slow motion, and elapsed-time video displays of the heart, lungs, and circulatory system performing their functions. The DSR will also image body sections much larger than can be imaged with conventional computerized tomography (CT) and it will provide much more discrimination in reconstructed images of the lung. Whereas the best CT scanner currently available produces a cross-section 5 to 10 millimeters thick in 2 seconds, the DSR produces 250 cross-sections, each 1 millimeter thick, in 1/100th of a second, and repeats the action 60 times per second. The technique will allow investigators to capture the three-dimensional dynamics of vital organs and to record rapid changes in the shape of organs.

Coronary Heart Disease
. . . Echocardiography To Measure Myocardial Infarction

For some time scientists have shown interest in the possibility of protecting ischemic myocardium or limiting the extent of irreversible cellular damage during periods of decreased blood flow to the heart. To evaluate potential therapeutic techniques, it is necessary to measure the extent of tissue damage. Current techniques involve enzyme, radioisotope, or electrogram mapping. Preliminary studies have demonstrated that two-dimensional echocardiography can be useful as a noninvasive technique for locating tissue damage and for identifying expansion of the damaged area when it occurs. Echocardiographic equipment, already available in many medical centers, may allow clinicians to evaluate the role of infarct expansion and myocardial deterioration in congestive heart failure.

Emphysema
. . . Synthetic Inhibitors Reduce Severity

Over a million Americans suffer from emphysema, a progressive debilitating lung disease. There is no cure for the disease, and its treatment is palliative. It may be caused by an excessive breakdown of lung elastin by the enzyme elastase, due to a change in either the amount or binding ability of naturally occurring inhibitors. If molecules capable of inhibiting the enzyme can be made synthetically, it might be possible to administer them to emphysema victims and arrest the development of the disease. Recently, several synthetic elastase inhibitors were tested in an experimental animal model of emphysema and the findings were promising. When administered before experimental emphysema was produced, the synthetic inhibitors prevented the manifestation of the disease. When given the inhibitors after the disease was induced, the animals developed smaller and fewer lung lesions. While these results have been attained only in an experimental animal model of emphysema, and the synthetic inhibitors are still not safe for humans, this approach appears to hold out a promise that it may some day be possible to prevent or lessen the severity of emphysema in high-risk individuals.

Myocardial Infarction
. . . Advance in Early Diagnosis

Following myocardial infarction, a patient's prognosis can be vastly improved with prompt diagnosis and treatment. However, many cases of small infarction are difficult to diagnose in the early stages; infarcts that are several

days old may also be elusive. After an infarction begins, components of affected muscle fibers begin to degenerate and are released into the serum. These dissolved muscle components could be measured as indicators of the extent of damage.

Recently a radioimmunoassay for myosin light chains has been used to diagnose myocardial infarctions in man. Antibodies to myosin light chains generally remain distinct from skeletal or smooth muscle light chains, and thus allow the measurement of dissolved heart muscle components. In a number of patients with acute myocardial infarction, myosin light chains have been observed to appear within 1 to 4 hours of the onset of symptoms. Unlike other intracellular products, increased plasma concentrations of major light chains appear in the early stages of infarction and persist for a number of days following the infarction, allowing early diagnosis as well as diagnosis of more remote infarcts.

Respiratory Distress Syndrome
. . . Role of Insulin Clarified

Each year, nearly 40,000 infants are born with respiratory distress syndrome (RDS). Many would die without prompt treatment. In RDS, the newborn's lungs are immature and are unable to synthesize adequate amounts of surfactant, a substance that reduces the surface tension of pulmonary fluids and so contributes to the elastic properties of lung tissue. For some time, it has been known that infants born to diabetic mothers have an increased incidence of RDS. Investigators have now developed a model system—the cultured fetal rat lung—which facilitates studies to determine the effect of insulin on fetal lung maturation. Results of initial studies indicate that insulin delays morphological maturation in the cultured fetal rat lung, a finding which may explain why RDS is so common in infants born in diabetic mothers. *In utero* these infants are exposed to high levels of insulin as glucose from the hyperglycemic mother freely crosses the placenta and stimulates the fetal pancreas to produce insulin. This basic understanding presents new opportunities and challenges for developing a means of preventing immature lung development in infants born to diabetic mothers.

Measurement of Pulmonary Function
. . . Equipment at Lower Cost

Measurement of respiratory gases is crucial to the management of critically ill patients. Although a variety of gas analysis instruments are presently on the market, most of them are limited to a single gas and most are plagued by slow response time, unreliability over extended periods of use, high costs, and excessive manpower requirements for use and maintenance. Application of pulmonary function measurements will not become part of routine diagnostic care in nonacademic settings until these major problems are solved. Development and clinical evaluation of two multigas analyzers have provided examples that such technology is available and is clinically reliable.

A multigas pulmonary function analyzer has been developed that is capable of simultaneously measuring carbon monoxide, methane, and acetylene. The capability to measure these three gases with a fast response time and high accuracy makes this a low-cost instrument that can be used to measure the important pulmonary function parameters of diffusing capacity, lung volume, and cardiac output.

A second multigas analyzer (O_2, N_2, CO_2, N_2O, C_2H_2, and H_2O) has been developed and clinically evaluated. It has a proven accuracy of ± 1 to 2 percent full scale with a response time of less than 30 milliseconds. This instrument is comparable to a mass spectrometer for pulmonary measurements at only a fraction of the cost.

These new devices will provide the flexibility of making most of the currently used pulmonary function measurements accurate, simple, and economical. They have already stimulated the market to begin the development of other devices that should significantly simplify the routine measurement of pulmonary function, lower costs, and decrease manpower requirements.

Lung Function
. . . New Method Accurately Estimates Size of Children's Airways

Most tests for evaluating lung function in children are modifications of techniques developed for testing adults; however, the

available tests require such cooperation that they are difficult to perform with children under 6 years of age. It is, therefore, important to develop techniques more suitable for evaluating lung function in young children. One such method has been developed. It measures the configuration of the large airways (the major part of the windpipe that carries air to the lung) by vibrating air in front of the mouth in such a way that the air is bounced against the walls of the airways. The waves of air can be analyzed by a computer and translated into a picture of the airway.

Making this technique applicable for the child required that major technical problems be solved. One difficulty was in connecting the apparatus to the mouth and introducing the airwave into the airways without losing part of the wave. This problem has now been solved by the development of a soft and pleasant-tasting dental cast that prevents the tongue and jaw from interfering with the airwave. Another technical problem was overcome by use of a gas mixture that is lighter than air (20 percent oxygen and 80 percent helium) and which depicts the airway dimensions with accuracy comparable to that of an X-ray. This simple and safe procedure permits frequent assessment of an important aspect of lung function and offers a capability of detecting obstruction in the large airways.

Management of Adult Respiratory Distress Syndrome

. . . Blood Gas Measurement

Methods that permit rapid and continuous monitoring of changes in arterial blood gases are essential to effective management of adult respiratory distress syndrome (a condition that may occur in adults whose lungs were previously normal but who are suffering from trauma, drug overdose, viral pneumonia, or burns, or who have undergone major surgery). New methods are now being assessed; available devices are being miniaturized and their compatibility with blood improved. Mass spectrometer and gas chromatograph systems coupled to gas sampling catheters are being evaluated in critically ill adults. A noninvasive reflective oximeter for *in vivo* measurement of oxygen saturation is undergoing assessment in animals. The hyperoxic depression of 5-hydroxytryptamine uptake by the lung is being studied as a possible probe for detection of early oxygen damage to the blood vessel lining. An index of pulmonary insufficiency has been developed to define the clinical status of patients in respiratory failure, and is now being correlated with information from lung biopsy, coagulation changes, physiologic information, and death statistics.

Pulmonary Hypertension

. . . Use of Microbubbles for Noninvasive Assessment

Diagnosing high blood pressure in the lung and evaluating its severity present a clinical challenge. Although symptoms and clinical X-ray and electrographic signs may suggest the presence of pulmonary hypertension, they are reliable indicators only when pulmonary artery pressure is markedly elevated or when moderate to severe pulmonary hypertension has lasted for a long time. A noninvasive method of measuring pulmonary artery pressure is now being developed to record the resonance frequency produced by microbubbles as they pass through the pulmonary artery. The frequency with which the bubbles pass various sites is compared to the frequency with which they pass the injection site in a peripheral vein. Adverse side effects are minimized because the bubbles remain in the bloodstream a very short time, are very small, and are needed in only a small quantity. Nitrogen bubbles encapsulated with gelatin have been used successfully, and sugar-coated bubbles, which have the advantage of dissolving very rapidly, are being tested. A simple noninvasive technique such as this allows clinicians to evaluate the impact of therapies to reduce pulmonary artery pressure and to diagnose pulmonary hypertension and cor pulmonale (heart disease caused by certain lung disorders).

Interstitial Lung Diseases

. . . New Procedure Measures Alveolar-Capillary Permeability

An increase in the permeability of the alveolar-capillary membrane is characteristic of a number of interstitial lung diseases. A new method utilizing radionuclide imaging is being used to measure alveolar-capillary membrane

permeability. The patient inhales an aerosol containing minute doses of two radioactive indicators and the indicator clearance in six regions of the lung is determined with a scintillation camera. The clearance of the lower molecular weight indicator, which diffuses more readily across the alveolar-capillary membrane, is greater in patients with interstitial lung disease (pneumoconioses, granulomatous infections, collagen disorders, and a variety of fibrotic diseases) than in normal control subjects. This is a simple, sensitive, and relatively noninvasive method for quantifying alveolar-capillary permeability in adult respiratory distress syndrome patients. The method is also potentially useful for monitoring the course of therapeutic regimens where the injury to the alveolar-capillary membrane may improve.

Automated Plasmapheresis

. . . Development of a Continuous-Flow Plasmapheresis System

A completely closed, continuous-flow plasmapheresis system (or system for separating blood components) has been developed. The system, a form of automated plasmapheresis which employs microporous membrane filtration technology, will probably be the most significant technological development in blood banking over the next few years. The automated device is designed to reduce plasma collection time from the 1-1/2 hours currently required to perform a manual plasmapheresis procedure, to 30 minutes. It is predicted that this device, which will make plasmapheresis more convenient for donors, will significantly increase the number of volunteer plasma donors and reduce dependence on commercial plasma. Unlike automated plasmapheresis based on centrifugation technology, this microporous membrane filtration offers added safety because it is a completely closed system. It is anticipated that the device will be developed commercially and marketed in the near future.

Sickle Cell Disease

. . . New Leads for Future Treatment

In sickle cell disease the red blood cells contain an abnormal hemoglobin. In the presence of low oxygen concentration, this abnormal hemoglobin S forms long polymers which bring about a gel-like state and distort the cells into irregular shapes resembling sickles. Thus, a major concept in sickle cell disease research has been that partial inhibition of intracellular hemoglobin S polymerization (the process that distorts the red blood cells) should result in decreased clinical severity, while complete inhibition should produce a cure. Many significant advances in our understanding of the polymerization process have occurred, and there are various techniques in use to study hemoglobin S polymerization and to assess the therapeutic potential of inhibition.

Among the variety of strategies proposed to inhibit intracellular polymerization, the most exciting and straightforward is the use of small molecules that can bind specific regions of the hemoglobin S molecular surface. A detailed knowledge of the regions of the hemoglobin S molecular surface that are involved in intermolecular bonding is essential to the design of stereospecific inhibitors. Significant advances have been made and much information about these regions has recently become available, thus increasing the possibility for development of antisickling drugs.

Hepatitis

. . . Virtual Elimination of Type B as a Transfusion Hazard and Progress Toward Controlling Non-A, Non-B Type

Heparitis B, caused by transmission of infectious agents in the bloodstream of seemingly healthy donors, is a serious hazard connected with the transfusion of blood and blood derivatives such as antihemophilic factor. The infection, the major cause of post-transfusion hepatitis in the United States, can give rise to a protracted, disabling illness and may be fatal.

With identification of the hepatitis B virus and development of tests for the presence of this virus, it became possible to screen blood donors, so that today hepatitis B has been virtually eliminated as a transfusion hazard. In a recent report from a large blood center in the Midwest, only two instances of post-transfusion hepatitis were caused by hepatitis B virus in recipients of blood from some 80,000 donors. While the virus is widespread and can be transmitted in other ways, for example from mother to newborn infant and by the fecal-oral route, transmission by blood transfusion has proven preventable as the result of research of the last decade.

It has been found, however, that hepatitis B virus is no longer the cause of a significant number of cases of post-transfusion hepatitis. Since neither hepatitis B nor the virus of epidemic hepatitis (hepatitis A) can be demonstrated in these residual cases, it is postulated that one or more non-A, non-B viruses are responsible, and an intensive search for such viruses has begun with the aim of instituting control methods similar to those used to control hepatitis B virus. The development of tests for the detection of the unknown agent depends on the demonstration of the virus, and a large step toward this goal was taken during the past 2 years with the successful transmission of non-A, non-B hepatitis to chimpanzees. Although positive identification of this virus has not yet been achieved, the possibility of propagating it in experimental animals vastly increases the speed of research.

Pending identification of the agent or agents responsible for non-A, non-B hepatitis and the development of diagnostic and screening tests, epidemiological studies have yielded vital information on this form of post-transfusion hepatitis. It behaves in important respects much like hepatitis B, in that it is more often transmitted from paid than from volunteer donors and it is most prevalent in lower socioeconomic levels. Therefore, many of the same methods that have been used effectively for the control of hepatitis B can now be applied to non-A, non-B hepatitis.

Hemophilia

. . . *Prenatal Diagnosis*

Hemophilia is a sex-linked, inherited, hemorrhagic disorder that occurs almost exclusively in males. Classical hemophilia (hemophilia A) is caused by a deficiency of Factor VIII in the blood. Severely affected patients suffer from recurrent bleeding into joints and other sites and require treatment with Factor VIII replacement products. As a result, they undergo a great deal of discomfort and inconvenience, and the threat of serious hemorrhage continues to present an emotional, physical, and financial burden for both the patient and his family.

With use of a direct, fetoscopic blood sampling method, plasma samples can be obtained in the midtrimester from fetuses at risk for severe hemophilia A. A radioimmunoassay for Factor VIII coagulant activity VIII:C (Ag) permits the diagnosis of hemophilia, and a therapeutic abortion can be carried out if appropriate. This addition to genetic counseling may be applicable in the future to the diagnosis of hemophilia B and other hemorrhagic disorders.

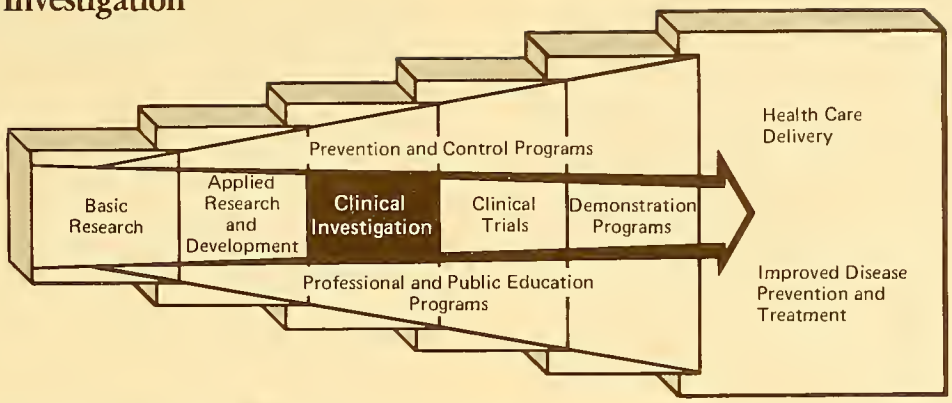
Erythropoietin

. . . *Progress in Radioimmunoassay Development*

Erythropoietin is one of the prime regulators of red blood cell production, and determination of plasma erythropoietin may be important in the diagnosis and treatment of disorders such as iron deficiency anemia, aplastic anemia, megaloblastic anemia, and loss of red cells from either hemolysis or hemorrhage (all of which are usually associated with increased blood and urinary titers of erythropoietin) and anemias resulting from decreased production of red cells and the anemia of chronic renal failure (usually resulting in lower titers).

The currently available bioassay for erythropoietin is not sensitive enough to detect normal levels; however, a recently reported radioimmunoassay appears to offer significant advantages over the existing method. The radioimmunoassay is sensitive to an absolute amount of erythropoietin approximately 100 times smaller than the amount required for the bioassay, and the results obtained are comparable to the bioassay results where the latter test is valid. With improvements, modification, and validation, this method offers promise of being a simple, reliable assay of use as both a diagnostic aid and a research tool.

Clinical Investigation



Clinical investigation is the vital link between basic and applied research and clinical practice. It provides the mechanisms for translating fundamental research results into potential clinical regimens. Clinical investigations, coupled with basic and applied research, are critical to developing effective therapies to alleviate or delay the effects and progression of disease as well as the design of preventive measures. Further, clinical research translates clinical observations into research focused on determining disease etiology.

Hypertension

. . . New Orally Active Compound for Long-Term Treatment

Renin and angiotensin are two substances involved in the regulatory system for blood pressure. For some time, inhibitors of these substances have been used to investigate blood pressure disorders. In the early 1970's, two types of inhibitors of the renin-angiotensin system became available for clinical research, but both had severe shortcomings such as the inability to be used for chronic blockade, inherent antagonistic properties, or stimulation of circulatory bradykinin. Thus, though these inhibitors have helped researchers gain additional insight into the functions of the renin system, the role of renin in clinical hypertension remains obscure.

Recently, captopril, an orally active inhibitor of the angiotensin-converting enzyme, was developed. Captopril (D-2-methyl-3-mercaplopropanoyl-L-proline, also known as SQ14,225) has been found to be an unusually effective antihypertensive drug. It is effective for both crisis and long-term maintenance and seems to be relatively free of side effects. The degree of blood pressure reduction is correlated with (1) the pretreatment plasma renin activity; (2) the induced suppression of urinary aldosterone excretion; and (3) the consequent changes in potassium balance. This new means of controlling high blood pressure represents an advance in treatment and may provide important new insights into the pathophysiology of the disease.

Ischemic Heart Disease

. . . Identification of High-Risk Patients

Thallium imaging is a technique used to evaluate blood flow to the heart tissue to diagnose ischemic heart disease. Thallium will not localize in areas of the heart muscle that lack or have poor blood flow; such areas appear as "cold spots" on scanning. With the use of a new computer-assisted method for analyzing thallium images, called circumferential profiles, it is possible to determine the size of the involved area and to compute a score (defect score) that indicates what percentage of the heart muscle is affected by abnormal blood flow.

In recent studies of patients who have suffered an acute myocardial infarction (tissue damaged by poor blood flow), those with an initial thallium defect score representing a 30 to 40 percent circumferential defect were found to be at very high risk for consequent death. In contrast, patients with lower defect scores were at significantly less risk. Thallium defect scores were more accurate in identifying high-risk patients than were electrocardiograms, chest X-rays, or serum enzymes, either singly or in combination. Identification of high-risk patients would permit their consideration for possible coronary bypass surgery.

Atherosclerosis

. . . Obesity in Young Adults Associated with Adverse Lipoprotein Levels

Several lipoprotein fractions have been found to be predictive of coronary heart disease in the

Framingham Heart Study, the Honolulu Heart Study, and other cohorts participating in the Lipoprotein Phenotyping Project. In particular, elevated low density lipoprotein (LDL) cholesterol and decreased high density lipoprotein (HDL) cholesterol are associated with increased risk of coronary heart disease. Much research is being aimed at determining the factors that govern lipoprotein patterns. The Framingham Offspring Study, consisting of examination and followup of the offspring and their spouses of the original Framingham cohort, has provided new insights into some of the factors operating in young adulthood.

Among 4,260 men and women aged 16 to 49 in the Framingham Offspring Study, a distinct relation was found between obesity and adverse lipoprotein levels, with the relations being strongest in the youngest ages. In young males a distinctly more favorable lipoprotein profile was found in the leanest group. These individuals displayed lower LDL and very low density lipoprotein (VLDL) levels, and higher HDL levels. Among women, the tendency toward an unfavorable lipoprotein profile was limited to the very obese (more than 30 percent above ideal weight). The findings suggest that much of this increase in adverse lipoprotein profiles between ages 20 and 40 may result from the rapid increase in obesity in this age group.

Sudden Cardiac Death

. . . Impact of Bystander-Initiated CPR

While more than half of coronary heart disease fatalities occur outside of hospitals, rapid-response emergency care systems have allowed successful resuscitation for many out-of-hospital cardiac arrest victims. Nevertheless, the number of deaths is substantial, and some persons suffer anoxic brain damage despite prompt medical aid. Because prompt resuscitation is crucial, many professionals feel that training should be provided community-wide so that bystanders can begin to administer cardiopulmonary resuscitation (CPR) before emergency medical personnel arrive.

A recent study has assessed the effects of bystander-initiated CPR on patients treated for ventricular fibrillation (a chaotic disorder of heart rhythm in which the heart muscle quivers rather than contracts), the major cause of sudden cardiac death. The results of this investigation suggest that bystander intervention improved patient outcomes. Survival rates were 21 percent without bystander intervention and 43 percent with intervention. Other studies report similarly improved survival rates, and subsequent neurologic disorders are observed to be markedly reduced when prompt resuscitation by a bystander is given as an adjunct to high-quality emergency care.

