Ninth Report of the Director
National Heart, Lung, and Blood Institute
Research Pathways to Modern Medicine

U.S. Department of Health and Human Services
Public Health Service
National Institutes of Health

Crystals of pure cholesterol showing interference colors in the microscope.

Cholesterol, a ubiquitous substance, forms about 0.2% of the total human body weight. As an essential component of the membranes of most cells, it is vital to the normal functions of the heart, lungs, and blood. Abnormal levels of cholesterol in the blood are implicated in the development or modification of such serious pathological conditions as atherosclerosis, coronary heart disease, hypertension, embolus formation, and abnormalities in lung fluids.

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Preface

This volume marks the ninth year since the inception of the National Program Plan to combat diseases of the heart, lungs, and blood. During the past 9 years, there have been remarkable advances toward control of these disorders. Most encouraging of all is the steady decline in deaths from cardiovascular diseases.

Previous Director's reports focused on various component programs of the National Heart, Lung, and Blood Institute—biomedical research and clinical trials, among others. This year, the emphasis is on research pathways to modern medicine. Dramatic advances toward disease prevention and control are engendered through research, as evidenced by the history of progress in the treatment of certain ailments.

In this report, three disease areas are highlighted: hypertension, chronic obstructive pulmonary disease (COPD), and hepatitis. Accounts of progress in these areas show that while research has resulted in significant advances in detection, diagnosis, prevention, and treatment, further study is essential if we are to achieve complete understanding and control of these diseases.

In chapter 3 of this volume, we trace the history of scientific investigations on three diseases: hypertension, chronic obstructive pulmonary disease, and hepatitis. In chapter 4, we describe some of the important accomplishments and new findings achieved in the past year. As is often the case in science, the more we learn about an unsolved problem, the more we recognize what we need to know.

Continued biomedical and applied research, through clinical investigations and trials, and systematic demonstrations of applicable findings are the key to prevention and control of heart, lung, and blood diseases. In my 6 years as Director of the National Heart, Lung, and Blood Institute, I have witnessed an explosion of new and promising achievements in biomedical research. I am confident that substantial gains in reducing the suffering and death due to the diseases that the Institute is responsible for are close at hand, and I have the deepest respect and appreciation for the many talented researchers working on our yet unsolved problems.

Robert I. Levy, M.D.
Director

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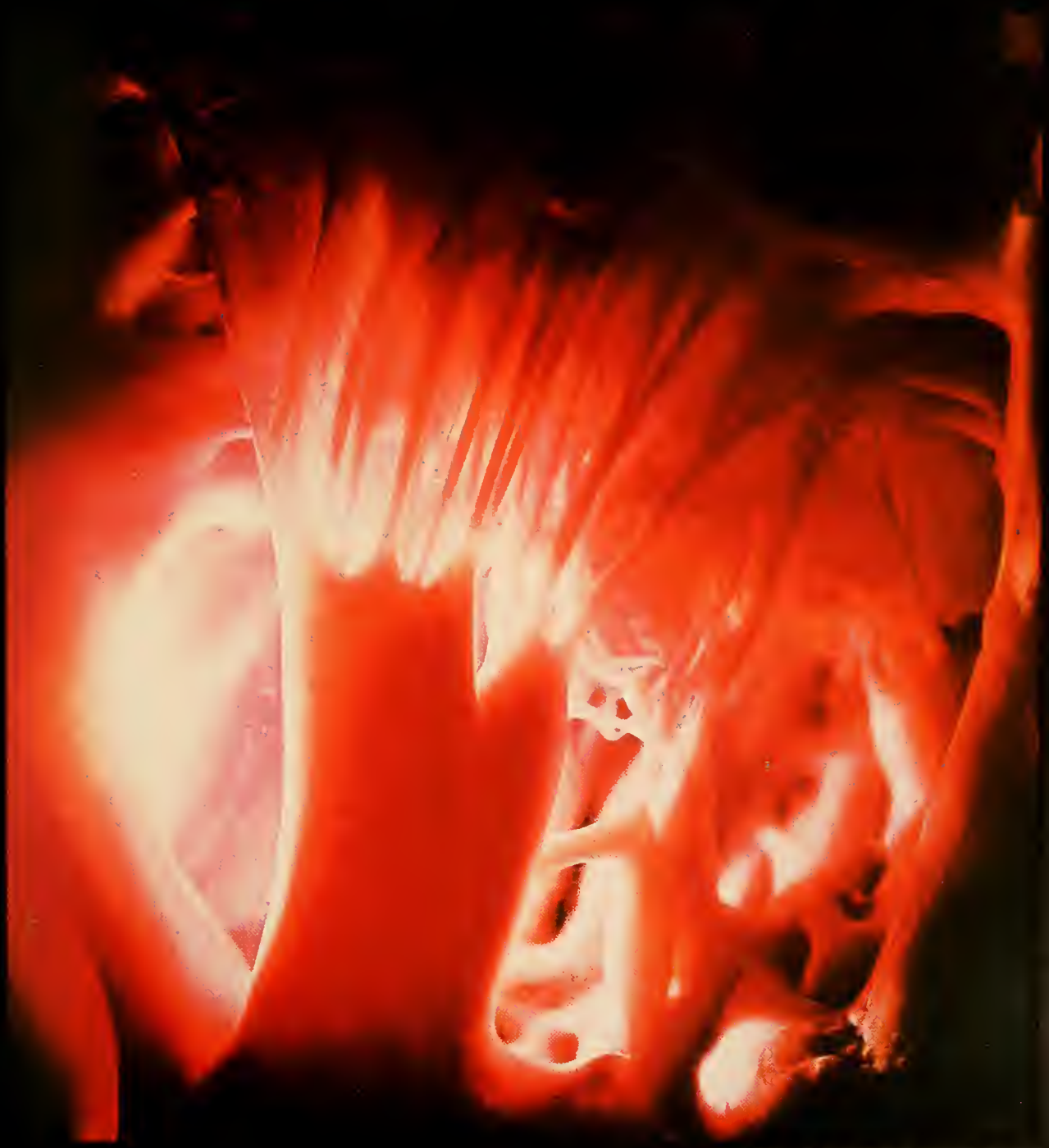
1. Magnitude of the Problem