Coronary Heart Disease

. . . Increased Mortality in Relatives of Hypercholesterolemic Schoolchildren

For some time scientists have held that heredity can play a role in coronary mortality. Recent studies have added evidence to support this theory and have even suggested that analysis of family relationships may aid in identifying persons at high risk for coronary heart disease. It has been found that the risk of developing coronary heart disease is greater for the adult relatives of children with elevated cholesterol levels. A community-wide screening program has related the cholesterol measurements of schoolchildren to cholesterol measurements in their relatives and then related the elevated cholesterol levels in the schoolchildren to excess coronary mortality in their families. The finding that there is a significantly increased frequency of cardiovascular disease mortality in the relatives of the group found to have high levels of cholesterol helps to support the belief that childhood cholesterol elevation may help identify adult family members who have a high risk of early death from heart and blood vessel disorders.

Coronary Heart Disease

. . . Menopause and Coronary Heart Disease

The Framingham Heart Study is one of the few prospective studies that include women. Since, with any combination of risk factors, women have been found to have half the incidence of cardiovascular disease that men have, the protection of women cannot be attributed to differences in the level of risk factors between the two sexes. To explore this possibly biologic immunity, investigators have examined the incidence of cardiovascular disease in relation to menopausal status over a 24-year period. While no premenopausal women developed a myocardial infarction or died of coronary

heart disease, such events were common in postmenopausal women. Even in women under age 55, 40 percent of the cases of postmenopausal coronary heart disease presented with myocardial infarctions or deaths, whether menopause was natural or surgical. In cases of surgical menopause, there was excess incidence regardless of whether the ovaries were removed. Postmenopausal women who were taking hormones had a doubled risk of coronary heart disease compared to postmenopausal women who were not taking hormones.

Congestive Heart Failure
. . . New Use of Vasodilator Drugs

Digitalis and diuretics are often used to treat congestive heart failure, a condition in which the heart cannot pump enough blood, resulting in fluid accumulation in the abdomen, legs, or lungs. But some patients fail to respond to the usual drug treatment. Recently, drugs such as sodium nitroprusside, sympathomimetic amines such as dopamine and phentolamine, and hexamethonium have been used in an effort to restore responsiveness to diuretics and to increase the heart's ability to contract.

A new vasodilator, prazosin, has been shown to be effective in improving ventricular function and exercise tolerance. In recent studies, prazosin was evaluated in the treatment of chronic congestive heart failure that did not respond to conventional digitalis and diuretic therapy. Prazosin was shown to have a prolonged dilating action on both the arterial and venous systems and, as a result, relieved congestive heart failure and increased cardiac output. However, more clinical research is needed to evaluate the feasibility of long-term therapy with prazosin and other potentially effective vasodilators.

Vasospastic Myocardial Ischemia
. . . New Understanding of Pathogenic Mechanisms

Angina pectoris is a condition characterized by chest pain due to coronary blood flow that is inadequate to meet the heart's workload. One form of this disorder, variant angina, can be identified by transient elevated ST segments in electrocardiograms. Variant angina was once thought to be a rare condition, but through the more frequent use of electrocardiographic monitoring, the condition is seen more commonly. Studies strongly suggest that spasms of the coronary arteries play a major role in variant angina attacks caused by obstructed blood flow. However, the clinical and angiographic characteristics of variant angina are not fully known, and its relationship to other forms of angina, myocardial infarction, and sudden death has not been fully defined. A recent study characterizing 138 cases of variant angina is shedding light on several aspects of the condition. Findings suggest that variant angina is only one aspect of coronary blood flow obstruction caused by blood vessel spasms. It appears that vasospastic myocardial ischemia can occur in patients with variable degrees of coronary atherosclerosis regardless of whether there is a history of previous heart damage or pain associated with exertion. Vasospastic myocardial ischemia may be accompanied by chest pain, but it may remain asymptomatic until it evolves into myocardial infarction and sudden death.

These findings have broad implications for the monitoring and treatment of anginal attacks. The apparent relationship between coronary vasospasm and sudden cardiac death strongly suggests that further research is needed on the pathogenic mechanism of coronary vasospasm.

Variant Angina Pectoris
. . . Altered Adrenergic Activity in Coronary Arterial Spasm

Spasms of the heart arteries have been shown to cause variant angina (chest pain caused by inadequate blood flow to the heart). What causes these spasms, however, has only recently been understood. One hypothesis has been that the involuntary nervous system is involved in coronary spasms. Studies reveal that alterations of the sympathetic nervous system presage coronary spasm in some patients with variant angina and may be the physiologic cause of the restricted blood flow. Studies have shown that alpha-adrenergic blocking agents can reverse coronary spasm, thus suggesting that disorders of the alpha-adrenergic system may be the underlying cause of some cases of variant angina pectoris.

Arrhythmias

. . . Evaluating Appropriate Drugs for Long-Term Antiarrhythmic Therapy

Chronic recurrent ventricular tachycardia is a disorder of cardiac rhythm which can deteriorate into fatal ventricular fibrillation in a significant number of cases. The condition often fails to respond to drug therapy. Studies have indicated that an aggressive therapeutic approach involving careful antiarrhythmic drug trials can produce symptomatic improvement in some patients. However, the approach currently available often requires multiple therapeutic trials and prolonged hospitalization to determine the best drug regimen. The period of delay until adequate therapy is established causes risk, inconvenience, and significant expense to the patient.

Recent studies have resulted in improved techniques for selecting appropriate drugs for long-term antiarrhythmic therapy. Analyses of many patients' experiences and the use of drug trials and electrophysiological studies have aided in determining the long-term efficacy of specific drugs for individual patients. As demonstrated by the studies, a drug that exerts a strong prophylactic effect against previously inducible ventricular tachycardia in the laboratory is likely to be effective during chronic oral therapy.

Congestive Heart Failure

. . . Cardiac Toxicity of a Drug Used To Treat Cancer

Doxorubicin (Adriamycin) is one of the most effective chemicals used to treat cancer. It is the single most effective agent for treating breast cancer and soft-tissue sarcomas, and it has substantial activity in childhood tumors, testicular cancer, gastric cancer, ovarian cancer, and oat-cell cancer of the lung. Unfortunately, doxorubicin also has a chronic heart toxicity which is manifested by both acute temporary electrocardiographic changes—usually benign arrhythmias—and cardiomyopathy or congestive heart failure. Now that this is a well-recognized complication, the drug is usually discontinued at the first signs of congestive heart failure.

Noninvasive techniques for repeated study of cardiac performance are needed to identify which patients are at risk for developing congestive heart failure and which could safely continue high-dose chemotherapy. A new technique, quantitative radionuclide angiocardiography, is being applied repeatedly to assess heart function in patients under treatment with varying dosages of doxorubicin. It has has found that the radionuclide technique can reliably detect doxorubicin toxicity before clinical signs of left ventricular dysfunction develop. Guidelines for the use of this technique have been developed, and it is hoped that the technique will allow much-improved monitoring of heart function in patients receiving doxorubicin.

Hypertrophic Cardiomyopathy

. . . Possible Inheritance Pattern

Hypertrophic cardiomyopathy is a heart muscle disorder characterized by asymmetric enlargement of the wall between the ventricles, improper functioning of the mitral valve, and myofiber disarray in the wall between the chambers of the ventricles. Studies have shown the condition to be hereditary, but there is disagreement about the occurrence of sporadic cases and whether the condition involves systemic hypertension.

Recently investigators have examined inheritance patterns for the disorder and have related findings to the occurrence of hypertension in the study group. Study findings indicate that there are two forms of hypertrophic cardiomyopathy: one which is inherited but does *not* involve hypertension; and one which is sporadic and *is* associated with systemic hypertension. In addition, investigators have identified certain human leukocyte antigens that may be helpful in distinguishing between hereditary and sporadic forms of the disorder. Moreover, these antigens may provide a simple screening method for the families of persons diagnosed as having the hereditary form of the disorder. Further study is needed to determine diagnostic criteria, define the etiology of hypertrophic cardiomyopathy, and explain the precise role of systemic hypertension in the disorder.

Chronic Obstructive Lung Disease

. . . Normal Breathing Patterns May Provide Criteria for Treatment

Temporary cessation of breathing for a few seconds to a minute or more during sleep results in low blood oxygen levels and has been reported in various clinical syndromes including chronic

obstructive lung disease (COLD). In an attempt to establish the association between COLD and breathing cessation during sleep, baseline data were first obtained from a group of male and female subjects without any history of pulmonary disease. Interestingly, the same breathing disorders previously reported for subjects with COLD occurred in normal subjects. This incidence of abnormal breathing was seen almost exclusively in males and correlated positively with increasing age and obesity. It appears, therefore, that the severely lowered oxygen levels observed in male patients with COLD reflect the superimposition of the lowered oxygen level that results from the respiratory disease on a normal male tendency toward temporary breathing cessation and hypoxia during sleep. Since there are no known anatomic differences in breathing apparatus of the male compared to that of the female to explain the difference in sex distribution of periodic breathing, it has been suggested that increased levels of progesterone, a respiratory stimulant, in women may prevent abnormal breathing during sleep. Understanding the sleep patterns that occur in the normal individual may provide better criteria for the treatment of patients with chronic obstructive lung disease.

Sickle Cell Disease

. . . Prenatal Diagnosis

A major advance toward the prenatal diagnosis of sickle cell disease has been reported. By analyzing DNA from the amniotic fluid, investigators have identified what may be a genetic marker for sickle cell disease in the form of polymorphism in a DNA sequence adjacent to the human beta-globin genes. Cleavage of normal DNA usually produces a 7.6 kilobase (kb) restriction fragment containing the beta-globin structural gene. Two variants (of 7.0 kb and 13.0 kb in length) have been found. While the 7.0 and 7.6 kb fragments are commonly found with the hemoglobin A (HbA) gene, the 13.0 kb variant is found in approximately 80 percent of people with the hemoglobin S (HbS) gene but only occasionally in individuals lacking this form of hemoglobin. Additionally, this fragment has been found rarely in Asians or Caucasians, and family studies indicate that the variants are inherited in a mendelian manner. This finding has been applied successfully to prenatal diagnosis in pregnancies in which the fetus was at risk for sickle cell disease. The beta S gene was linked to the 13.0 kb fragment and used as a genetic marker. In one case, there were both the 13.0 fragment (found in HbS) and the 7.6 fragment (found in HbA) indicating the prenatal diagnosis of sickle cell trait. This diagnosis was later confirmed using fetal blood. In a sickle cell disease patient, only the 13.0 kb fragment was found.

This method may be applicable to as many as 60 percent of at-risk pregnancies. Since the diagnosis involves amniotic cells, the problems of fetal sampling may be avoided. Fetal sampling, a procedure which involves obtaining blood directly from a fetal vessel *in utero,* currently carries a 5 to 10 percent risk to the fetus;

however, amniocentesis has proven to be a relatively safe procedure with minimal risk to both the mother and the fetus.

This technique presents a new approach to detecting genetic markers and may also be applicable to other genetic disorders if specific polymorphism in the DNA can be demonstrated. In addition to sickle cell disease, diagnosis of thalassemia is being investigated.

Clinical Diagnosis

. . . Rheological and Biophysical Parameters of Blood May Be Used As a Diagnostic Tool

The biophysical properties of blood are being examined for potentially useful diagnostic variables. Patients in a variety of medical and surgical categories have been studied in comparisons with clinically normal control groups.

Women taking oral contraceptives display a significant increase in apparent whole blood and plasma viscosities, with a concomitant increase in the erythrocyte sedimentation rate. In addition, the fibrinogen serum protein levels are above those of a female control group not using oral contraceptives. There were markedly shorter coagulation times for women taking oral contraceptives. These observations tend to reinforce the idea that oral contraceptives may produce hypercoagulability which, in certain circumstances, leads to thromboembolic disorders.

For patients undergoing total knee replacement surgery, there are significant increases in whole

blood, plasma, and serum viscosities as well as coagulation time. The most critical period for this group appears to be the day after surgery when hypercoagulability is present. This situation returns to normal by the eighth day following surgery.

Hepatitis

. . . Duration of Hepatitis B Surface Antigen

The presence of hepatitis B surface antigen (HBsAg) in serum indicates that a person's liver is infected with hepatitis B virus. When this antigen is found, the person has a risk of transmitting hepatitis B to others and, in some cases, may have chronic liver disease. Tests for HBsAg are an important means of screening blood donors to prevent transfusion infections.

The screening of blood donors for HBsAg has identified large numbers of people with no history of hepatitis who nonetheless carry HBsAg. Recent studies indicate that the carrier state persists for long periods of time and that after a certain period HBsAg is seldom cleared. In particular, patients on a regimen of hemodialysis often become antigenemic and a recent study indicates that once the antigenemia has persisted for a long period of time, the chances of clearing HBsAg are slight. In two study populations of persons undergoing hemodialysis, no patient with HBsAg for 11 months cleared the antigen.

While there is no current treatment to eliminate the carrier state, these studies do identify patients for whom measures to prevent transmission of the virus should be taken. Further studies in populations with a high frequency of chronic hepatitis B infection will hopefully explain why some individuals become chronic carriers while others are able to spontaneously clear their infection. Answers to these questions might allow development of therapeutic interventions to terminate the carrier state.

Alpha Thalassemia

. . . Alpha-Globin Genes in the Chinese Alpha-Thalassemia Syndromes

The alpha-thalassemia syndromes are a group of hereditary anemias caused by deletion of the alpha-globin structural genes. In Asian populations the severity of these syndromes varies with the number of alpha-globin genes deleted or absent from the chain of genes located on the chromosome.

Recently investigators have mapped gene patterns to better define these syndromes. Restriction endonuclease techniques have allowed investigators to establish the nature of the deletion that results in the single alpha-globin locus in deletion type hemoglobin H disease. A piece of DNA that contains the 5′ alpha-globin locus is the deleted fragment.

These findings provide a method for detecting the alpha-thalassemia-2 gene, and now the previously undetectable silent carrier state can be diagnosed. The sensitivity of this technique provides a more rapid means of prenatal diagnosis.

Diabetes

. . . Monitoring the Effectiveness of Treatment

Measuring two minor hemoglobin fractions (HbA_{1c} and $HbA_{1a^{+b}}$) has value in monitoring the control of plasma glucose in patients with diabetes. Hyperglycemia, or high blood sugar, causes an increase in HbA_{1c} as a result of a chemical reaction between sugar and normal hemoglobin. Unlike single measurements of plasma glucose or 24-hour urine glucose, this new measurement technique provides an assessment of the degree of hyperglycemia over a period of time equal to the life span of the red blood cell. Because of its suitability for routine lab testing, this method may have practical use in managing diabetes. The micro-method can be accurate for a large number of samples, and HbA_{1c} can also be measured by immunologic methods. Not only can these tests be used to monitor the control of diabetes but also they are useful in studying other proteins which may play a role in diabetes pathogenesis.

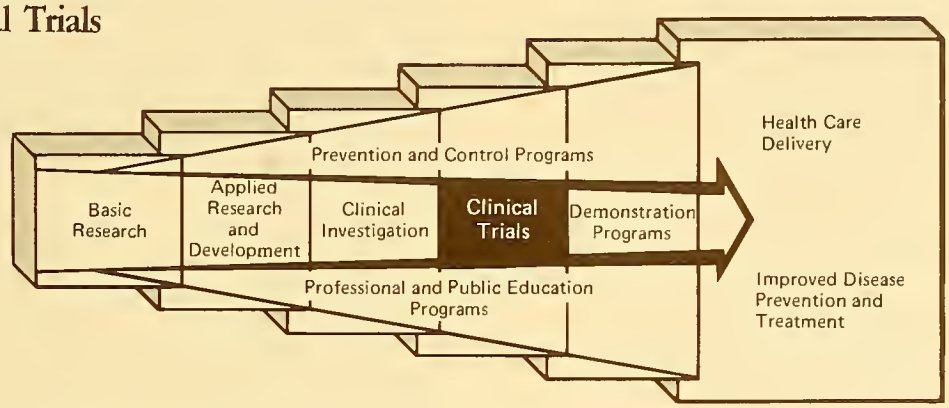
Blood Donation and Anemia

. . . Frequency of Donations Related to Sex and to Iron Deficiency

Bleeding results in mobilization of iron from body stores. As stores decrease, iron absorption increases. With continued bleeding, an individual reaches equilibrium at a lower level of iron stores or becomes anemic. These considerations apply directly to people who donate blood. While the frequency of blood donation has been adjusted to prevent anemia in most donors, quantitative information concerning the iron status of donors is limited.

Serum ferritin was measured in 2,982 male and female blood donors. Blood donation was associated with a decrease in serum ferritin. One unit of blood per year, equivalent to an increased requirement of 0.65 mg of iron per day, halved the serum ferritin level in the male for 4 to 6 months after donation. More frequent donations were associated with further decreases. From the data obtained, it would appear that male donors, while depleting their iron stores, were able to donate two to three units of blood per year without an appreciable incidence of iron deficiency. Women could donate only about half that amount, and more frequent donations were associated with a high incidence of iron deficiency and donor dropout.

Clinical Trials



Clinical trials test, in a carefully controlled setting, the efficacy and safety of preventive and therapeutic regimens with the potential to save hundreds of thousands of lives and billions of dollars each year. The clinical trial is a key step in the long, difficult, and complex process which converts research findings to clinically applicable prevention or treatment regimens.

The objective of the large-scale clinical trial—a critical activity in the biomedical research spectrum—is to gain information regarding the effect of a given form of medical or surgical intervention. Clinical trials are used to test new drugs, compare alternative patient management modes, determine the effectiveness of different treatments, or measure the efficacy of intervention programs for high-risk populations. Trial results validate the projection of potential consequences of successful intervention—risk reductions, changes in longevity, morbidity, and mortality, and economic savings.

The conduct of a clinical trial involves a series of steps, each with its own stringent requirements. Consequently, the time needed to successfully complete a trial can range anywhere from 2 to 10 years depending on the size and complexity of the trial. Successful completion of a trial involves the concerted effort of literally hundreds of scientists, clinicians, analysts, and support personnel; and the cost can reach tens of millions of dollars by the time a trial is completed and its results disseminated. Therefore, the decision to undertake a clinical trial is not made without considerable deliberation. Often, a small pilot trial is used to determine the feasibility of, and gains to be expected from, a larger trial.

Throughout the course of any clinical trial, its progress and results are monitored by a board of objective, uninvolved experts. Results of the trial, however, are not revealed until some significant result is achieved or until the trial has run its full, allotted time course.

Coronary Heart Disease

. . . *Quantifying Risk of Complications of Coronary Arteriography*

Coronary arteriography is a diagnostic technique in which a catheter is threaded through an artery in the extremities to the heart to allow X-rays of the coronary arterial tree and to otherwise test for and measure the severity of coronary heart disease. Data from the NHLBI collaborative Coronary Artery Surgery Study, which has the primary goal of assessing long-term results of coronary artery bypass surgery, have provided a basis for a prospective study assessing coronary arteriography and the accompanying risks of complications. In 7,553 consecutive coronary angiograms at 13 participating institutions, there were 15 deaths and 19 nonfatal myocardial infarctions on the day of angiography or the following day—rates of 0.2 percent and 0.25 percent, respectively. Almost all deaths were in patients with at least 70 percent narrowing of all three major coronary arteries, though only 31 percent of patients had three-vessel disease. Significant narrowing of the left main coronary artery (50 percent or more) was

also associated with a markedly increased risk. Other identified risk factors for complications of angiography include decreased ejection fraction, congestive heart failure, multiple premature ventricular contractions, and hypertension. Another finding confirms earlier reports that heparin does not exert a protective effect during angiography.

Chronic Obstructive Pulmonary Diseases
. . . Reevaluation of Respiratory Therapy Methods

For several decades clinicians have held that retention of excessive secretions in the respiratory tract is harmful to lung function and can lead to serious complications. In response to this widely held view, prophylactic respiratory physical therapy involving a variety of manipulations directed at removing sputum from the lungs has been developed for patients with chronic obstructive lung disease. Among the current techniques are chest percussion, vibration, and postural drainage, with or without aerosols. However, a 1974 NHLBI-sponsored conference noted the fact that the long-term effects of temporarily reducing the amount of retained sputum were totally unknown.

Recently several long-term effects have been investigated. One study has demonstrated no difference in the duration of fever, the amount of expectoration, or the results of arterial-blood analysis between patients who received chronic physiotherapy in conjunction with other treatment and those who did not. A second study showed that the forced expiratory volume in 1 second, a test that reflects the behavior of the large and small airways, actually worsened after chest percussion. A third study revealed no consistent change in either specific airways conductance, or in arterial-blood partial pressure of oxygen, carbon dioxide, or pH. These investigations raise serious questions about the effectiveness of chronic chest physiotherapy in patients who do not retain large volumes of secretions. Even in patients who do retain large volumes of secretions, the long-term results of chest physiotherapy may be questioned.

An NHLBI conference on the scientific basis for respiratory therapy administered in the hospital has proposed studies to resolve issues concerning respiratory therapy and related matters.

Acute Respiratory Failure
. . . Use of Extracorporeal Membrane Oxygenators

Acute respiratory failure, characterized by the inability to oxygenate the blood, is often seen in young, previously healthy adults and is usually fatal. It is associated with many diverse conditions, usually severe illness requiring hospitalization. Some of the conditions that may lead to acute respiratory failure include shock due to blood loss or infection, severe chest or general body injury, severe viral pneumonia, drug overdoses, inhalation or aspiration of corrosive chemical substances, and widespread fat emboli.

A major clinical trial to evaluate the use of the extracorporeal membrane oxygenator (ECMO) for the treatment of patients with acute respiratory failure has been completed. The trial, begun in 1973 and completed in 1977, involved 831 patients. Of the 831 patients, 90 were randomly assigned to two subgroups: The first group received conventional treatment; the second group received conventional treatment and ECMO care too. The remaining 741 patients were followed to assess the natural history of adult respiratory distress syndrome. Results show that ECMO fails to increase survival rates over those achieved with conventional care. The lung pathology data showed that ECMO support did not alter the irreversible lung damage associated with acute respiratory failure.

This clinical trial illustrates the value of evaluating new therapies before they are promoted for general use. Although the results of the study discourage promotion of ECMO, they point to new approaches to the problem of acute respiratory failure. Significant advances in diagnosis and treatment of RDS will require multidisciplinary research on the mechanisms of lung injury and repair.

Bacterial Infection in Infants
. . . Prevention of Infection

Bacterial infection is a significant cause of illness and a contributory cause of death in newborn infants with respiratory distress syndrome. Such infection has been difficult to manage and often does not respond to antibiotics. Recent preliminary findings have suggested that the presence of

normal bacterial flora can provide an effective host defense mechanism against harmful bacteria. A small pilot study has indicated that colonization of infants with a carefully selected nonvirulent strain of alpha-streptococci can be done with minimal risk and is very successful in preventing serious infections. As a result of this study, a controlled trial is now determining the efficacy of this method. Infants in this trial will be followed for a year. If the procedure is validated, it will be a major advance toward prevention and control of one of the primary causes of sickness and death in infants with respiratory distress syndrome.

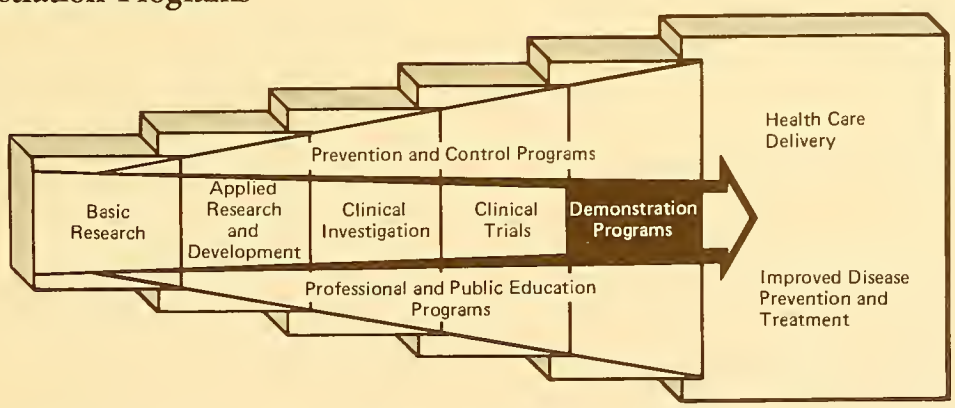
Hemophilia

. . . Role of Spontaneously Occurring Antibodies

Classical hemophilia (hemophilia A) is treated by transfusion to correct the patient's deficiency of Factor VIII in the blood. A significant number of multitransfused patients, however, have developed antibodies to Factor VIII and thus become refractory to further Factor VIII therapy. A cooperative, multicenter study is now in progress to investigate the development of naturally occurring inhibitors in hemophilia patients, the effects of the inhibitors on the clinical course of patients so affected, and the impact on the national blood resource.

Of the 1,547 hemophilia patients enrolled in the study, 223 (14.7 percent) are classified as inhibitor patients. Data from the study group will yield valuable information about liver function, hypertension, and product utilization in hemophilia patients; the prevalency of Factor VIII inhibitors and their relationship to genetic factors and replacement therapy; the need for replacement therapy in inhibitor patients; and secondary immune response to Factor IX concentrates. As part of the natural history study, a randomized, controlled, double-blind technique is used to test the effectiveness of Factor IX concentrates in the treatment of bleeding episodes in patients who have inhibitors to Factor VIII.

Demonstration Programs



Demonstration programs test methods to introduce or facilitate delivering health care advances to the public. Demonstration activities, which are a recent addition to the Institute's programs, have been implemented to effectively translate research findings into health practices. Such programs will be of even greater importance as more clinically applicable information becomes available for dissemination from ongoing clinical trials.

Nutrition

. . . Assessment of the Effects of Nutrition Education on Consumer Food Purchases

Assessing the kinds and quantities of foods that people eat is central to nutrition education efforts. NHLBI has undertaken several nutrition education programs designed to inform people about food choices at the points where they make food decisions, such as at vending machines, cafeterias, and grocery stores. In the "Foods for Health" program, heart-health and nutrition issues are presented in biweekly pamphlets for supermarket shoppers. Topics include coronary heart disease and cholesterol, basic food groups, seasonal meal planning, and food labeling information, particularly sodium and sugar content. The

program is intended to (1) communicate accurate information to the consumer about the relationship of nutrition and cardiovascular disease and (2) evaluate the feasibility and impact of communicating health information at the point of purchase.

Hypertension

. . . Educational Programs Begun in Worksettings

Cooperation with private organizations in business and industry is an important aspect of NHLBI's educational efforts. The University of Michigan and the Ford Motor Company have evaluated four different approaches to delivering high blood pressure control services in an industrial setting. Two additional contracts with other groups are for evaluation of other types of high blood pressure services in industrial settings.

Another demonstration worksetting effort is the Blue Cross Association education and training project. The aim of this program is to train Blue Cross account executives to provide their clients with consultation on planning and implementing high blood pressure control programs at the work site.

Hypertension

. . . High Blood Pressure Education and Control

For the past 7 years there has been a national effort to control high blood pressure. Today we have definite information indicating progress. From 1972 through 1977, age-adjusted death rates for hypertension-related cardiovascular diseases declined by 20 percent, while the decline for cardiovascular diseases not related to hypertension declined only 9 percent. Recently acquired data indicate that public knowledge is improving and misconceptions held by the public are not as widely held as they were in 1976 when the National High Blood Pressure Education Program focused on them. Further, a recent FDA survey indicates that physicians' practices generally concur with national treatment recommendations in areas of screening, detection, and management. Because of the success of this effort, the NHBPEP was awarded a Commendation for Leadership by the Society of Public Health Educators in October 1978.

The NHBPEP is a national cooperative effort to reduce death and illness by educating professionals, patients, and the public about high blood pressure. It is coordinated and staffed by the NHLBI and involves numerous Federal agencies, state health departments, and more than 150 private sector organizations. The current initiatives of the program are revision of treatment recommendations for physicians, overcoming barriers to cooperation among health professionals, improving dietary management of high blood pressure, improving interaction between patients and health professionals, and assisting in developing better high blood pressure control in rural communities and in worksettings. In addition, the program maintains a core of activities including an information center, technical assistance at the state and local levels, and materials development.

The NHLBI is also sponsoring demonstration programs in statewide control, control in rural communities, and control in worksettings, which will provide additional resources and understanding about effective approaches to high blood pressure control.

Asthma

. . . Self-Management of Childhood Asthma

When a child has an attack of asthma, the effects may range from mild disability to a life-threatening inability to breathe. Unfortunately, the most common response of both parents and children is panic, which serves only to exacerbate the child's condition. A program is now under way to help asthmatic children and their families practice behaviors to cope with asthma. Strategies being tested are designed to increase self-management skills, increase individual responsibility for health, and reduce dependence on the health care system. Preliminary results indicate that the educational programs lead to positive changes in the children's attitudes toward themselves, less frequent use of the emergency room, fewer absences from school, more effective use of medication, and a decrease in the child's health care costs.

Pulmonary Embolism

. . . Improving Heparin Therapy in Community Hospitals

Pulmonary embolic disease, a life-threatening condition, is a major cause of hospitalization in

the United States with a high rate of mortality among those hospitalized. Heparin, a key drug in the management of this serious disease, is the only drug available to the physician to anticoagulate a patient's blood immediately. Of greater significance, however, is the confusion in the literature on how to evaluate and regulate continuous heparin therapy. As part of the continuing medical education program, a step-by-step procedure for the initiation and control of continuous heparin therapy has been developed, tested, and evaluated. It is simple to follow and appears to provide community hospitals with a safe, closely controlled method for administering heparin—one that can be delegated to the nurse at the bedside. More experience is needed in a variety of settings before the full impact of this procedure can be established.

Thalassemia

. . . Measuring Effectiveness of Counseling Methods

NHLBI is supporting screening for thalassemia minor and the evaluation of genetic counseling presented in a highly structured videotape program, as opposed to face-to-face personalized counseling. Screening of two health care organizations with a total of 48,000 subscribers should identify approximately 270 individuals with thalassemia trait.

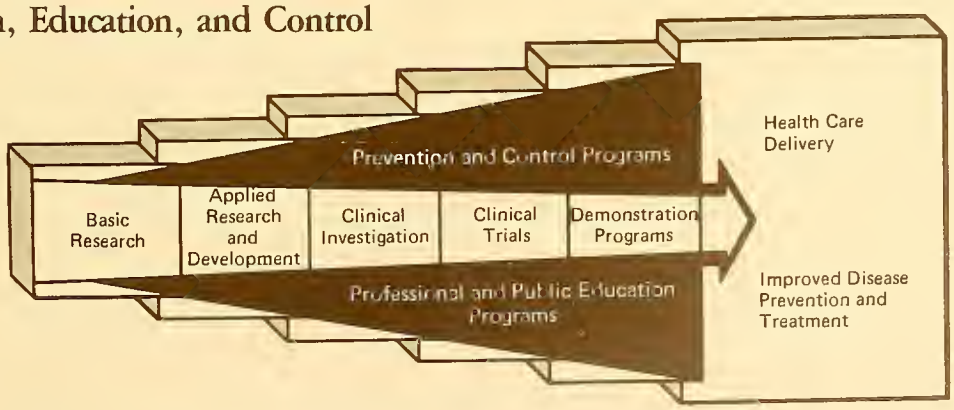
To date, 18,500 individuals have been screened and 154 trait patients identified; 116 of the 154 have come in for counseling. Preliminary data indicate that instruction by videotape had an advantage over face-to-face instruction by a physician, specifically in the area of preventive genetic information. This advantage was not counterbalanced by any detrimental effect on subject mood changes for patients. About 50 percent of the spouses for whom referral by the thalassemia trait patient might be considered appropriate have come in for screening. Spouse referral is an indication of the success of the counseling.

Sickle Cell Disease

. . . Expanding Public Education

The Health/Science Teacher Training Seminar program is designed to introduce concepts about sickle cell disease at the high school level and encourage regional, state, and local organizations to promote educational programs. Sixteen seminars have been scheduled through September 1979 in major cities throughout the country. Attendance at the training sessions has been good, and high levels of interest and enthusiasm are evident. The high school teachers attending have generally indicated that seminar materials are useful and stimulating for classroom presentations. Preliminary analysis of data from the seminars indicates that the sessions have been extremely effective in increasing knowledge about sickle cell disease among the teacher-trainees. These teachers will be able to present to their students valuable information about the nature of and risks associated with sickle cell trait and the disease.

Prevention, Education, and Control



Clearly, the ultimate focus of the biomedical research spectrum—shown by the direction of the arrow in the diagram above—is improved prevention, education, and treatment of the cardiovascular, pulmonary, and blood diseases for which the Institute has responsibility.

Through the efforts of investigators at all levels of the research spectrum, several advances have emerged which offer great potential for the treatment and prevention of disease.

Atherosclerosis
. . . Stress Behavioral Science Approaches in Nutrition Counseling

Over the years experience has indicated that it is not sufficient merely to tell the public what foods to eat and how to prepare them in order to promote cardiovascular health. The public must be motivated to follow such advice in order to achieve long-term change in dietary habits. NHLBI has convened conferences and a series of ongoing workshops to develop the best approaches to public education and motivation. In addition, three NHLBI-sponsored papers dealing with behavioral science and nutrition counseling were published in the April 1978 issue of the *Journal of the American Dietetic Association* and have been issued as a pamphlet by NHLBI's Public Inquiries and Reports Branch as a "Science to Practitioner" publication. This series represents one of NHLBI's efforts to assist nutrition counselors in applying sound behavioral methods to nutrition counseling.

Atherosclerosis and Hypertension
. . . Cooperation with the American Heart Association

In collaboration with the American Heart Association's Subcommittee of Nutritionists, NHLBI nutritionists have made major contributions to nutrition education through school lunch programs, revising public education materials, developing the Creative Cuisine Program, and preparing two publications—*Guidelines for Nutrition Programs* and *Heart Health in the Young*. They have also furnished guidance to the American Heart Association's Committee on Atherosclerosis and Hypertension in Childhood by preparing nutrition education material for teenagers with hyperlipidemia. These examples illustrate some of the varied approaches NHLBI is using to speed application of new knowledge to primary and secondary prevention practices.

Atherosclerosis
. . . Effective Counseling and Heart Attack Prevention

A workshop bringing together applied nutritionists, local physicians, and behavioral scientists was presented in October 1978. The workshop, presented in collaboration with the Division of Scientific Affairs of the American Heart Association, the New Jersey affiliate of the American Heart Association, and the College of Medicine and Dentistry of New Jersey, was prepared in an effort to reach practitioners at the local level. The objective was to educate them in better methods of nutritional counseling to reduce coronary heart disease risk. During the workshop, issues related to low-fat diets and diet adherence were highlighted. Response to the workshop was good and many enrollees have independently sought additional training. Plans are being made to repeat the program in 1980.

Nutrition
. . . Encouraging Training in Behavioral Science and Nutrition

NHLBI's long-term objective of making nutrition education more accessible to the consumer requires attention to research and training in the behavioral sciences for the nutritional practitioner. In an effort to stimulate the academic community's interest in this research training need, experts from the fields of applied nutrition and behavioral science were invited to an informational meeting in June 1978. They were encouraged to use the ongoing Institutional Research Training Grants Program to plan educational programs at the doctoral and postdoctoral levels. Such programs would provide behavioral scientists with nutritional intervention skills and provide nutritionists with behavioral science expertise.

V. Special Emphasis Areas for 1979

NHLBI Technology Transfer Activities

Introduction

Since World War II, new technologies have been applied increasingly to the practice of medicine. Remarkable advances in biomedical research have led to increased knowledge of basic disease processes, and, more recently, growing attention is being given to preventive interventions and methods of disease control. For example, the list of diagnostic technologies introduced in recent decades includes automated clinical laboratory equipment, intensive care monitoring techniques, electronic fetal monitoring, fiberoptics, ultrasound, and computer tomography. A large number of similarly advanced techniques have emerged in the prevention and treatment facets of medical practice.

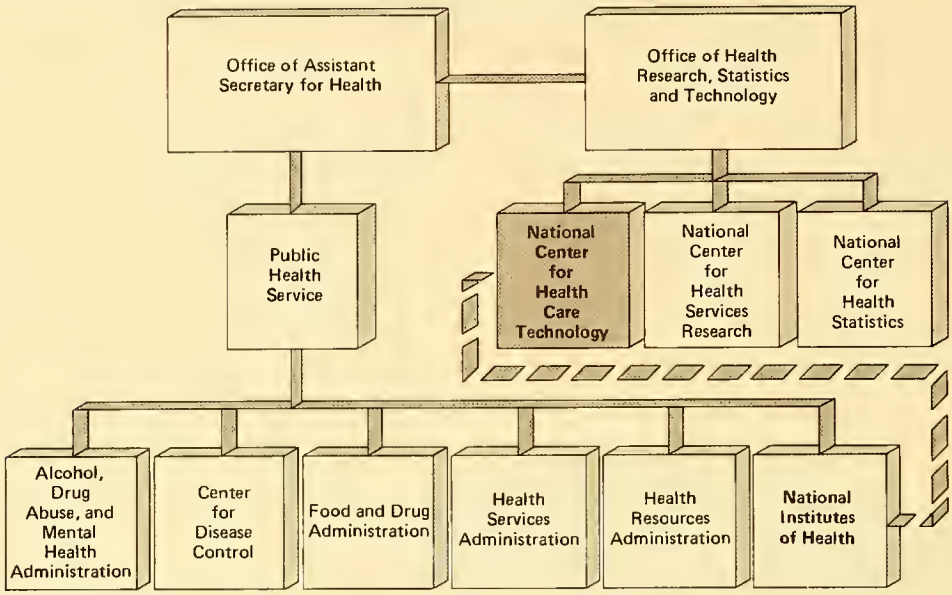
Concomitant with these scientific developments, public expectations concerning the benefits of biomedical research have also increased. Both public and private sector leaders have expressed the expectation that biomedical research and development should lead to improved clinical practices, the benefits of which are readily perceivable by society as a whole.

Congressional Mandates

In response to these advances and growing expectations, Congress and the Department of Health, Education, and Welfare have recognized the need for research agencies to systematically assess and transfer new technologies and have noted that the NIH role is vitally important. Recent Congressional actions directly affecting the National Institutes of Health reflect increased concern that formal technology transfer processes be implemented or expanded within Federal research programs.

The Health Services Research, Health Statistics, and Health Care Technology Act of 1978 authorized DHEW to establish the National Center for Health Care Technology (NCHCT) to

Figure 7.—NHLBI technology transfer: Relationship of NIH to NCHCT

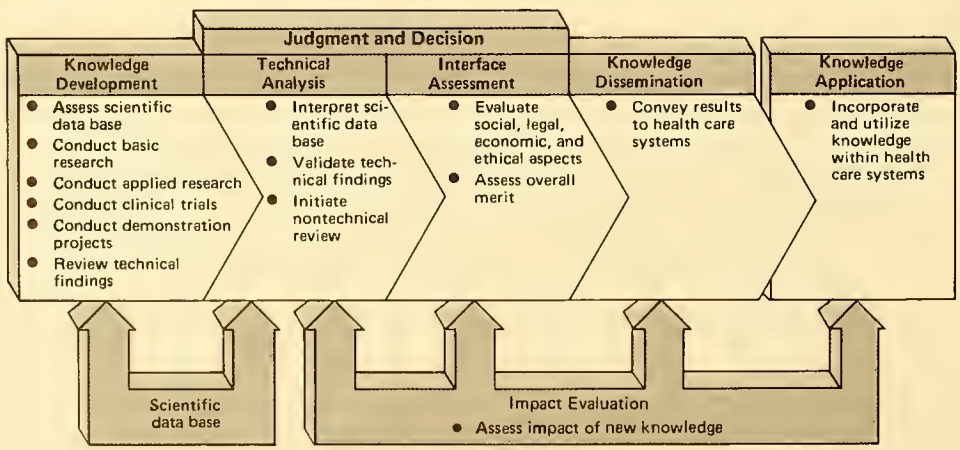


stimulate assessment and rapid dissemination of validated biomedical technologies. The Act states that "The Director of the National Institutes of Health . . . [and other health agencies] shall make available to the Center a listing of all health care technologies of which he is aware that are under development and appear likely to be used in the practice of medicine." The organizational relationship between NIH and the new National Center for Health Care Technology is shown in figure 7.

The legislative and administrative mandate to NHLBI is equally clear. Congress included technology transfer guidelines or mandates within the following four pieces of legislation, which form a comprehensive set of requirements:

- *National Heart, Blood Vessel, Lung, and Blood Act of 1972 (P.L. 94-423)*—This act stipulated technology transfer activities including technology application and evaluation, field testing/evaluation, professional education, and interagency coordination. Senate and House Committees, in considering this Act, concurred on the importance of rapidly disseminating and applying newly developed knowledge and practices. With passage and implementation of this Act, the mandate for NHLBI to expand its technology transfer efforts was clear.

Figure 8.—Technology transfer process



The resulting Institute prevention, education, and control effort has been a response to the legislative emphasis on preventive medicine in particular.

- *Health Research and Health Service Amendments of 1976 (P.L. 94-278)*—These amendments added new technology transfer responsibilities to NHLBI's program in blood diseases and resources. The accompanying bill report reemphasized technology transfer concerns in stating, "It is of utmost importance that the knowledge obtained through the National Heart, Blood Vessel, Lung, and Blood Disease Program be effectively evaluated and demonstrated in the community."
- *Biomedical Research Extension Act of 1977 (P.L. 95-83)*—In hearings, Congress reinforced its statement of interest in technology transfer, particularly disease prevention: "These [NHLBI prevention, education, and control] programs are the primary means of disseminating information to the public and the health professions concerning important factors in the prevention of these diseases . . . these programs should be augmented."
- *Biomedical Research and Research Training Amendments of 1978 (P.L. 95-622)*—These amendments added mandates requiring that dissemination occur "on a timely basis." The Congressional stress on timely distribution of this information was directed at NIH in general and NHLBI in particular. As the House Committee on Interstate and Foreign Commerce itself explained, "These latter words were added in order to emphasize the importance of putting the latest information regarding the nature of heart, blood vessel, lung, and blood diseases and new methods for their treatment into the hands of health professionals and the public as soon as possible."

NHLBI Technology Transfer Process

Though recent events have called increased attention to the issue of technology transfer (including knowledge of medical procedures and therapies as well as instrumentation), NHLBI's programs have long taken technology transfer concerns into account. In the 31 years since its establishment as the National Heart Institute, the Institute has conducted a wide range of technology transfer projects which have been systematically integrated in an overall process that gives coherence and direction to the NHLBI's efforts.

From the Institute's perspective, the technology transfer process involves six interrelated stages. Each of these stages is illustrated in figure 8 and briefly explained in the following narrative.

Knowledge development includes all biomedical, behavioral, and educational research directly related to the Institute's mission. This stage includes basic research, applied research and development, clinical investigations, and clinical trials, as well as the behavioral, motivational, and educational research components of prevention, education, and control programs.

Technical analysis is a process whereby agreement is reached by most of those concerned about the soundness and feasibility of a technology. A technical analysis exercise is intended to assure that the technology or knowledge is ready for general application; that it has been validated for safety and efficacy; and, if not so validated, that the gaps in the knowledge base have been delineated. Points of disagreement as well as agreement must be recognized.

Interface assessment embodies a full consideration of the nonscientific factors involved in moving a new technology into the health care delivery system. These factors can include economic, ethical, legal, regulatory, social, and other issues, as considered by specialists from these fields and the biomedical professions.

Knowledge dissemination is the diffusion of the results of knowledge development, technical analysis, and interface assessment to the health delivery community and to the public, as appropriate, and uses both traditional and newer channels of scientific communication.

Knowledge application is the acceptance, adoption, and appropriate use of validated technologies by the health care community and by the public.

In impact evaluation, the progress of an individual medical technology's movement into the health care system is monitored and evaluated, with attention given to the extent and impact of

its application. The results of this evaluation are fed back to earlier stages to ensure periodic reassessment and revision of the technology as necessary.

It is important to note that movement from one stage of the technology transfer process to the next is guided by scientific progress. It is the gradual accumulation of biomedical information and knowledge which allows development of prevention and treatment approaches.

Each step in the technology transfer process requires the development of additional knowledge, which can be gained only through a painstaking examination of biological processes, interpretation of scientific findings, assessment of the social and methodological feasibility of applying findings, examination of communications channels, and the establishment of appropriate relationships between new technologies and the existing body of biomedical practices.

1979 Technology Transfer Examples

NHLBI has undertaken a number of technology transfer projects during the past year. The following are highlights of NHLBI technology transfer activities undertaken during 1978-1979.

- *Working Group on Hypertension*—This group examined the state of the art in hypertension research and reported on gaps in knowledge of the mechanism of hypertension, areas where greater emphasis should be placed, and promising areas of research which currently receive too little attention. It looked closely at the extent and appropriateness of clinical applications of currently available information. This latter activity is especially important as it is expected that known scientific findings in a number of areas identified can be analyzed to develop specific clinical applications.

- *Scientific Basis of Respiratory Therapy of Hospitalized Patients*—In-hospital respiratory therapy has become a major adjunct to the care provided hospitalized patients. Intermittent positive pressure breathing, physical therapy, and other forms of respiratory therapy are routinely used for most surgical, trauma, and chronic lung patients. Data show that in recent years, over 10 percent of all admitted hospital patients receive inhalation treatment at least once, with an average use of approximately 10 treatments per patient. For 1977 alone, this totals over 20 million treatments of inhalation therapy in the United States. The exponential growth of these therapies has been in the absence of adequate controlled assessments of their efficacy. A 3-day meeting was held to develop technical consensus. Modes of treatment were examined and recommendations for in-hospital respiratory care were made.

- *Management of Pregnancy in Sickle Cell Disease Patients with Hypertransfusion Therapy*—Sickle cell disease is associated with increased maternal morbidity and mortality and fetal loss or diminution as a complication of pregnancy. Historically, regular transfusions have been used in the management of pregnant patients with sickle cell hemoglobinopathies during crises and for severe anemia. The prophylactic use of exchange transfusions in the treatment of patients with sickle cell disease was initiated in 1964. In some medical circles it has gained acceptance, but generally there has been considerable speculation regarding the potential value of this therapy. This exercise was designed to evaluate present modes of therapy for managing patients with sickle cell disease during pregnancy and make recommendations on whether this information is ready for widespread implementation or whether further research studies are needed.

- *Workshop on the Diffusion of Innovative Nutrition Counseling Skills*—The aim of this workshop was to stimulate interest in improving nutrition counseling skills at the level of the local practicing nutritionist/dietitian, physician, or other professional health counselor. The presentation and followup of these workshops has served as a means of reaching local counselors, and the favorable response suggests that the workshops will be used as models for participating organizations to expand the effort.

- *Workshop on Early Hospital Discharge of Patients with Uncomplicated Myocardial Infarction*—The objective of the workshop was to establish a consensus on whether a recommendation for early discharge of patients should be made or whether further investigation of the problem is deemed necessary. Findings of the workshop have been prepared in a report to the Institute.
- *Panel on Coronary Prone (Type A) Behavior*—A multidisciplinary group of distinguished scientists has completed a consensus building exercise, critically reviewing all available research data which relate coronary prone behavior pattern to coronary heart disease. This panel of experts considered the relationship as a whole as well as the state of knowledge in five subareas: (1) evidence for the association of coronary prone behavior pattern and coronary heart disease, (2) assessment of the pattern, (3) physiological mechanisms related to coronary prone behavior, (4) developmental aspects of the behavior, and (5) techniques most likely to be used for intervention or alteration of coronary prone behavior. Further consideration was given to appropriate means for communicating findings concerning interventions to the clinical community.
- *Workshop on Assessment of the State of the Art in Cooley's Anemia Research and Treatment*—These meetings were designed to ascertain the size and distribution of the Cooley's anemia population in the United States; to evaluate resources for delivering care to Cooley's anemia patients; to develop practical standards for optimal clinical services; to study the impact of the disease on patients and their families; and to analyze current research and make recommendations for future research. A report of findings has been prepared and is helping to guide the Institute in planning its future activities. This report made specific recommendations concerning the guidelines for all aspects of treatment and has surveyed current treatment practices in the major centers where patients are seen. Moreover, the report moves into the realm of patient acceptance in that it includes investigation of the social, psychologic, and financial aspects of long-term medical care for Cooley's anemia.
- *Workshop on Voluntary Guidelines for Blood Pressure Measurement Devices*—The purpose was to assist in the consensus building process by developing a scientific, professional, and technical consensus on standards for mechanical and electronic blood pressure measurement devices.

While certain aspects of the discussion of the NHLBI technology transfer process are relatively new, the activities involved have been going on for many years. Throughout this history of activity, NHLBI has been involved in an integrated process that spans the entire range of research efforts and that seeks to derive the maximum benefits from increases in biomedical knowledge.

Future NHLBI Roles

The traditional and more recent mechanisms for technology transfer can help meet current needs but are clearly not sufficient. There remains much work to be done before the theoretical base and practice of technology transfer can be considered fully comprehensive. In the future, the processes already developed will continue to be modified; the roles of all agencies involved, including NHLBI, will consequently be redefined. It is, therefore, essential that some attention be given to the potential roles and responsibilities of the various participants in developing both the theory and the practice of technology transfer.

Definition of Concepts, Terms, and Objectives

As suggested earlier, the concepts behind the practice of technology transfer are being rapidly developed, and are almost as rapidly being revised. Because technology transfer is a developing science, NHLBI feels that ongoing Institute participation is required. NHLBI believes that the Federal research establishment must move toward standard definitions concerning adoption and use of technology as well as means of disseminating information.

To this end, the NHLBI staff is planning a major conference, "Development and Dissemination of Biomedical Innovations: Foundations for Programs," to be held in March 1980. To facilitate the development of effective biomedical innovations, it is important that scientists and policymakers improve their understanding of each of the stages of technical consensus: the origin, development, transfer, diffusion, adoption, and impact of health care technologies. This understanding of the stages of medical care innovation needs to withstand tests of the same analytical rigor applied to the results of scientific research. The planned conferences will consider ways to foster such understanding. The findings of this and related efforts, together with practical experience gained from consensus efforts currently under way, should contribute to a clearer definition of the technology transfer process and a comprehensive understanding of the NHLBI role within that process.

Interaction of New and Traditional NHLBI Technology Transfer Processes

In recent years NIH has designed processes specifically intended to facilitate assessment and dissemination of biomedical technology. These newly developed transfer mechanisms, such as consensus conferences, are an addition to the many traditional activities (publications, meetings, National Library of Medicine manual and computerized bibliographic services) being used. The distinction between newer and more traditional processes must be seen as an opportunity for action.

The question facing NHLBI, then, is how best to encourage cooperation among proponents of the various new and more traditional transfer mechanisms. The central objective is to ensure that the newer efforts complement rather than conflict with traditional mechanisms.

Interaction with Non-NIH Federal Organizations

Concurrent with growing Congressional and public interest in technology transfer, existing Federal organizations outside NIH have been created or expanded. The roles of these organizations will continue to expand, providing an opportunity for NHLBI to work with these groups toward common goals. Since no single Federal organization (including NIH) has expert capability at all phases of the transfer process, interagency cooperation becomes even more essential in moving a technology from basic research to dissemination and application.

In considering the roles of NHLBI and other agencies, NHLBI and NIH realize that a number of questions must be addressed, for example:

- To what degree should NHLBI communicate with each agency? What roles can the Office for Medical Applications of Research and the Office of the Director/National Institutes of Health play to maximize the usefulness of such communication?
- What types of information should be exchanged periodically between NHLBI and other agencies?

Learning from Early Experience

In the recent past, several Federal agencies have developed technology transfer processes, with varying degrees of success. For example, the U.S. Department of Agriculture's Cooperative Extension Service has frequently been cited as a successful technology transfer model. NHLBI believes that the experiences of other agencies should be assessed, so that it can learn from the positive and negative experiences of these agencies. Additionally, it would be useful to observe current programs within other agencies, both to learn from their experiences and to assess opportunities for interagency cooperation.

Expanding Public Information Distribution Capabilities

Another suggestion has been that NHLBI expand the role of its information distribution program. This expanded program could stock and distribute bulk quantities of conference and other meeting reports, research project summaries, and other program documents, much as the NHLBI National High Blood Pressure Education Program currently does.

However, belief in the effectiveness of information clearinghouses is not universal. The trade-offs can be significant, with publication expenditures draining resources from more pressing needs. Also, there is some debate as to whether such information truly reaches the public and medical audiences who need it most. Nevertheless, given that information dissemination and utilization is a primary goal of any technology transfer program, prudent planning and

development of public information programs will be an NHLBI concern in the near future.

Meeting Resource Needs

Congress, NIH, and NHLBI agree that technology transfer should be a major NHLBI goal. Congress has also reemphasized that the fundamental concern of NHLBI is biomedical research. Given the minimal growth in funds appropriated to NIH, however, simultaneous achievement of research progress and technology transfer goals becomes more difficult.

Increasingly, NHLBI must rely on existing program mechanisms to fulfill the technology transfer mandate. Many of these mechanisms were not originally developed for that purpose, but instead were developed to fulfill research objectives. In the coming years, NHLBI must continue to search for ways to adapt its program, and to see if it is possible to selectively incorporate technology transfer capabilities into existing research efforts.

National Program Coordination—The Interagency Technical Committee

In providing leadership for the National Program, the NHLBI has a major responsibility for coordinating those aspects of all Federal biomedical/health programs related to cardiovascular, pulmonary, and blood diseases and blood resources. Almost 50 Federal organizations conduct or support programs related to the national effort that includes basic and applied biomedical research, clinical investigations and clinical trials, health services research and delivery, and health care financing, as well as the evaluation and regulation of these activities. An indication of the nature and extent of Federal participation and support for heart, lung, and blood research in fiscal year 1977 is shown in figures 9 and 10 and table 4. Over 7,500 research projects were federally supported, covering all of the major areas of the Program. Thus, the National Program encompasses not only the research supported by the NHLBI but also the relevant research efforts of other Institutes of NIH, many components of DHEW, and parts of other Federal departments and agencies.

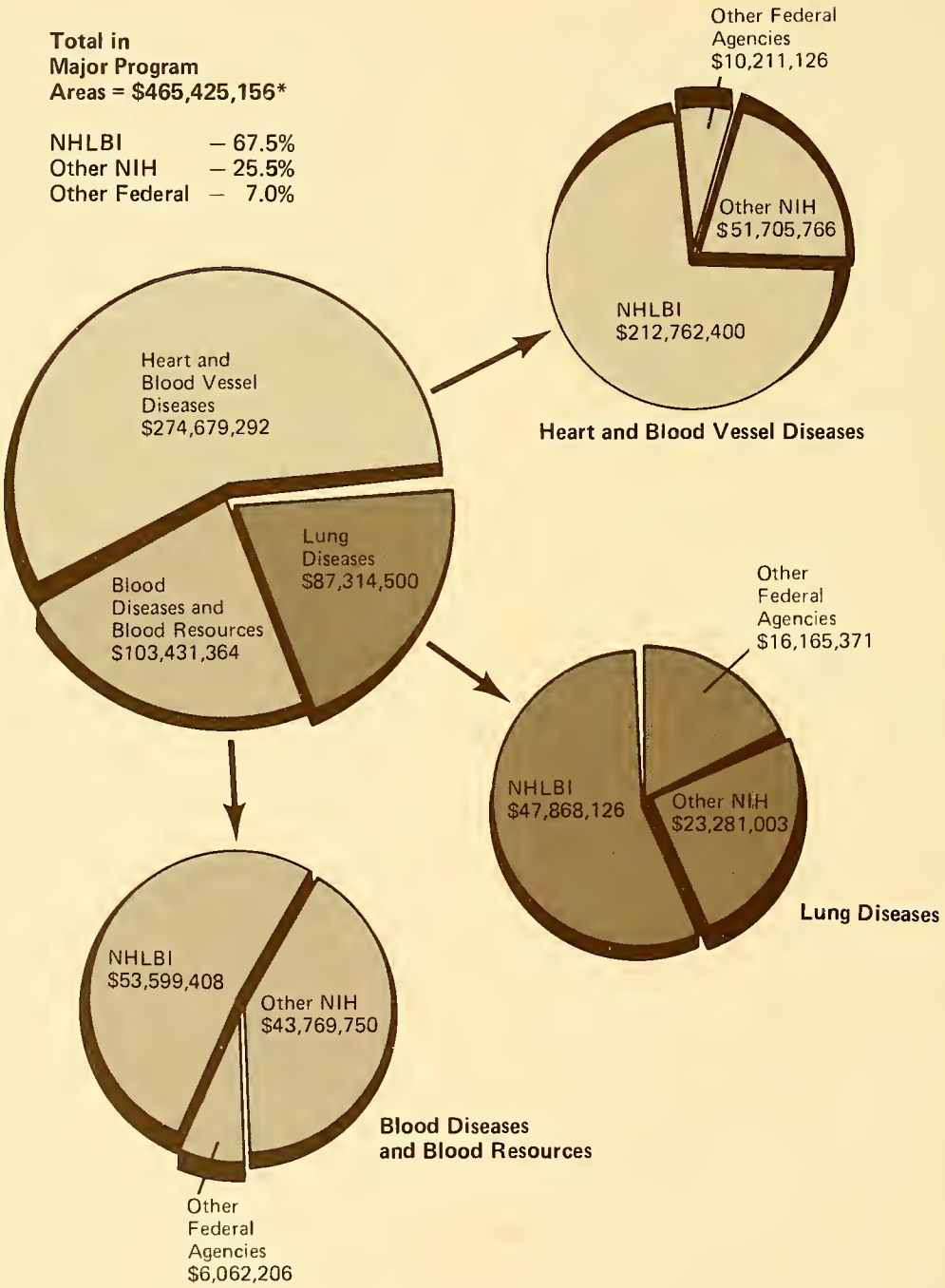
The coordination of this diverse involvement has significant benefits for the Program, as well as for the individual Federal agencies contributing to it. Areas that warrant greater emphasis are identified; the roles of various agencies in pursuing these new thrusts are delineated; unnecessary duplication of effort is minimized; the overall impact of efforts can be assessed from multiple perspectives; and agency planning and program management relative to this area are facilitated. Furthermore, the broad, long-range goals of the National Program provide many opportunities for cooperative/collaborative efforts among these organizations. This allows for efficient utilization of available resources and extension of the Program to encompass many related activities which benefit the missions of both NHLBI and other Federal organizations, and contribute significantly to the achievement of the goals of the Program.

In view of the vastness and complexity of the National Program and the number of agencies involved in supporting related efforts, the NHLBI utilizes a range of formal and informal mechanisms for fostering National Program coordination. One of the most important of these formal mechanisms is the Congressionally mandated Interagency Technical Committee (IATC) on Heart, Blood Vessel, Lung, and Blood Diseases and Blood Resources.

Since its establishment in 1972, the Interagency Technical Committee has evolved into a forum through which interagency cooperation and involvement within the scope of the National Program can be fostered. The membership of the committee, shown in figure 11, currently represents the Federal agencies whose program activities are linked to the National Program. Furthermore, since the activities of the member agencies reflect all phases of the biomedical research spectrum—from basic research to health care delivery and regulation—the IATC is an ideal framework for facilitating functional interaction and collaborative efforts in areas of mutual interest related to the goals of the National Program.

The IATC plays an important role in the coordination of the National Program and supports the achievement of the National Program goals through exchanging programmatic

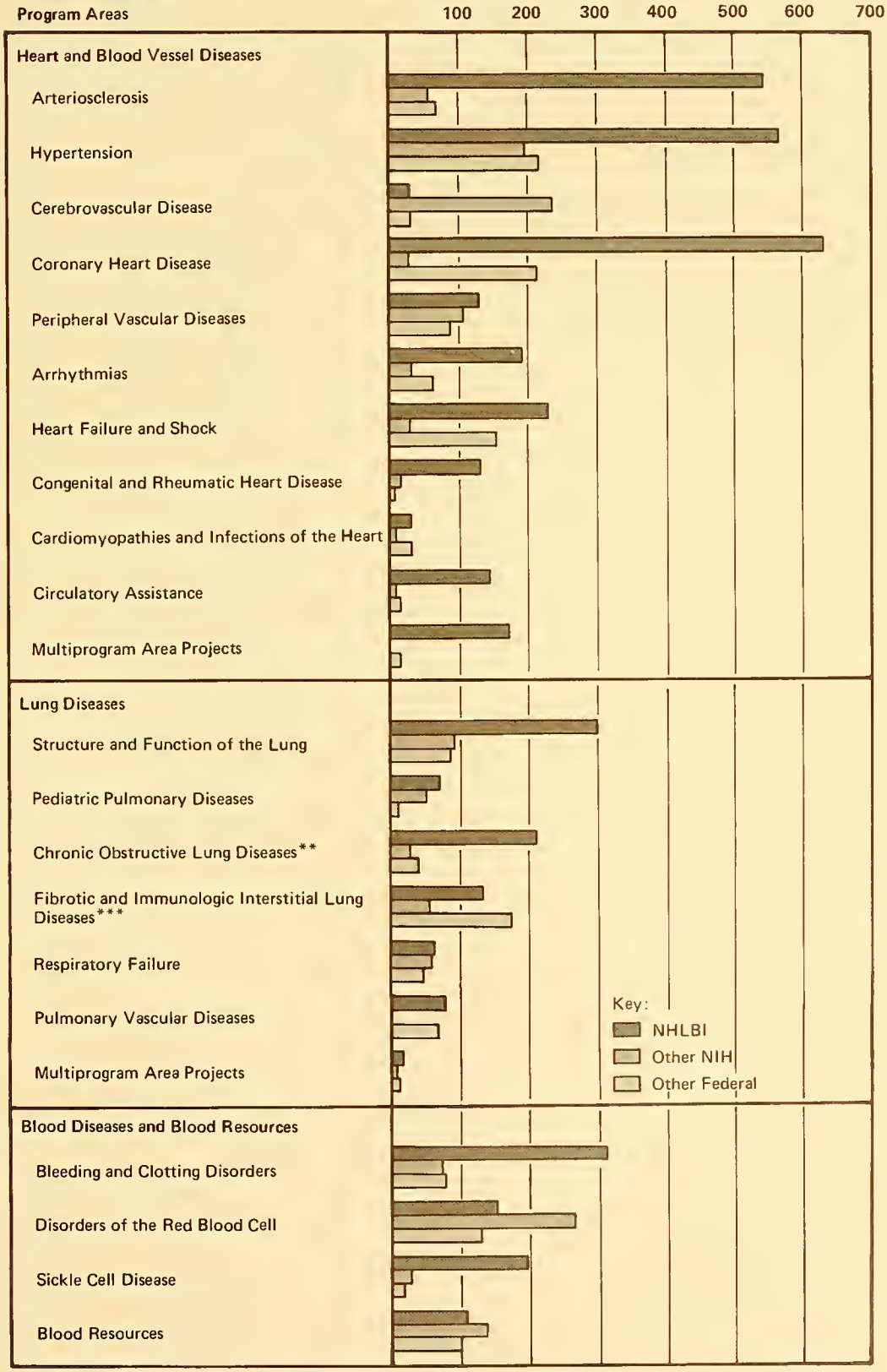
Figure 9.—Distribution of funding (FY 1977) among Federal agencies by major program area



*Total does not include unavailable funding data indicated in table 4.

information, providing technical expertise, and promoting collaboration among its member agencies. To determine the scope of Federal support of research relevant to the National Program and provide a foundation for this interagency forum which promotes information exchange and collaborative efforts, the NHLBI, in conjunction with the IATC, developed an inventory of federally supported activities related to the National Program. The results

Figure 10.—National Heart, Blood Vessel, Lung, and Blood Program: Number of federally funded research projects* in each major program area, FY 1977



*Number of projects in a given program area is not indicative of the funding level.
**Formerly Emphysema and Chronic Bronchitis.
***Formerly Fibrotic and Immunologic Lung Diseases.

of this inventory are presented in the *Index of Federally Supported Programs in Heart, Blood Vessel, Lung, and Blood Disorders—FY 77* (DHEW Publication No. [NIH] 78-1476). The data in that report are being updated as a basis for maintaining an annual review and tracking of the total Federal commitment to facilitate overall coordination of the National Program.

A basic practical function of the IATC is to provide a forum for communication and exchange of necessary information relating to the diverse Federal components of the total National Program. Highlights of particular agency programs and projects are discussed, mutual problems are identified, technical advice is provided, and opportunities for coordination and collaboration are examined.

To promote broad awareness and facilitate the national coordination effort, the data from the inventory, together with information on IATC collaborative efforts were integrated into an NHLBI/IATC report, *Progress Through Coordination: The National Heart, Blood Vessel, Lung, and Blood Program* (DHEW Publication No. [NIH] 78-1475). This report contains descriptions of cooperative and coordinated activities with some 40 Federal organizations. The extent of this coordinated effort against heart, blood vessel, lung, and blood disorders is shown in table 5. Thirteen components of the National Institutes of Health and 12 other agencies within the Department of Health, Education, and Welfare are engaged in projects relating to the National Program. In addition to DHEW, 15 Federal agencies are also involved with

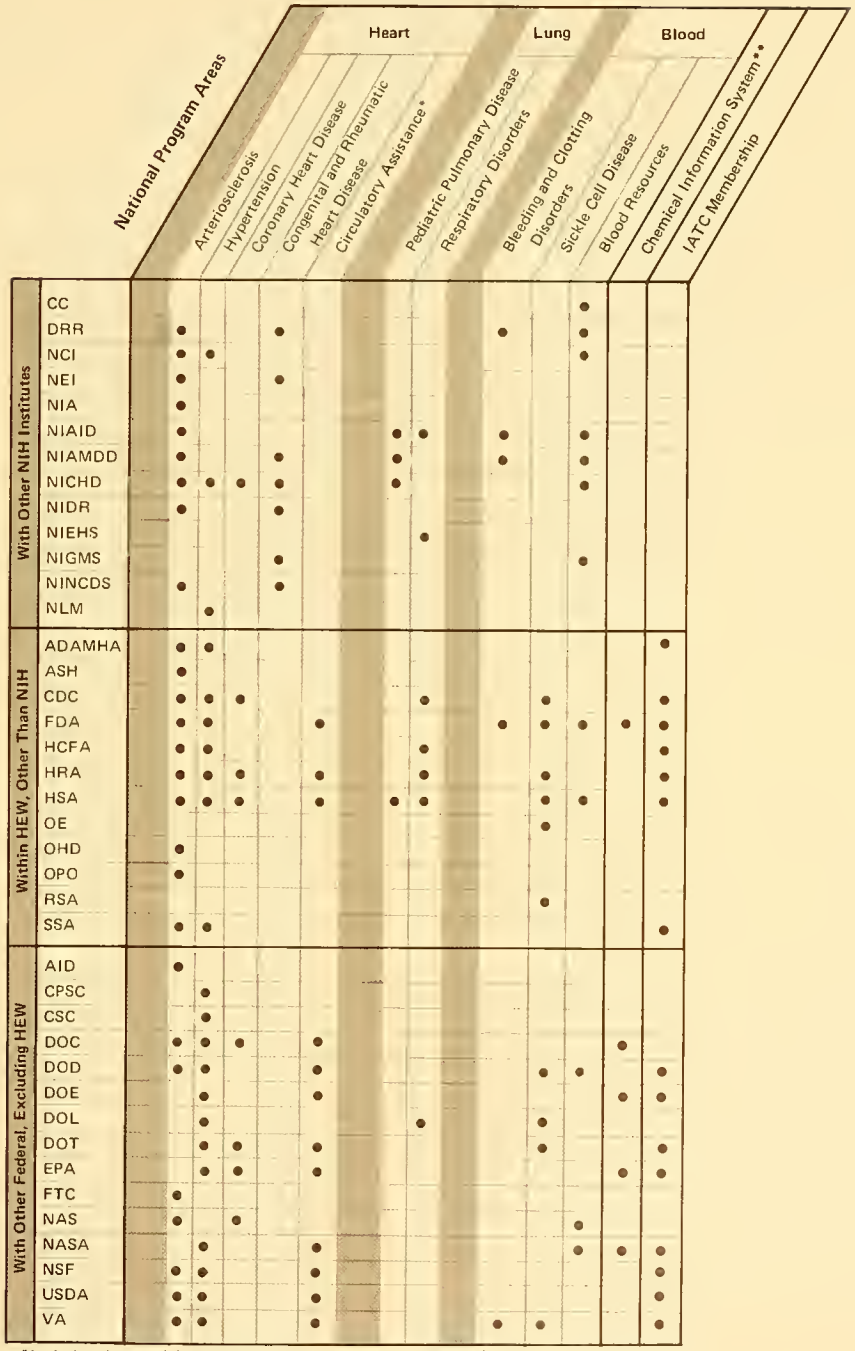
Table 4.—National heart, blood vessel, lung, and blood research program funding, FY 1977

Federal Agencies	Major Program Areas			
	Heart and Blood Vessel Diseases	Lung Diseases	Blood Diseases and Blood Resources	Total
National Heart, Lung, and Blood Institute	$212,762,400	$47,868,126	$ 53,599,408	$314,229,934
Other NIH				
Division of Research Resources	10,792,588	3,723,535*	8,513,074	23,029,197*
National Cancer Institute	326,215	441,770	14,011,941	14,779,926
National Eye Institute	5,306,069	88,799	—	5,394,868
National Institute of Allergy and Infectious Diseases	441,573	2,312,378	2,755,418	5,509,369
National Institute of Arthritis, Metabolism, and Digestive Diseases	11,394,382	1,459,220	12,497,433	25,351,035
National Institute of Child Health and Human Development	3,151,081	5,975,932	1,267,296	10,394,309
National Institute of Dental Research	192,698	—	202,832	395,530
National Institute of Environmental Health Sciences	301,870	7,104,784	556,122	7,962,776
National Institute of General Medical Sciences	6,390,477	1,748,700	3,767,437	11,906,614
National Institute of Neurological and Communicative Disorders and Stroke	12,432,524	387,178	46,342	12,866,044
National Institute on Aging	976,289	38,707	151,855	1,166,851
Total Other NIH	51,705,766	23,281,003	43,769,750	118,756,519
Other Federal				
Alcohol, Drug Abuse, and Mental Health Administration	1,525,758	278,536	345,678	2,149,972
Center for Disease Control	25,835	1,493,144	98,446	1,617,425
Department of Agriculture	**	**	**	**
Department of Commerce	10,000	63,300	—	73,300
Department of Defense	2,740,033	2,597,360	2,105,932	7,443,325
Department of Energy	497,000	4,187,000	1,232,180	5,916,180
Department of the Interior	**	—	—	**
Department of Transportation	—	**	—	**
Environmental Protection Agency	1,547,000	6,643,571	87,479	8,278,050
Food and Drug Administration	—	203,000	700,203	903,203
Health Resources Administration	2,171,544	72,968	130,656	2,375,168
Health Services Administration	274,253	136,466	36,530	447,249
National Aeronautics and Space Administration	325,971	75,000	118,814	519,785
National Science Foundation	1,093,732	415,026	1,206,288	2,715,046
Rehabilitation Services Administration	—	**	—	**
Veterans Administration	**	**	**	**
Total Other Federal	10,211,126	16,165,371	6,062,206	32,438,703
Total Federal	$274,679,292	$87,314,500	$103,431,364	$465,425,156

*Division of Research Resources funding figures estimated for FY 1977.

**Funding data not available.

Table 5. – NHLBI formal collaboration and coordination



*Includes biomaterials and cardiovascular biomedical engineering.
**Intramural program.

ADAMHA – Alcohol, Drug Abuse, and Mental Health Administration
ASH – Office of the Assistant Secretary for Health
AID – Agency for International Development
CC – Clinical Center
CDC – Center for Disease Control
CPSC – Consumer Products Safety Commission
CSC – Civil Service Commission
DOC – Department of Commerce
DOD – Department of Defense
DOE – Department of Energy
DOL – Department of Labor
DOT – Department of Transportation
DRR – Division of Research Resources
EPA – Environmental Protection Agency
FDA – Food and Drug Administration
FTC – Federal Trade Commission
HCFA – Health Care Financing Administration
HRA – Health Resources Administration
HSA – Health Services Administration
NAS – National Academy of Sciences
NASA – National Aeronautics and Space Administration
NCI – National Cancer Institute
NEI – National Eye Institute
NIA – National Institute on Aging
NIAID – National Institute of Allergy and Infectious Diseases
NIAMDD – National Institute of Arthritis, Metabolism, and Digestive Diseases
NICHD – National Institute of Child Health and Human Development
NIDR – National Institute of Dental Research
NIEHS – National Institute of Environmental Health Sciences
NIGMS – National Institute of General Medical Sciences
NINCDS – National Institute of Neurological and Communicative Disorders and Stroke
NLM – National Library of Medicine
NSF – National Science Foundation
OE – Office of Education
OHD – Office of Human Development
OPO – Office of Program Operations
RSA – Rehabilitation Services Administration
SSA – Social Security Administration
USDA – Department of Agriculture
VA – Veterans Administration

NHLBI in interagency projects that relate to several areas of the Program.

To strengthen the coordination and collaboration among Federal agencies concerned with various aspects of heart, blood vessel, lung, and blood disorders, particularly at the programmatic level, categorical working groups of the IATC have been established to address specific issues of importance to the overall program. These working groups are an important mechanism for focusing the combined expertise of various health-related Federal agencies upon specific issues or areas of the Program and fostering the development of collaborative approaches to meeting specific program objectives. The working groups plan and undertake or participate in specific projects of particular significance to the National Program.

The functional relationship between the working groups and the IATC parent committee is shown in figure 12.

The IATC parent committee provides a focal point for communication among member agencies, providing a forum in which a number of issues are addressed, including effects of legislation, identification of new thrusts by member agencies and the relationship to the National Program, identification of areas of mutual interest to member agencies, and development of mechanisms for fostering collaborative efforts. Closely interacting with the parent committee, the categorical working groups translate the general issues and methods that are identified into focused programmatic activities coordinated among group members. In addition, the working groups assure the timely exchange and review of technical and administrative information which facilitates mutual program objectives and helps to minimize undesirable duplication in Federal programs related to heart, blood vessel, lung, and blood diseases and blood resources. Recommendations for implementing new collaborative program initiatives, or for continuing existing coordination, are also developed by each interagency working group and presented to the IATC parent committee. Finally, the Program Impact Analysis Working Group, the evaluation group of the IATC, provides assistance to the other IATC components in assessing the impact of coordinated efforts.

Thus, within the IATC, there is continual development, implementation, and evaluative feedback on activities directed at achieving the objectives of the National Program.

Highlights of IATC Activities

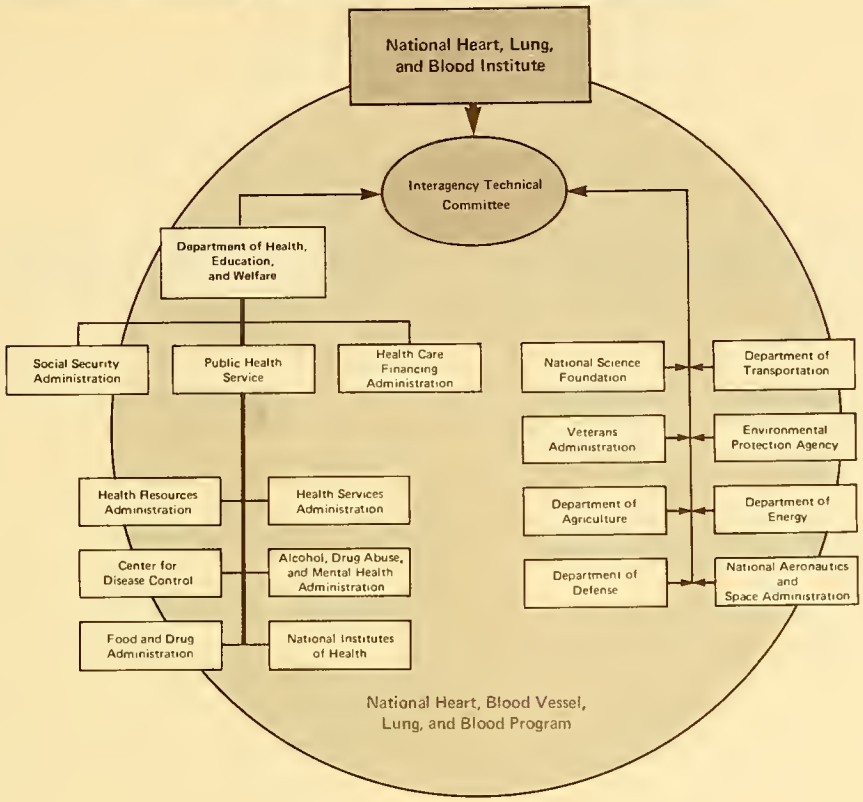
Parent Committee

Over the past year, the parent committee has continued to serve as the forum for identifying legislative changes which may affect activities of member agencies related to the National Program; discussing the relationships among the ongoing and planned activities; reporting on the organizational changes in member agencies and their relationship to pursuit of Program objectives; identifying potential areas of collaboration; and reviewing activities and plans of the working groups. In addition, the timely transfer of biomedical research results into clinical practice, a major concern of the biomedical community and the general public, has become a major theme of the IATC. To initiate efforts related to the knowledge/technology transfer process, the committee has begun to review current concepts and existing or planned approaches of its member agencies. To date, the committee has systematically considered the processes of the National Aeronautics and Space Administration and the NHLBI. As a result of these presentations and discussions on technology transfer, a number of the IATC working groups have begun to formulate plans to explore this area. The parent committee will play an active role in assisting these working groups in pursuing specific efforts related to technology transfer.

Cardiovascular Biomedical Engineering Working Group

In exploring new mechanisms for facilitating cardiovascular device research and development, the Cardiovascular Biomedical Engineering Working Group has begun to focus on particular aspects and problems of device development and transfer. Since the membership of the working group represents Federal organizations responsible for support of research and development, regulatory activities, and health care delivery, the group plays an important role in the technology transfer process by dealing with biomedical engineering issues along the entire biomedical research/development spectrum.

Figure 11.—Federal agencies of the Interagency Technical Committee



Through its next series of meetings, the group will address such issues as means for establishing improved relations between Federal agencies and private research, patent rights in device development, costs of device development and transfer, methods for collecting data on success or failure of devices, and device promulgation. The working group is also considering involvement in development of guidelines and standards for monitoring device development.

Nutrient Composition of Foods Working Group

Under the sponsorship of the IATC working group, a special subgroup was formed to consider issues related to establishment of nutritional priorities of cardiovascular disease. Group memberships included representatives from the working group, other staff from Federal agencies, researchers, medical practitioners, and representatives from food manufacturing. Through a series of meetings, the subgroup focused on refining the philosophy and approaches to determine food and nutrient priorities and utilize this information in programs for the public. The recommendations of this special subgroup may be used by the working group to coordinate the efforts of the member agencies in developing nutritional guidelines related to disease treatment and prevention.

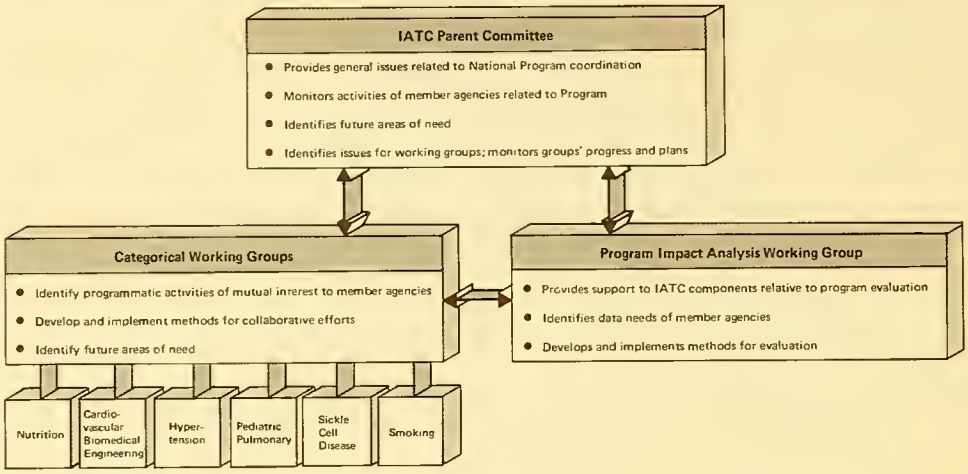
Working Group on Hypertension Control

Under the sponsorship of this working group, a conference on high blood pressure education and control for Federal employees was undertaken. The results and recommendations are presented in a report of the Conference on High Blood Pressure Control in the Federal Work Setting. As a result of the conference recommendations, a number of activities have been initiated by Federal and other public agencies.

The importance of health education was stressed by conference participants, particularly at the level of local health units. NHLBI is assisting in the development, distribution, and promotion of materials. The Office of Personnel Management is now beginning a study of the effectiveness of the program.

The need for community resources for support of employee health units was identified. Through

Figure 12.—Structure and interrelationships of the Interagency Technical Committee



the NHLBI, a directory of high blood pressure units has been compiled. The Institute is currently holding regional seminars and is involved in the development of guidelines for creation of centers.

Program Impact Analysis Working Group

The Program Impact Analysis Working Group serves as a focal point for collaborative efforts within other IATC groups in which assessment tasks are being discussed or planned. In this respect, this group provides advice and assistance in project design and data collection and analysis procedures. In addition, the working group is involved in developing specific evaluation activities which are based on the data and evaluation needs of the member agencies. Currently, the group is formulating future directions which encompass activities related to identifying relevant data bases and sources extant in the Federal Government, identifying data needs of member agencies, and developing means for utilizing available data on cardiovascular and pulmonary diseases, including studies on trends in various risk factors. The working group is also considering various approaches to facilitate the Institute's efforts to assess changes in risk factors and patterns of care thar are associated with the continuing decline in coronary heart disease mortality.

In addition to the ongoing activities of the IATC, as specific areas of significance for interagency collaboration are identified, new working groups are created to focus upon particular issues of concern. One such working group is currently being formed to deal with smoking and heart, lung, and blood diseases. An outgrowth of the NHLBI's new initiatives in this area, this IATC working group is intended to "coordinate aspects of Federal programs which are directed at reducing the morbidity and mortality associated with heart, lung, and blood disease caused or exacerbated by smoking." The working group will work in cooperation with the NHLBI planning group, both to share information and expertise concerning all Federal smoking programs and to make recommendations to the NHLBI for its research, education, and control efforts. The major emphasis of both groups will center on examining existing smoking programs, assessing their activities as they relate to heart, lung, and blood problems, identifying any unmet needs, and pointing out alternatives for future programs. Future programs may take the form of NHLBI initiatives or may be developed as cooperative endeavors between NHLBI and other Federal organizations that specifically focus on smoking and heart, lung, and blood diseases.

The IATC continues to provide an important functional approach to coordination of the National Program efforts. The committee represents a formal mechanism for fostering communication, coordination, and knowledge transfer among NHLBI and other Federal agencies. The IATC also provides a stimulus for other formal and informal collaborative mechanisms, which have been the subject of program coordination in previous reports.

International Programs

The National Heart, Lung, and Blood Institute's international programs represent an endeavor in the best tradition of medicine, which recognizes no national boundaries in the struggle to prevent and relieve human suffering. In the past year, the Institute further expanded its international activities and a series of meetings was held with officials from other countries to explore mutual interests.

During the past year scientists from other nations showed particular interest in joint international activities related to the so-called major cardiovascular risk factors: hypertension, hyperlipidemia, and smoking. "Hypertension Etiology, Treatment, and Prevention" was approved as a new program within the U.S.-U.S.S.R. exchange in cardiovascular diseases. The collaboration was initiated with a joint U.S.-U.S.S.R. symposium on hypertension held in Sochi in June 1978. A joint United States-Federal Republic of Germany memorandum of understanding was signed for collaboration on hypertension and arteriosclerosis. Under this agreement a workshop on hypertension and arteriosclerosis was held in Heidelberg in August 1978, with followup discussions in Bonn among representatives from the three government agencies responsible for relevant health research programs. Representatives from the Federal Republic of Germany have requested U.S. collaboration in developing and sharing data on epidemiological studies and risk factor intervention programs. A joint memorandum of understanding was also negotiated with the Republic of Italy for collaboration on heart disease prevention. Followup planning meetings were held for a joint United States-Italy workshop on cardiovascular risk factors.

In addition, the NHLBI continued collaborative programs with the Soviet Union and formal joint activities in Israel, Yugoslavia, Poland, Great Britain, France, Egypt, and Japan, and with representatives of the World Health Organization. Canadian institutions have participated in the Coronary Artery Surgery Study (CASS) clinical trial and cooperated in the Specialized Centers of Research. The Institute also funded a number of fellowships, contracts, and research grants to investigators in other countries and received visiting scientists from many nations.

U.S.-U.S.S.R. Exchange Program

The largest and most diverse of NHLBI's formal international programs is the U.S.-U.S.S.R. Health Exchange Program. Cooperative activities are carried out under two agreements, the first one in medical science and public health and the second one in artificial heart research and development. The first DHEW-wide agreement includes research in cancer and environmental health as well as several other areas. Seven cardiovascular programs are currently conducted under this agreement. These are:

- Pathogenesis of Arteriosclerosis;
- Management of Ischemic Heart Disease;
- Myocardial Metabolism;
- Congenital Heart Disease;
- Sudden Cardiac Death;
- Blood Transfusion, Blood Components, and Prevention of Hepatitis with Particular Reference to Cardiovascular Surgery; and
- Hypertension Etiology, Treatment, and Prevention.

Heart disease is the principal cause of death in both the Soviet Union and the United States. It is an area of intense public and scientific interest in both countries. In the past year progress was made through the further development of joint areas of research, exchanges of information and data, and publication of papers on joint research. During the past 6 years of cooperation, 339 scientists participated in the U.S.-U.S.S.R. exchanges. More than 100 institutions have participated, and the proceedings of 9 symposia have been published in English and Russian. A total of over 300 scientific reports, abstracts, and related articles on cardiovascular topics have been published under the auspices of the U.S.-U.S.S.R. exchange.

Cooperation with Israel

The Jerusalem Lipid Research Clinic is a component of the NHLBI Lipid Research Clinics Program. It was established in 1975, and during 1978 progress continued in the prevalence study of dyslipidemia and its national history in the Jewish population of Jerusalem.

The study screens 17-year-old men and women when they report for preinduction physicals for the army. Already, important findings have been noted on differences in lipid distribution in the population, dietary differences in fat intake, and comparative data on the national diets in the United States and Israel.

Cooperation with the Republic of Italy

The United States-Italy collaborative effort was initiated during the past year. A series of joint planning meetings has been held and plans call for three types of initial activity: exchange of information on U.S. and Italian studies; translation of documents; and a joint workshop on measurement and control of cardiovascular risk factors.

Cooperation with Poland

Activities under the United States-Poland agreements have included a symposium on cardiovascular diseases and progress on a research agreement for the Polish component of the ongoing European Collaborative Trial in Multifactorial Prevention of Coronary Heart Disease.

Cooperation with Yugoslavia

Under existing agreements, NHLBI scientists have collaborated with their Yugoslavian counterparts in two projects. One is concerned with the epidemiology of cardiovascular diseases and the other with epidemiology of respiratory diseases. Joint review and analysis of the data have continued in the past year. An especially interesting result of the respiratory studies is the discovery of a new antitrypsin gene.

Cooperation with Great Britain

Scientists for the NHLBI Division of Intramural Research have continued their cooperation with British scientists to develop a computer-based chemical information system. Other countries currently cooperating in developing this system include Finland, France, Germany, Holland, Hungary, Japan, Poland, Sweden, Switzerland, the U.S.S.R., and Yugoslavia.

Coordination with the World Health Organization

During 1978 the Director of the NHLBI was appointed advisor to the World Health Organization (WHO) in long-range planning for programs in cardiovascular diseases, and NHLBI staff members have participated in a variety of WHO planning workshops.

Planned Activities

The world problems in cardiovascular, lung, and blood diseases and blood resources are interrelated. Nationally and internationally, there is a new emphasis on the relationships among economic considerations, health status, and health outcomes. The costs and resources required to bring about various levels of improvement in health status by different means, whether scientific, economic, or social in nature, are being compared, as are various systems of delivery for these improvements. The Institute is aware of these concerns and plans to continue ongoing bilateral exchange programs and its collaboration with the World Health Organization in the planning and development of long-range international programs in cardiovascular disease.

Overview of Targeted Activities

Specialized Centers of Research

Specialized Centers of Research (SCOR's) were initiated to provide a planned, coordinated national program of basic and clinical research focusing on the diagnosis, treatment, and prevention of specific diseases. Because of the unusually large adverse impact of arteriosclerosis, hypertension, ischemic heart disease, pulmonary diseases, and thrombosis, NHLBI has given high priority to developing SCOR's to study these problems.

A SCOR is an organizational unit located within a larger institution. This unit draws together a variety of research projects that are related by a central theme. Each SCOR must meet rigid requirements that distinguish it from regular project grants and enhance the focusing of resources, clinical trained manpower, and scientific knowledge.

Each SCOR conducts a planned approach to a particular disease or group of diseases. The SCOR involves a group of established investigators in both basic and clinical sciences with an interest in the particular disease. The investigators have access to sophisticated facilities for clinical investigations and an

appropriate complement of patients for study and long-term followup. The SCOR includes the research laboratories and pathology, data management, biostatistical, and other support needed to study the targeted disease.

In addition to resources, the SCOR provides organizational opportunities to enhance scientific communication. Within the individual SCOR, investigators have opportunities for collaboration both with scientists working in the SCOR and with scientists working in related areas within the host institution. Moreover, each SCOR participates in a continuous process of assessment and interaction internally and with other related SCOR's. This type of organization has improved opportunities for coordinated studies and has provided communication channels that expedite dissemination of research results.

The SCOR program is now in its eighth year and the numerous SCOR accomplishments attest to the value of the program's approach. Some of the recent scientific accomplishments are summarized in the following paragraphs.

Hypertension SCOR's

NHLBI supports four SCOR's that emphasize research in hypertension. In the past year, several noteworthy advances have occurred:

- Genetic studies of twins and half-siblings have provided a means to identify hereditary determinants of blood pressure control while controlling for environmental effects. Preliminary data suggest that suppressed activity of the renin-aldosterone system and low urinary excretion rates for norepinephrine (a hormone which is produced primarily in response to low blood pressure) may be genetically controlled. It has been suggested also that the kidney's ability to handle intravenous salt load may be hereditary. These early observations, while not conclusive, are especially relevant to ongoing studies of factors which increase the risk of developing high blood pressure.

- Increased plasma renin activity has been suspected as a cause of essential hypertension for some time. Kallikrein (an enzyme derived from kidney tissue) is highly active in converting inactive renin into the active form. In fact, kallikrein has recently been found to be more active, by weight, than any other known substance in activating inactive renin. It seems possible that renal kallikrein is a physiologically imporant substance that activates renin in response to various stimuli such as psychologic stress. This is an especially attractive hypothesis considering that kallikrein is located in parts of the kidneys which are adjacent to the site of renin storage and release.

- Research during the past year suggests that impaired metabolism of cortisol (an adrenal hormone) may produce excessive mineralocorteroid activity, which could cause high blood pressure. In the past year it has become apparent that the most consistent of the abnormalities in certain high blood pressure patients is a decrease in the metabolizing of cortisol to cortisone. This is yet another clue in the search for an as-yet-unidentified steroid which might cause high blood pressure in humans.

Arteriosclerosis SCOR's

NHLBI supports eight Arteriosclerosis SCOR's. Current activities center on study of hyperlipidemia and vascular disease. In addition to clinical research they include animal and tissue studies and basic laboratory investigations. Some of the recent accomplishments of Arteriosclerosis SCOR's are summarized below.

- Studies have demonstrated increases in coronary artery atherosclerosis in animals whose plasma cholesterol levels are elevated due to the production of low density lipoproteins (LDL) with an abnormal composition. The molecular mechanisms of this abnormality are being studied by measuring the ability of normal and abnormal LDL to deliver cholesterol to the arterial smooth muscle cells. The abnormal LDL delivers significantly more cholesterol and it would appear that the smooth muscle cells themselves have only a limited ability to regulate the process.

- Studies in African green monkeys indicate that in these animals the absorption of dietary cholesterol is automatically controlled. When fed high cholesterol diets for 100 days, the monkeys displayed

increased cholesterol absorption for 40 days but the absorption decreased dramatically after that point. Understanding how this regulation is accomplished would have considerable potential for controlling diet-induced hypercholesterolemia in man.

- Preliminary investigations have shown that more extensive diet-induced atherosclerosis develops in vasectomized monkeys than in sham-vasectomized control monkeys fed the same diet. The effect is most pronounced in the abdominal aortas, carotid arteries, distal segments of the coronary arteries, and intracranial cerebral arteries. Antisperm antibodies have developed in all the vasectomized monkeys, and complement as well as immunoglobulins have been observed in association with atherosclerosis plaques from some of the animals in the experimental group. This suggests that the immunological response to sperm antigens which often accompanies vasectomy can exacerbate experimentally induced atherosclerosis.

- Recent studies have suggested the possibility that lipoproteins may play a role in inhibiting viral infectivity. All previously described antiviral immune mechanisms of the plasma have depended on the interaction of immunoglobulins with viral antigens. Now, a new mechanism of humoral immunity has been observed. This mechanism is not dependent on immune globulins, and it involves a potent inhibition of infectivity which is attributable to certain lipoproteins. The effect has been demonstrated with the murine xenotropic-C virus. In its infectious form, this virus is coated with lipoprotein. Cells become infected when the viral coat of lipid fuses with the plasma membrane. In animals, the normal resistance to infections of this virus depends on high density lipoproteins. Resistance is attributable to a transferable polypeptide which is bound to the lipoprotein complex. Resistance is increased by fat feeding followed by the appearance of high density lipoproteins as dietary lipidemia subsides. Removal of lipids abolished inhibitory activity.

  Because a number of viruses have lipoprotein coats, it is possible that this mechanism may involve other kinds of viruses in addition to the endogenous C viruses. Even if this mechanism is restricted to the C viruses, the significance of these viruses in cellular biology, and especially in the onset of cancer, suggests that this newly discovered control mechanism may be very important.

- Animal studies have provided interesting observations during the past year concerning high sucrose (sugar) diets. In three monkey species, even in the absence of dietary cholesterol, a high sucrose diet produced an increase in the total amount of cholesterol in the serum. High sucrose diets in the presence of dietary cholesterol resulted in an exceptional increase in total serum cholesterol and low density and high density lipoproteins. In addition, animal studies suggested that there is a link between high blood pressure and an interaction between salt and sucrose. These findings are particularly interesting in light of other studies of diet in children. Data indicate that American children consume large amounts of sucrose, salt, and fat, especially from snack foods. Children are consuming much more salt than adults are, and their sucrose intake is also high. These studies provide a background for considering dietary changes that might help prevent high blood pressure and atherosclerosis.

Ischemic Heart Disease SCOR's

NHLBI supports nine Ischemic Heart Disease SCOR's. Current research in these SCOR's is directed at a variety of issues such as protecting heart tissue during periods of decreased oxygen supply, measuring the extent of heart muscle damage, and testing methods to treat angina pectoris. A number of scientific accomplishments have been made in the past year and some of these are summarized below.

- A new technique using perfused heart tissue from guinea pigs has been used to investigate biochemical markers of ischemia (decreased blood flow). The technique has allowed investigations of the metabolism

of alanine (an amino acid component of heart tissue). Such amino acids are dissolved in the blood following ischemia and tissue damage. Thus measurements of the levels of such amino acids in the blood is a possible means of assessing the extent of damaged heart tissue early after the injury.

- Angiographic infarct size and hemodynamics of isolated left anterior descending occlusion have been evaluated in 170 patients undergoing cardiac catheterization within 30 days of acute infarction. Twenty-two patients had isolated 90 to 100 percent left anterior descending stenosis. In correlating clinical and catheterization findings it was observed that isolated left anterior descending occlusions occur mostly in young men, generally produce large myocardial infarctions, significantly reduce left ventricular ejection fraction when the stenosis is proximal, and are associated with with a high incidence of clinical complications.

- A major advance in radioisotope-labeling of a myosin-specific antibody has brought its application in human imaging closer. Prior imaging studies have employed antibody fragments labeled with isotopes of iodine. These were unsuitable for clinical imaging because of either inappropriate gamma ray energy or excessive radiation dose to the patient. A derivative of the antibody containing the chelating agent DTPA covalently bonded to the protein has now been synthesized. Such antibody derivatives will accept any radionuclide that is a bi- or trivalent cation. Imaging now has been successful with ^{111} indium-labeled antibody. Of particular interest is the application of an antibody carrying a positron-emitting isotope of gallium. Precise three-dimensional reconstructions of infarcts have now been possible utilizing this antibody derivative and the positron camera.

- Aggressive therapeutic intervention in myocardial infarction appears to be both beneficial and safe. Utilizing a natural history study of the evolution of electrocardiographic changes in acute anterior myocardial infarction, it appeared that significant evolution of injury (particularly Q waves) was completed within 4 hours, indicating the importance of early intervention. A study of patients with acute anterior myocardial infarction without cardiogenic shock indicated that a combination of interventions, particularly early balloon counter-pulsation as well as the maximal doses of propranolol and nitroglycerine, resulted in a reversal of the apparent electrocardiographic signs of myocardial injury. It was of great interest that in those patients who did not respond to these interventions, angiographic evidence of fully occluded coronary arteries was obtained, whereas in those who responded well, partial patency remained in arteries perfusing the infarcted segments. In patients with a minimal residual lumen, the intercoronary introduction of propranolol resulted in marked improvement in electrocardiographic signs without apparent global hemodynamic effects.

- An animal model has been developed to simulate sudden death. This model permits assessing regional electrophysiological and biochemical changes *in vivo* with a close association among apparent regional adrenergic activity, the incidence of ventricular fibrillation, and a strongly implicated biochemical mediator, lysophospholipid. This offers promise that an approach to prophylaxis of malignant dysrhythmia and sudden death may be developed.

- Another recent development is the application of positron emission transaxial tomography with ^{11}C-palmitate to measure heart tissue damage. The method produces images of cross-sections of the heart *in vivo* while the heart is beating and has been especially useful in patients with remote myocardial infarction. Since differentiation between depressed metabolism and irreversible injury is possible with this technique, the approach should permit prompt assessment of the extent of myocardium in jeopardy from ischemia as a baseline for assessing the effect of interventions designed to reduce infarct size.

- A study has been completed to reduce the risk of ischemic injury to the myocardium early during cardiac surgery using the cardiac enzyme creatine kinase-MB for the detection of injury. Early in the study it was noted that a significant contribution to risk of injury occurred in the interval between induction of anesthesia and cardiopulmonary bypass. Emphasis was then placed on improving the management of the patient during this interval with the result of decreasing the frequency of myocardial injury. This study has provided a rationale for meaningful assessment of techniques for myocardial protection during cardiac operative procedures.

Pulmonary SCOR's

NHLBI supports 19 SCOR's concerned with the problem of pulmonary disease. In the past year these SCOR's have conducted a variety of basic, applied, and clinical studies. Some of the scientific accomplishments of these projects are described below.

- Many lung diseases are associated with an increase in the permeability of the lung blood vessels, resulting in an accumulation of excess fluid and protein in the lungs. In a sheep model, pulmonary emboli have been used to increase the permeability of the lung capillaries. Infusions of prostaglandin E_1 prevent or reverse the damage to the capillaries in response to emboli. Therefore, prostaglandin E_1 may be potentially useful in the treatment of diseases such as pulmonary embolism that involve an increase in the permeability of lung vessels, a finding which is consistent with the fact that inhibiting prostaglandin synthesis results in an increase in pulmonary vascular permeability.

- Respiratory distress syndrome of the newborn is believed to be caused by deficiency of pulmonary surfactant, the surface active material which lines the alveoli of the lung and prevents collapse due to surface tension. Disaturated phosphatidylcholine, a phospholipid which is the major component of surfactant, is synthesized and secreted by specialized cells in the lung, the alveolar type II cells. The factors which control the secretion of surfactant can be studied directly in isolated type II cells and this paves the way to learning about the mechanism of action of the secretory process in a specific lung cell type. Up to now progress has been hampered because the cellular heterogeneity of the lung prevented differentiating the direct effects of factors on the type II cell itself from effects which might be mediated through other cells.

- It has long been recognized that there is a synergistic effect between cigarette smoking and environmental pollution or toxic dusts inhaled in a work environment. Results from a magnetic detector technique now provide evidence that cigarette smokers have an impaired ability to clear inhaled particles. Inhalation of a harmless trace amount of a magnetic dust and measurement of dust retention with a sensitive magnetic detector provide evidence that clearance of the magnetic dust is considerably slower and much less complete in smokers than in nonsmokers. This impairment in clearance of the magnetic dust suggests impaired clearance in smokers of other dusts such as toxic occupational and urban dusts. The higher retention of these dusts may contribute to the high incidence of lung diseases in smokers.

- Trauma and postsurgery patients are very susceptible to bacterial infections, which can result in pulmonary edema. In unanesthetized sheep given *E. coli* endotoxin, the pulmonary artery pressure increases and the lung capillaries are damaged, causing excessive amounts of fluid and protein to leak from the capillaries and resulting in pulmonary edema. These are similar to the changes that occur in humans with bacterial infection. Sheep treated with indomethacin, an inhibitor of prostaglandin synthesis, do not get an increase in pulmonary artery pressure but appear to have even more damage to the capillaries when given *E. coli* endotoxin. This suggests that some of the prostaglandins produced by the lung in response to endotoxin cause vessels to

constrict, but other prostaglandins may act to limit the capillary damage. This finding is important because there is no drug known which will reverse damage to capillaries once it has occurred. If some prostaglandins can prevent capillary damage, they would be potentially beneficial in treating diseases of the pulmonary vasculature. Histamine has been demonstrated to damage lung capillaries, and has been shown to be released from the lungs when sheep are given endotoxin. If the antihistamine agent diphenhydramine is given before endotoxin, the pulmonary artery pressure increases, but there is less damage to the capillaries. These findings suggest that prostaglandins and antihistamines may be useful in treating patients with pulmonary edema resulting from bacterial infection.

- Sarcoidosis is a disease whose diagnosis as well as pathogenesis have remained an enigma for many years. Despite many studies to establish an etiology, a basic immunologic mechanism operative in the disease, or a reliable *in vitro* diagnostic test, little progress has been made. Preliminary results, however, have recently been reported on a small number of sarcoidosis patients which indicate that all of the patients studied had a significant increase in the number of activated T lymphocytes compared to normal subjects. This would imply that these cells are associated with the disease process, although their presence in the bloodstream may be purely circumstantial. Even though the specific reactivity of these lymphocytes needs to be established in order to define better their role in the disease process, the correlation is nonetheless important since it may provide a simple, quick, and relatively noninvasive method for the diagnosis of sarcoidosis.

Thrombosis SCOR's

NHLBI supports three SCOR's focused on thrombosis. These SCOR's emphasize the study of the fundamental processes of blood clot formation, the development of clotting disorders, and the methods for diagnosis. In 1978, the Thrombosis SCOR's accomplished a number of scientific advances and some examples of these are described below.

- The production of prostaglandins and their derivatives in platelets and cells lining the blood vessels has received considerable attention. Prostacyclin (PGI_2), a potent inhibitor of platelet aggregation, is synthesized in cultured vascular cells primarily from arachidonic acid via endogenous cyclooxygenase activity. However, synthesis from exogenous arachidonic acid can be stimulated by thrombin and other agents which cause platelets to stick to the vessel walls. Therefore, production of thrombin at sites of vascular injury could, by this stimulation, limit the number of platelets involved in the primary hemostatic response and help to localize thrombus formation.

- Studies on the effects of aspirin on platelet cyclooxygenase activity in normal subjects have shown that a very low dose of aspirin should completely inactivate the enzyme. This would inhibit the production of thromboxane A_2, a potent platelet aggregating agent produced in the platelet and thereby inhibit platelet aggregation. Cells from human aorta in culture have been shown to be about 60 times less sensitive to aspirin than platelets. This is good, since the cyclooxygenase system in endothelial cells produce prostacyclin, a protective, *anti*-aggregating agent. A clinical study is currently under way to compare the effects of 160 mg of aspirin/day and of placebos on the platelet aggregation in the arteriovenous shunts of patients undergoing chronic renal dialysis.

- The search continues for a satisfactory, sensitive and specific method of detecting a thrombus (clot) by localization of a radiolabeled protein or cell. Platelets with ^{111} indium-labels have been shown to have an advantage over the ^{51} chromium-labeled platelets for thrombokinetic studies. The usefulness of this method in the detection of thrombi is being evaluated. The proenzyme plasminogen has also been investigated as a clot-localizing agent when labeled with ^{131} iodine or ^{111} indium.

- An instrument has been constructed which can simultaneously measure aggregation, Ca^{++} secretion, oxygen uptake, and pH in a platelet suspension and still allow subsampling. Using this instrument it has been shown that, under select conditions, ATP is consumed to drive both aggregation and secretion. In addition, pyrophosphate is stored in a metabolically inert form in the dense granules, from which it is secreted together with 5-hydroxytriptamine, ATP, ADP, and Ca^{++}. Studies such as these provide useful new information regarding platelet metabolism and how it relates to functional activities.

Clinical Trials

NHLBI has an extensive program of clinical trials dealing with critical issues in the prevention and treatment of heart, lung, and blood diseases. These trials constitute a crucial activity in the biomedical research spectrum and in the process of technology transfer.

The clinical trial is an important step in validating health care technologies. It provides the test of safety and effectiveness of preventive and treatment regimens that should precede their introduction into widespread practice. Clinical trials link clinical research with demonstration, prevention, education, and control activities. In some cases trials are used to determine which of several alternative treatments already in use is the most effective. The trial itself may vary in size from small studies involving only a few patients to large investigations involving thousands of patients and many health care facilities across the country. But in all cases, the clinical trial presents a definitive test, in a human population, of the validity, safety, and effectiveness of a preventive or therapeutic regimen.

Because of the considerable resources required for large-scale clinical trials and the enormous potential impact on medical practice, the decision to undertake a particular clinical trial must be analytical and deliberate. The Institute undertakes a clinical trial only after careful study and detailed planning. In most cases, the trial is part of a logical progression of concepts as they emerge from basic science through clinical research to the points at which large-scale testing is required. At each decision point a number of groups review the progress of the trial and attempt to balance a set of often disparate factors. These decision factors generally fall into four major categories: the *state of the science* related to the trial; the *feasibility* of the effort based on the state of knowledge and available resources; the *potential impact* of the trial on health care and on research; and various *ethical considerations* inherent in the use of human subjects. Through experience the Institute has found that the phased approach to management allows careful consideration of each of these decision factors at stages in the trial at which full resources have not yet been fully committed. Thus, the process allows the changing state of science and the health care system to influence these projects so that they can be formulated to be maximally responsive to the state of knowledge and societal needs.

The results of the NHLBI Coronary Drug Project are an excellent illustration of the benefits that can accrue from a successful clinical trial. This project has brought about a significant change in the medical treatment of coronary heart disease and at the same time has greatly reduced treatment expenditures.

In 1970, clofibrate (a drug used to lower serum cholesterol levels) was being used in the treatment of coronary heart disease. Many clinicians felt that clofibrate was an appropriate treatment for persons who had experienced a heart attack. It was believed that clofibrate therapy would lessen the risk of subsequent heart attacks and the deaths associated with them. In fact, it is estimated that clofibrate was prescribed in nearly 0.9 million patient visits during 1970. Moreover, the drug gained popularity so rapidly that by 1974 clofibrate was prescribed in about 1.8 million patient visits.

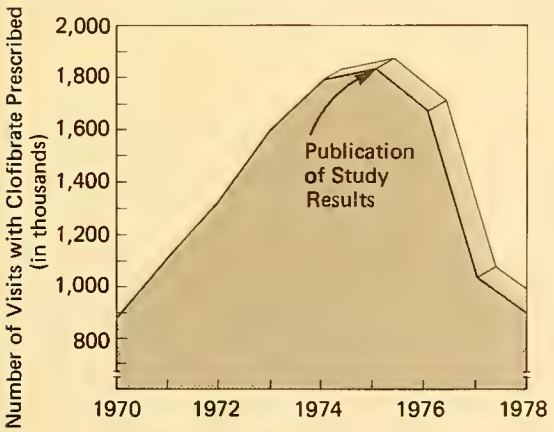
Despite this rapid increase in use, the effectiveness of clofibrate therapy had not been validated through a clinical trial. It had long been known that high serum cholesterol levels were associated with coronary heart disease and increased risk of death. The use of clofibrate was based on the drug's ability to lower serum cholesterol levels. Yet, no clinical trial had definitely demonstrated whether or not clofibrate could prevent coronary heart disease, whether it could prevent new coronary heart disease events

in persons who were already afflicted, or whether the drug was reasonably free of adverse side effects in long-term use.

In 1969, NHLBI undertook a nationwide collaborative clinical trial of clofibrate and several similar drugs. The study found that there is no evidence that clofibrate therapy significantly decreases either overall death rates or coronary heart disease death rates. Over a 5-year period, the study found no significant difference in the death rates for persons who took clofibrate and those who did not. Neither did any subgroup of the study population taking clofibrate show a decreased death rate. Furthermore, a number of undesired side effects were observed in persons taking clofibrate. There was a statistically significant excess incidence of cholelithiasis, thromboembolism, angina pectoris, intermittent claudication, and cardiac arrhythmia in the group taking clofibrate.

In 1975 the Coronary Drug Project concluded that its studies provided no evidence on which to recommend the use of clofibrate to treat persons with coronary heart disease. These conclusions were released and published in that same year and the response of the medical community was almost immediate: The rise in the use of clofibrate leveled off between 1974 and 1975 and began to drop very rapidly thereafter. Between 1975 and 1978, the number of patient visits in which clofibrate was prescribed dropped from 1.8 million to about 0.9 million. (See figure 13.)

Figure 13.—Clofibrate usage: Patient visits to physicians during which clofibrate was prescribed, 1970-1978



The financial savings from this decrease in the use of clofibrate are dramatic. The savings in decreased expenditures for clofibrate in 1 year alone exceed the cost of the entire, nationwide, clinical trial of this and several similar drugs. In 1975 patients spent approximately $91.5 million for clofibrate. By 1978, clofibrate expenditure had dropped to only $43.5 million —an annual cost savings of $48 million.

Table 6 lists NHLBI's ongoing clinical trials and indicates the current status of each. A clinical trial consists of four phases as shown in figure 14. In Phase 0, the trial is conceptualized and preliminary planning takes place; Phase 1 involves the detailed planning of the trial and finalizing the protocol and operational procedures; Phase 2, the actual conduct of the trial, involves patient recruitment, intervention, followup activities, and ongoing analysis of results; Phase 3 encompasses the final analysis of the trial results and their dissemination. The following paragraphs briefly highlight the clinical trials NHLBI currently sponsors.

Division of Heart and Vascular Diseases

The Division of Heart and Vascular Diseases has a number of trials now under way which are aimed at the primary prevention of coronary heart diseases. These clinical trials test the effects of reducing various risk factors. Blood cholesterol reduction is under test in the Lipid Research Clinic's Coronary Primary Prevention Trial (CPPT). It is also under test, along with cigarette smoking reduction and hypertension control, in the Multiple Risk Factor Intervention Trial (MRFIT) for the prevention of coronary heart diseases, which is determining the effectiveness of acting on these risk factors simultaneously. The effectiveness of treating moderate and mild hypertension is under test in the Hypertension Detection and Followup Program in 14 communities. All of these trials have as their objective the reduction of morbidity and/or mortality related to coronary heart disease.

The Institute has several clinical trials related to secondary prevention and therapy for cardiovascular diseases. The Unstable Angina Pectoris Trial has been comparing the effects of medical versus surgical (coronary artery bypass graft) therapy on the survival and quality of life

Table 6.—Ongoing NHLBI clinical trials

	Clinical Trials	Subjects	Status
Division of Heart and Vascular Diseases	Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPPT): Primary prevention of coronary heart disease in hypercholesterolemic patients with the cholesterol lowering drug cholestyramine.	3,810 subjects followed for 7 years at 12 clinics.	Initiated in 1973. Now in Recruitment and Intervention. Phase 2.
	Multiple Risk Factor Intervention Trial (MRFIT): Primary prevention of coronary heart disease by lowering serum cholesterol, reducing blood pressure, and reducing or eliminating cigarette smoking.	12,866 subjects followed for 6 years at 20 clinics.	Initiated in 1972. Now in Recruitment and Intervention. Phase 2.
	Hypertension Detection and Followup Program (HDFP): Evaluation of hypertension control to reduce total mortality.	10,940 subjects followed for at least 5 years at 14 clinics.	Initiated in 1971—Five-Year Intervention phase to be completed in 1979. Results being prepared for publication.
	Unstable Angina Pectoris Trial: Secondary prevention of coronary heart disease by coronary artery bypass surgery or medical management in patients with unstable angina pectoris.	288 subjects followed for at least 5 years at 9 clinics.	Initiated in 1972. Now in Analysis and Dissemination of first-year results, Phase 3. Long-term followup continuing.
	Coronary Artery Surgery Study (CASS): Treatment of coronary heart disease by coronary artery bypass surgery or medical management in patients with stable angina pectoris.	780 subjects have been entered into this randomized trial. Patients will be followed for at least 4 years at 10 clinics. The study also includes a registry of over 23,500 patients also to be followed at least 4 years at 15 clinics.	Initiated in 1973. Now in the followup stage of Phase 2, Recruitment and Intervention.
	Surgical Control of Hyperlipidemias: Prevention of myocardial infarction and death in survivors of myocardial infarction by partial ileal bypass surgery.	Approximately 180 subjects have been recruited into this trial, which has a goal of 1,000 subjects who are to be followed for 5 years at 3 clinics.	Initiated in 1973. Now in Recruitment and Intervention. Phase 2.
	Aspirin Myocardial Infarction Study (AMIS): Prevention of myocardial infarction and death in survivors of myocardial infarction with the drug aspirin.	4,524 subjects to be followed for 3 years at 30 clinics.	Initiated in 1975. Intervention Phase completed. Results being prepared for publication.
	Beta-Blocker Heart Attack Trial (BHAT): Prevention of myocardial infarction and death in survivors of myocardial infarction with the drug propranolol (a beta-blocker).	4,200 subjects are projected and will be followed for up to 4 years at 32 clinics.	Initiated in 1977. Now in Recruitment and Intervention. Phase 2.
	Multicenter Investigation of Limitation of Infarct Size (MILIS): Treatment of myocardial infarction with the drug propranolol or hyaluronidase.	About 1,000 patients will be followed for 6 months in 5 clinics.	Initiated in 1977. Now in Recruitment and Intervention. Phase 2.
	Treatment of Hypertension: Primary prevention of cardiovascular mortality and morbidity by drug treatment of hypertension with chlorothiazide plus *Rauwolfia serpentina*.	389 subjects followed for 7 to 9 years at 6 clinics.	Initiated in 1966. Recruitment and Intervention completed in 1976. Now in Analysis and Dissemination. Phase 3.

Table 6.—Ongoing NHLBI clinical trials (continued)

	Clinical Trials	Subjects	Status
Heart and Vascular (continued)	Management of Patent Ductus in Premature Infants: Comparison of treatment of patent ductus arteriosis with the drug indomethacin, or with surgery, and conventional medical therapy.	540 subjects to be followed for 1 year at 12 clinics.	Initiated in 1978. Now in Recruitment and Intervention. Phase 2.
Division of Lung Diseases	Neonatal Respiratory Distress Syndrome: Primary prevention of neonatal respiratory distress syndrome by administering corticosteroids before birth.	800 subjects to be followed for 3 years in 5 clinics.	Initiated in 1976. Now in Recruitment and Intervention. Phase 2.
	Intermittent Positive Pressure Breathing (IPPB): Treatment of chronic obstructive pulmonary disease with intermittent positive pressure breathing compared with powered nebulizer.	An estimated 1,000 subjects to be followed for 3 years in 5 clinics.	Initiated in 1976. Now in Recruitment and Intervention. Phase 2.
	Nocturnal Oxygen Therapy: Treatment of chronic hypoxic lung disease with nocturnal 12-hour oxygen therapy compared to continuous low-flow oxygen therapy.	300 subjects followed for up to 30 months in 6 clinics.	Initiated in 1966. Now in Recruitment and Intervention. Phase 2.
	Extracorporeal Support for Respiratory Insufficiency (ECMO): Treatment of acute respiratory failure with an extracorporeal membrane oxygenator.	90 subjects were followed for at least 5 days in 9 clinics.	Initiated in 1974. Recruitment and Intervention completed in 1977. Now in Analysis and Dissemination. Phase 3.
Division of Blood Diseases and Resources	Granulocytes Transfusion Study: Primary prevention and treatment of infection in patients undergoing chemotherapy for leukemia.	An estimated 250 subjects to be followed for 3 years in 4 clinics.	Initiated in 1976. Now in Recruitment and Intervention. Phase 2.
	Cooperative Study of Factor VIII Inhibitors: Factor IX treatment of persons with hemophilia A and inhibitors to Factor VIII.	223 subjects followed for varying lengths of time in 10 clinics.	Initiated in 1978. Now in Recruitment and Intervention. Phase 2.
Division of Intramural Research	NHLBI Type II Coronary Intervention Study: Evaluation of lowering cholesterol with the drug cholestyramine in Type II hyperlipidemics in coronary artery disease regression.	143 subjects followed for 5 years at 1 clinic.	Initiated in 1971. Now in the Intervention stage of Phase 2.
	Diffuse Fibrotic Lung Disease: Treatment of idiopathic pulmonary fibrosis by azathioprine versus prednisone.	30 subjects followed for 1 to 3 years in 1 clinic.	Initiated in 1974. Recruitment and Intervention completed in 1978. Now in Analysis and Dissemination. Phase 3.
	Evaluation of Subcutaneous Desferrioxamine as Treatment for Transfusional Hemochromatosis: Treatment of iron-overload with the agent desferrioxamine.	50 to 65 eligible subjects followed for 3 years in 2 clinics.	Initiated in 1973. Now in Recruitment and Intervention. Phase 2.

for patients with unstable angina. The Coronary Artery Surgery Study is a major comparison of coronary artery surgery and medical management in patients with ischemic heart diseases. All patients undergoing coronary angiography in participating institutions are included in the study; particular attention is focused on three rather common subsets of patients with specific clinical and angiographic characteristics, who are invited to participate in randomized allocation to either medical or surgical therapy. Two other studies are concerned with drug therapy for the secondary treatment of cardiovascular diseases. The Aspirin Myocardial Infarction Study (AMIS) is examining the effect of chronic administration of aspirin on morbidity and mortality in postmyocardial infarction patients. The Beta-Blocker Heart Attack Trial (BHAT) is considering the effects of chronic use of beta-blocker drugs in such patients. The mechanisms by which these two drugs act are significantly different. The beta-blocker drug acts on the electrical activity of the heart and the autonomic nervous system; aspirin affects blood platelets and thus possibly affects arteriosclerosis development. The Multicenter Investigation of the Limitation of Infarct Size trial (MILIS) is concerned with limiting the amount of heart muscle irreversibly damaged during acute myocardial infarction and, in this sense, is a trial aimed at improving treatment of cardiovascular diseases.

Division of Lung Diseases

In the Division of Lung Diseases, a primary prevention trial of neonatal respiratory distress syndrome is aimed at newborns, particularly premature infants. The Extracorporeal Membrane Oxygenator Study, which was to determine the efficacy of this mode of treatment, has been completed and the results are now being disseminated. Still other studies in the Division include a comparison of Intermittent Positive Pressure Breathing (IPPB) with the powered nebulizer, and the Nocturnal Oxygen Therapy Study, which compares that treatment to continuous low-flow oxygen therapy in patients with chronic hypoxic lung disease.

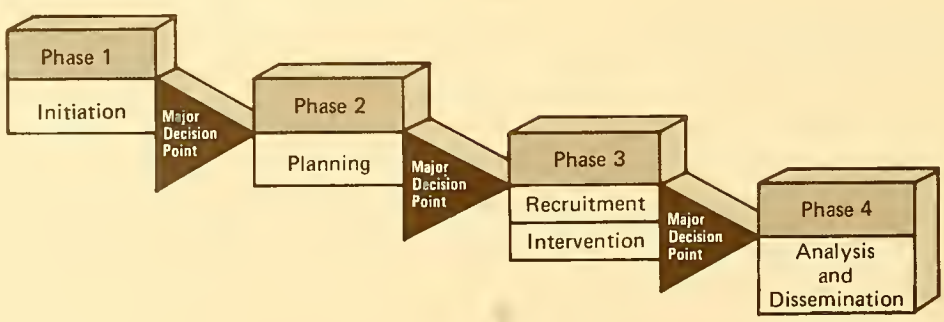
Division of Blood Diseases and Resources

The Division of Blood Diseases and Resources is supporting the prevention- and treatment-oriented Granulocyte Transfusion Study which is testing the prophylactic and therapeutic use of granulocytes to prevent or treat infections in patients with granulocytopenia. The Cooperative Study of Factor VIII Inhibitors, a therapeutic trial, seeks to evaluate the therapeutic value of prothrombin complex concentrates (Factor IX) in patients with hemophilia A who have inhibitors to Factor VIII.

Division of Intramural Research

The Division of Intramural Research is supporting three clinical trials. The NHLBI Type II Coronary Intervention Study is assessing the effect of lowering cholesterol in patients with hypercholesterolemia and angiographically demonstrated coronary disease. It is using angiography to measure regression, thus providing a quantitative endpoint on the regression of atherosclerosis. The Diffuse Fibrotic Lung Disease Study is determining the relative effect of azathioprine and cortisone therapy on interstitial lung diseases. In a trial on the evaluation of chronic chelation therapy for the treatment of transfusional hemosiderosis, thalassemia patients are being treated for iron-overload with desferrioxamine.

Figure 14.—Clinical trial decision process



Research and Demonstration Centers

While the National Heart, Blood Vessel, Lung, and Blood Act of 1972 and the 1976 Amendments authorize 30 research and demonstration centers, funding has become available for only 3 such centers. NHLBI has implemented one center in each of the areas of heart, lung, and blood diseases and resources. These centers are NHLBI's initial response to the 1972 and 1976 mandates authorizing comprehensive centers to provide basic and clinical research, training, and demonstration concerning advanced diagnostic, preventive, and treatment methods.

The research and demonstration centers play a key role in the technology transfer process. They are specifically charged with applying the results of biomedical research to clinical practice. The centers encompass not only the two ends of the research-to-demonstration spectrum, but also the crucial juncture between new validated methodologies and the testing of their feasibility, acceptibility, and amenability to use in existing clinical environments. In this sense the centers perform a vital investigative and educational function without which technology transfer could not proceed at an accelerated pace.

The national research and demonstration center in cardiovascular diseases is particularly concerned with arteriosclerosis and related studies of smoking, nutrition, and hypertension.

The national research and demonstration center for pulmonary diseases works to improve understanding, primary and secondary prevention, and management of respiratory disorders, and the rehabilitation of those disabled by respiratory disease.

The national research and demonstration center in blood resources concentrates on acquiring, analyzing, and processing blood and blood products, in a continuous effort to improve blood services and resource management as well as clinical techniques and patient care.

The research and demonstration center concept has proven a rather successful approach to some of the problems of technology transfer. In particular, the centers provide an interface between laboratory scientists and practicing clinicians. This relationship is not merely an academic one but involves active collaboration and exchange of information which is directed toward resolving specific clinical issues. One important outcome is active participation in a process of mutual education. This education spans the range from laboratory to clinic, from research to provider, to consumer.

Prevention, Education, and Control

Throughout the NHLBI's history, its legislative mandates have emphasized preventive medicine and education for both the health professional and the public. As early as 1948, the National Heart Act authorized research and demonstrations in the causes, prevention, and methods of treatment and diagnosis for heart diseases; and Congress mandated an educational approach through the establishment of an information center, the use of publications, and other activities. Over the past three decades, Congress has reaffirmed its commitment to prevention, education, and control many times and has specifically mandated education programs for scientists, clinicians, and the public. These mandates have specified a cooperative approach in which NHLBI works with other governmental and private health agencies to establish prevention and control programs. More recently, legislation has recognized the important role that education plays in the process of technology transfer through general information dissemination and specific efforts in such areas as nutrition and environmental pollutants.

From its beginnings, NHLBI's responses to these mandates have stressed preventive approaches to the control of heart, lung, and blood disorders. The Institute has focused on both primary prevention, through which diseases can be avoided before they begin, and secondary prevention, through which early diagnosis and treatment can control the serious complications and sometimes devastating sequelae that follow the early stages of disease. Throughout its development, NHLBI has recognized that research results cannot improve the quality of life unless they are widely communicated and applied. NHLBI's program of prevention, education, and control is directed at speeding the transfer of knowledge into the mainstream of clinical medicine and personal health

practices. The programs are aimed at a broad audience including the general public, medical and scientific communities, and members of organized groups such as voluntary agencies, professional educators, media representatives, and state and local governments. NHLBI's programs are multifaceted and involve cooperative endeavors among the various components of the Institute and representatives of governments, charitable organizations, and private industry.

One example of the Institute's commitment to prevention, education, and control activities is the Public Inquiries and Reports Branch, which serves as NHLBI's information office. The branch disseminates information on current research and research results to an audience whose interests lie in all elements of the biomedical research spectrum. Participation in the planning that is essential for timely, effective communication is also part of the branch's responsibility; specialized training for information personnel has been emphasized.

The Public Inquiries and Reports Branch prepares, produces, promotes, distributes, and evaluates NHLBI publications prepared within the Institute and serves as a coordinating point for contractor-prepared NHLBI documents. Formal reports are an important part of that responsibility; however, numerous other types of information products are provided for professional and public consumption. The following is just a small sampling of the branch's recent projects:

- Fact sheets on arteriosclerosis, arrhythmias, and Cooley's anemia;
- Proceedings of symposia and workshops;
- Catalogs and bibliographies;
- Reprints, posters, and brochures;
- Exhibits;
- Press releases;
- Media kits;
- Journal articles; and
- Instruction in cardiopulmonary resuscitation.

Accurate and up-to-date information resources are acquired, maintained, and utilized by the Public Inquiries and Reports Branch. The branch obtains data from a variety of sources such as the Smithsonian Science Information Exchange, medical and scientific journals, and manuscripts provided by intramural and extramural researchers. Attendance at seminars and conferences is part of the branch's information-gathering function. With the best of available knowledge at hand, the staff is equipped to provide technical review and assistance to outside science writers developing stories on NHLBI-supported research, as well as to Institute personnel preparing the branch's own publications.

Significant demonstrations of the Institute's commitment are also found in the programs of the Health Education Branch. Programs of prevention through education for health care providers and consumers are actively seeking to reduce the incidence of heart, lung, and blood disorders. Education activities include workshops and seminars for professionals as well as public outreach programs such as the High Blood Pressure Education Program. Other efforts have been directed at a range of issues from deterring adolescent smoking to improving consumer judgments about food purchase at supermarkets, cafeterias, and vending machines. Highlights of some of the prevention, education, and control projects undertaken during the past year are discussed in section IV of this report.

The Institute's prevention, education, and control programs occupy a critical position in the technology transfer process. They form a vital link between knowledge of improved clinical and personal practices and the application of that knowedge. It is only through education that we can expect to gain observable changes in health status from the investment made in the many forms of research. Without this transfer of knowledge, many of the most promising biomedical discoveries would not find their way to everyday applications.

Training and Manpower Development Programs

Research training is crucial to accomplishment of NHLBI's goals. Educational programs are the most effective means of assuring that there are sufficient numbers of dedicated professionals knowledgeable in the most up-to-date methods of investigation and clinical application. This has become even more critical as the fields related to heart, lung, and blood diseases become even more sophisticated.

In response to this need, Congress has authorized NHLBI to support research and clinical training and instruction in matters relating to the diagnosis, prevention, and treatment of heart, lung, and blood diseases and the use of blood and blood products and the management of blood resources.

In 1979 NHLBI continued its support of research training to the extent that resources permitted. These efforts have been given special staff attention and the total number of trainees supported was 1,394 in 1979. This number is not as large as it may seem when one considers the growth of NHLBI mandates, covering newer and larger areas of investigation, since 1972, when there were 1,369 trainees.

A special problem is the dearth of physician investigators in the training program. Where there were 630 medical doctors in the 1972 training programs, there were only 295 medical doctors in the 1979 programs. This number is a slight increase over 1978, but the problem remains an important one.

The following paragraphs describe particular training awards made during the last year.

Programs and Awards

National Research Service Awards (NRSA). The National Research Service Awards are made for individual postdoctoral fellowships and institutional research training fellowships. Individual NRSA fellowships are awarded to beginning postdoctoral scientists, particularly in research areas where a documented need for trained manpower exists. Institutional research training fellowships are awarded to eligible institutions which in turn select and train postdoctoral and, in special instances, predoctoral candidates in specified research areas.

In the Division of Heart and Vascular Diseases, the broad spectrum of topics relating to heart and vascular diseases is of interest, with special needs in epidemiology, biostatistics, behavioral sciences, population genetics, and nutrition. The broad area of interest in the Division of Lung Diseases includes investigation of the normal and diseased lung and improved methods of prevention, diagnosis, and treatment. The areas of particular interest within the Division of Blood Diseases and Resources include blood resources and blood banking, thrombosis and hemostasis, and red cell disorders, including sickle cell disease and thalassemia.

Minority Biomedical Support Program. Through this cooperative program, which is administered by the NIH Division of Research Resources, the NHLBI encourages research participation by ethnic minority faculty, students, and investigators. The research supported during fiscal year 1979 included such diverse areas as trace metals and their relationship to cardiovascular diseases, stress mediation in hypertension, fatty acid metabolism, red cell structure and function, pharmacology of tissue from the lung, and the toxicity of photochemical reaction products of freons on the respiratory system. NHLBI investment in this program has risen from $113,696 in 1975 to $1,587,081 in 1979.

Minority Access to Research Careers (MARC) Program. This program, which is administered by the National Institute of General Medical Sciences, is designed to train minority scientists and teachers in the biomedical field. Included in this program are the MARC Faculty Fellowship Program, providing advanced research training for minority faculty members of 4-year colleges, universities, and health-professional schools with substantial minority student enrollment, and the MARC Visiting Scientist Award, providing financial support for minority visiting scientists. NHLBI support of MARC has grown from $16,000 in 1977 to $76,626 in 1979.

Minority Hypertension Research Development Summer Program. Initiated in 1976, this program enables minority faculty and graduate students to work in research areas related to hypertension at institutions with demonstrated excellence in that field. The goals of the program are to encourage students to enter research fields related to hypertension and to stimulate faculty members to develop a hypertension program (or a similar program in another biomedical area) when they return to their own institutions. In terms of both the number of faculty and students enrolled and the quality of research achieved, the program has been highly successful. During the past year alone, 40 graduate students and 80 faculty were enrolled in the program at 48 minority research institutions.

Special Emphasis Research Career Awards (SERCA) in Diabetes Mellitus: Cardiovascular, Metabolic, and Endocrinologic Aspects. The first seven awards under this new program were made in 1978, four supported by the NHLBI and three by the National Institute of Arthritis, Metabolism, and Digestive Diseases. SERCA encourages a multidisciplinary approach by enabling individuals to study several fundamental and clinical scientific disciplines important for research in the metabolic, endocrinologic, and cardiovascular aspects of diabetes mellitus.

National Pulmonary Faculty Training. The goal of this program is to strengthen pulmonary medical faculties by training junior faculty members at specialized medical centers. The first recipients were selected for training in 1976, and last year trainees were supported at six national training centers.

Pulmonary Academic Award Program. Interest in this program, which encourages medical students to pursue studies in respiratory medicine and diseases, remains high. A large portion of the program is devoted to providing senior staff for pulmonary disease curriculum development and research, and the program also supports students at 45 medical schools throughout the country.

NHLBI Clinical Investigator Award. The new clinical investigator award program, scheduled to begin in 1980, is intended to encourage newly trained clinicians to develop clinical and basic research interests and skills in the areas of cardiovascular, pulmonary, or blood diseases and blood resources and to increase the pool of physician investigators in these areas.

It is hoped that these awards will provide the opportunity for promising, clinically trained physicians with a commitment to research to develop into independent biomedical research investigators.

The award, made to a suitable institution, will enable candidates to undertake up to 5 years of special study and supervised experience tailored to individual needs with a sponsor (or sponsors) competent to provide research guidance. This award is intended to cover the transition between postdoctoral experience and a career in independent investigation. The clinical investigator award differs from the NIH Research Career Development Award (RCDA) in that it seeks to develop research ability in individuals with a clinical background very early in the candidate's career rather than to promote the further development of research skills of individuals already demonstrating significant research achievement.

Research Career Development Award Program. Initiated by NIH in 1961, this program finances 5-year stipends for individuals who show a high degree of promise for careers of productive research, who typically have at least 3 years of postdoctoral training or research experience, who have demonstrated their capacity for independent research, but who have not yet attained recognition as established investigators. The objective is to enhance the recipients' scientific research careers by freeing them from most of their other academic obligations.

Preventive Cardiology Academic Award. This new award program began in July 1979. By supporting a specialized faculty member in an educational institution, it is intended to:

- Encourage the development of high quality preventive cardiology curricula that will attract outstanding students to preventive cardiology research and medical practice;
- Develop superior faculty who have a major commitment to and possess educational skills for teaching research and practice of preventive cardiology; and
- Develop institutional ability to strengthen continuously the improved preventive cardiology curriculum with local funds subsequent to the award.

Future Prospects and Plans

The NHLBI continually analyzes its training and manpower program to determine and meet critical needs as they arise. Meeting the challenge of the Institute's mission to progress in the prevention and control of cardiovascular, pulmonary, and blood diseases, and in the availability of an adequate and safe blood supply, requires enlarged, flexible manpower and training programs. To this end, the NHLBI has developed plans for a new training program designed to provide extended educational experiences for senior investigators. The program will provide opportunities for established investigators to renew their interests and skills by broadening their areas of concentration and by learning new skills in areas that have opened since the investigators' earlier training.

VI. Resource Allocations

Since 1972, the NHLBI's mandate has expanded in a steady progression. Congress has given the Institute new responsibilities in the areas of:

- Lung diseases
- Blood diseases
- Blood resources
- Sickle cell disease
- Clinical trials
- Research and demonstration centers
- Prevention, education, and control
- High blood pressure education.

Each year NHLBI receives an increasing number of scientifically worthy research proposals that are directly relevant to the Program. Unfortunately, the number of creative and meritorious proposals far exceeds the Institute's ability to fund them. As the continuing record of research accomplishments attests, the Institute has demonstrated its commitment to keeping pace with the rapid progress of scientific knowledge. Nevertheless, the Institute lacks sufficient resources and professional staff to fully implement the National Heart, Blood Vessel, Lung, and Blood Diseases Program.

Fiscal Resources

To carry out its mandated responsibilities, the Institute must have its resources keep pace with both inflation and advances in the sophistication of scientific technologies. In 1972, the year in which the National Heart, Blood Vessel, Lung, and Blood Act was passed, the Institute's obligations amounted to $232.6 million (in actual dollars). By 1980, NHLBI projected appropriations had risen to $527.5 million. In view of inflation expressed in terms of constant 1972 dollars (using the standard cost of living index) this corresponds to only $297 million. However, medical care costs have risen at a rate considerably in excess of the overall cost of living, and this is also reflected in the increasing cost of medical research. Thus, constant dollar power has increased minimally, despite the continuing significant increases in Institute responsibility since 1972.

Even though the Institute's responsibilities have grown steadily, NHLBI's share of overall NIH resources has not increased. The NHLBI percentage of total NIH research funds has remained essentially constant, fluctuating between 16 and 17 percent since 1970.

The Institute's inability to fund many worthy research projects is a major concern. The number of competing research project grant applications submitted and reviewed has grown substantially, from 1,013 in 1970 to 2,245 in 1979 (table 7). Much of this increase can be attributed to the Institute's expanded mandate, but it is also a reflection of the growth in research opportunities. Over these years the number of grants approved for funding has increased as well, but because of the limited funds available, the fraction of approved grants which could actually be awarded has diminished significantly—from 68 percent in 1970, to 43 percent in 1979, to an estimated 25 percent in 1980.

The resources applied to the research project grant program have increased substantially, with direct costs rising from $68.5 million in 1970 to $189.8 million in 1979 (table 8). However, the indirect costs accompanying these grant awards have risen even more steeply—from $18.0 million in 1970 to $73.6 million in 1979.

In any consideration of the Institute's current and planned resource allocations, it should be noted that almost all projects supported by the Institute represent multiyear awards. Thus, in any given year a large fraction of the Institute's budget is required to continue the activities already ongoing and committed. Only a small fraction is available for the competitive renewal of existing projects and the initiation of new activities.

All of these factors constitute serious constraints upon NHLBI program planning and implementation activities and require very careful deliberation among competing priorities. Unfortunately, there are now many approved meritorious research grant applications which the NHLBI cannot support; there are also many important targeted initiatives which the Institute cannot undertake because of the tight competition for the limited new funds.

In summary, the expansion of mandated program responsibilities of the Institute, inflation, the increasing commitment base and number of grant applications, the growth of direct costs necessary for the conduct of research, and the steadily climbing indirect costs all severely limit the capability of the NHLBI to fund an adequate percentage of high priority investigator-initiated projects and maintain program balance.

NHLBI bases its projection of resource needs on a critical review of the state of the science, future research opportunities, and specific estimates of the resources needed to support both ongoing commitments and new initiatives. This critical review involves both scientific and professional assessment of the fiscal resources, personnel, and time required to sustain progress and accomplish National Program objectives.

Resource allocations represent resources needed to carry out the program activities in all areas of the Institute. In accordance with legislative requirements, at least 15 percent of the fiscal resources must be allocated for diseases of the lung, and at least 15 percent are allocated for blood diseases and blood resources.

Although restraint and austerity in many areas of the economy are appropriate, careful expansion of research directed against diseases of the heart, lung, and blood is indicated at this time. Health costs continue to rise alarmingly each year, and they can be controlled only by lessening the need for health care and developing new approaches and techniques that will decrease health care delivery costs.

The rationale behind the projected resource allocations presented in table 9 can be found in great detail in section III, Program Goals and Planned Activities. Projected lowerbound figures are given in table 10. The major issues that this year's projects address are summarized below.

- *Investigator-Initiated Research Program.* The current inflationary economic climate has severely limited the impact of the 1979 research dollar. Every category of the budget, from salaries and supplies to maintenance of apparatus and overhead, has continued to rise and erode available funds. The Institute is committed to a strong investigator-initiated research program. This commitment is reflected in the budget projection in each program area. The NHLBI cannot overemphasize the fact that the cost and

Table 7.—Trends in NHLBI investigator-initiated research: Competing research project grants*

Year	Reviewed	Approved	Total Eligible**	Awarded	Percentage of Eligible Grants Awarded
1970	1,013	624	672	456	68
1971	1,100	718	731	446	61
1972	1,167	773	944	492	52
1973	1,229	933	1,104	426	39
1974	1,501	1,117	1,512	662	44
1975	1,531	1,137	1,444	629	44
1976	1,615	1,192	1,492	707	40
1977	2,180	1,600	1,970	729	37
1978	2,129	1,595	1,985	759	38
1979	2,245	1,695	2,165	942	43

Source: DRG.
*Includes research project grant applications (R01's-types 1, 2, 3, and 9).
**Includes approved but unfunded grants still active from previous year.

Table 8.—Growth of indirect cost rates of research grants,* fiscal years 1972-1979

Fiscal Year	Direct	Indirect	Indirect Cost as a Percentage of Total Cost	Total Cost
1970	$ 68,466,617	$17,986,387	20.8	$ 86,453,004
1971	72,020,575	20,021,425	21.8	92,042,000
1972	81,350,199	25,035,497	23.5	106,385,696
1973	86,539,991	27,674,325	24.2	114,214,316
1974	109,691,890	37,797,863	25.6	147,489,753
1975	101,970,760	36,288,184	26.2	138,258,944
1976	124,915,900	44,436,926	26.4	168,352,826
1977	142,110,745	51,021,715	26.4	193,132,460
1978	157,696,047	59,122,100	27.3	216,818,147
1979 est.	189,771,003	73,584,464	27.9	263,355,467

*Includes regular project grants, program grants, and sickle cell centers. Excludes scientific evaluation, cooperative clinical research, and conference grants, research and development centers, and SCOR's.

number of research grant applications have grown markedly and that the growth in funds available for support has not kept pace. This has prevented the funding of an increasingly large percentage of approved meritorious applications. Table 9 estimates funds needed to meet the increasing research needs.

- *National Research and Demonstration Centers.* The projected budget for research and demonstration centers provides for another major competition in FY 1982. The centers play a vital role in the National Program as a focal point for the transfer of new technologies for improved health care.

- *Prevention, Education, and Control Programs.* New mandates given the Institute to identify cardiovascular risk factors and the effect of their modification on the health of the American public are reflected in the increased projections for prevention, education, and control activities.

- *Construction.* The importance of continued support for research facilities construction has been continually emphasized by the National Heart, Lung, and Blood Advisory Council. Projections for construction dollars in FY 1981 take into account the facility costs required to meet these pressing needs.

Table 9.—Projected resource allocation * for the National Heart, Blood Vessel, Lung and Blood Program, fiscal years 1981-1985 (dollars in millions) **

	1981	1982	1983	1984	1985
Extramural Research Programs					
Heart and Vascular Diseases	$255.0	$275.0	$299.0	$320.0	$348.0
Lung Diseases	67.6	74.0	86.6	95.0	99.6
Blood Diseases and Resources	71.9	79.9	89.5	97.0	103.2
National Research and Demonstration Centers	45.8	50.5	85.0	89.0	94.0
Prevention, Education, and Control Programs	55.0	60.0	65.0	75.0	80.0
Training	50.0	55.0	60.0	65.0	75.0
Construction	35.0	35.0	0	0	0
Total Extramural Research Programs	$580.3	$629.4	$685.1	$741.0	$799.8
Intramural Research	48.0	52.8	60.0	65.0	70.0
Direct Operations and Program Management	44.0	48.0	52.0	56.0	60.0
Total	$672.3	$730.2	$797.1	$862.0	$929.8

Table 10.—Projected lowerbound resource allocation* for the National Heart, Blood Vessel, Lung, and Blood Program, fiscal years 1981-1985 (dollars in millions)**

	1981	1982	1983	1984	1985
Extramural Research Programs					
Heart and Vascular Diseases	$257.9	$265.2	$280.0	$290.9	$310.8
Lung Diseases	66.9	69.6	75.6	83.0	85.6
Blood Diseases and Resources	70.9	74.2	78.9	89.8	93.2
National Research and Demonstration Centers	12.8	14.6	15.8	17.0	18.5
Prevention, Education, and Control Programs	43.9	46.4	48.0	52.0	55.0
Training	40.9	45.0	50.0	55.0	60.0
Construction	0	0	0	0	0
Total Extramural Research Programs	$488.3	$515.0	$548.3	$587.7	$623.1
Intramural Research	46.0	47.5	48.0	49.9	50.9
Direct Operations and Program Management	41.5	43.5	45.0	47.0	48.5
Total	$575.8	$606.0	$641.3	$684.6	$722.5

*These tabulations give the primary thrust of activities, even though the activities generally involve more than one subprogram.
**Based on NHLBI professional estimates.

- *Training.* The increase in training dollars in this year's projections reflects the Institute's commitment to reverse the steady decline in the number of physician investigators during the past 7 years. The Clinical Investigator Award was developed for implementation in FY 1980 to stabilize this downward trend and create a basis for steady increases in the number of new trainees.
- *Intramural Research.* As the NIH Ambulatory Care Facility construction phase nears completion, the intramural research budget projections reflect a moderate increase to sustain the construction activities through their completion. Additional dollars are also projected to meet increased staffing requirements for the intramural programs.

NHLBI Staff Allocation Plan

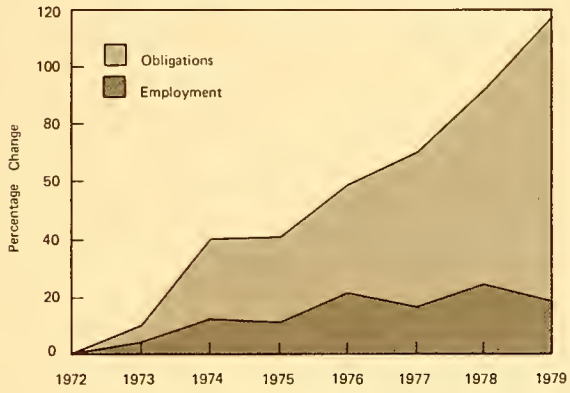
Since the enactment of the Institute's new legislative mandate in 1972, the NHLBI has suffered a personnel shortage. In response to the Act, the Institute has initiated activity in a number of new areas. Many new programs, especially those involving clinical trials and targeted activities, require a high ratio of staff manpower dollars. To operate the National Program effectively, the

NHLBI needs additional staff at both the middle and upper professional levels as well as in support positions. Programs such as disease prevention, control, and education and comprehensive centers are new to the National Institutes of Health. Their direction and administration, as well as review and evaluation, require new staff with knowledge and skills different from those previously available within the Institute. Since these programs require substantially greater staff involvement than do regular grants programs, manpower needs are particularly intense.

To initiate these extensive new programs with the currently available manpower resources, the Institute has conserved manpower in several ways. The Division of Technological Applications was abolished and its activities divided among the three categorical scientific divisions. The review function for programs supported by the grant and contract mechanism were centralized, and a number of top-level personnel took on dual organizational functions. Staff was taken from established ongoing programs to meet new program needs. This latter technique, however, has now exhausted all ongoing program flexibility and has left the Institute staff perilously overextended. Short-term overloading can be tolerated; long-term staff shortages have a serious adverse impact upon both the effectiveness and the cost of programs.

Figure 15 compares the percentage of increase in NHLBI obligations to the percentage of increase in employment between 1972 and 1979.

Figure 15.—Percentage of change in obligations and employment, FY 1972 to 1979



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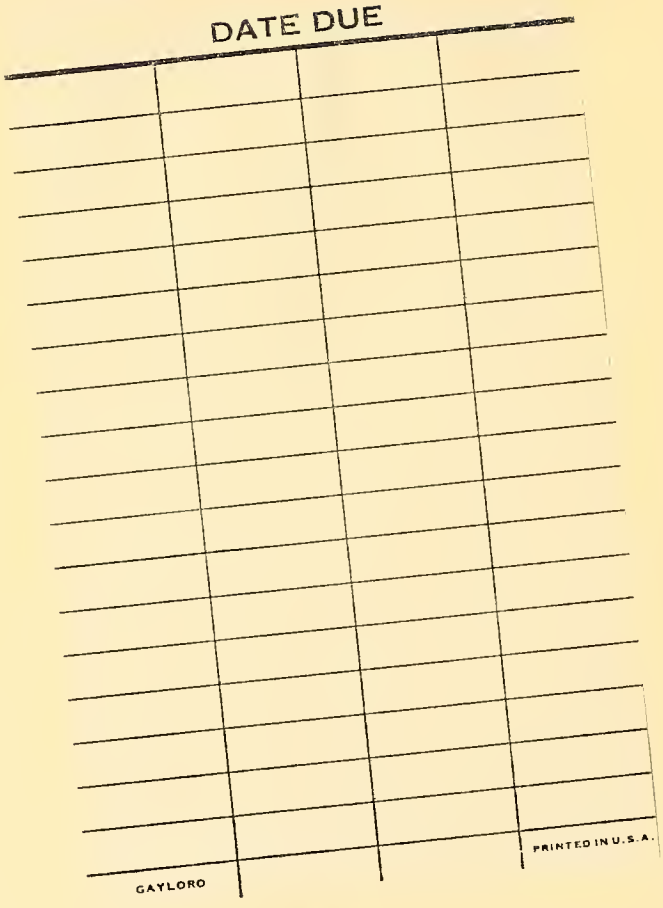

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