Stout papillary muscles and inelastic tendons are illuminated for an instant within the right ventricle of the heart.

1. Magnitude of the Problem

At the beginning of this century, for every 100,000 persons living in the United States, there were 195 deaths annually caused by tuberculosis and 202 by influenza and pneumonia. Heart disease accounted for 137 deaths for every 100,000 persons living at that time. Since then, there have been dramatic changes in these statistics. In 1980, deaths caused by tuberculosis amounted to less than 1 per 100,000 living persons, but influenza and pneumonia still claim 24 lives among every 100,000 living persons, and heart disease is the leading killer of Americans. It caused 342 deaths in 1980 for every 100,000 persons.

The leading causes of death in Americans during 1980 by totals, by rates for every 100,000 living persons, and by relevant percentages are listed in table 1. Four of the 10 leading causes of death in the United States continue to be the concern of the National Heart, Lung, and Blood Institute (NHLBI): heart diseases (first), cerebrovascular diseases (third), chronic obstructive pulmonary diseases (fifth), and atherosclerosis (ninth). Together, these heart and lung diseases accounted for over 1 million deaths in 1980—well over half the total deaths for that year.

The Institute is also concerned with pathological conditions in blood, such as arterial thrombosis, itself an integral part of the manifestation of heart attack and stroke. Venous thrombosis, frequently a lethal complication of a broad spectrum of medical and surgical diseases and sedentary living, is a major hazard to a productive life. Indeed, in 1978, more than 56,000 deaths from blood diseases were recorded in the United States; some 640,000 years of potential human lives were lost in the same year from such disorders, with almost 6 million days of hospital stay necessary for those who were affected.

The trend away from infectious diseases toward the present leading causes of mortality is traced in figure 1, which presents the 10 leading causes of death for 1900, 1940, 1960, 1970, and 1978. Despite a significant decline since 1978 in deaths from all cardiovascular disorders and coronary heart disease in particular, heart disease has remained since 1940 the single most deadly illness in the United States, and diseases of the heart, lungs, and blood are still among the Nation's most serious health problems.

Cardiovascular diseases constitute the leading cause of death in the United States for men over age 40 and for women over age 60. These accounted for 30 percent of all the potential years of life lost to illness in 1975. At least 40 million Americans have diseases of the heart and blood vessels. In addition, cardiovascular diseases caused 51 percent of all deaths in 1979. Heart disease, in fact, accounts for more bed days than any other condition. The total economic burden of cardiovascular disorders is estimated to be in excess of $75 billion annually. This amount equals over one-fifth of the total cost of illness in 1980 dollars.

The social and economic toll of diseases of the lungs and respiratory system is equally severe. While these diseases cause fewer deaths than cardiovascular diseases, they can kill earlier in life and account for more than 5 percent of all the potential years of life lost as a result of illness. The total economic costs in 1980 for lung and related respiratory diseases are over $25 billion. This amount is 8 percent of the total cost of illness and 15 percent of all morbidity costs (second only to morbidity costs of cardiovascular diseases).

Since blood diseases frequently strike during childhood, standard economic measures cannot fully reflect the loss or costs in terms of suffering and grief. These diseases, including the hemoglobinopathies, are the cause or complication of a variety of serious disorders. The true impact of disorders of blood is far greater than the mortality attributed to blood diseases. However, blood components as well may also play an important underlying role in other diseases. Death that is attributed to acute superimposed conditions often follows in those who are afflicted with serious chronic blood diseases.

The NHLBI is responsible both for coordinating research in diseases of the heart, blood vessels, lungs, and blood, and for research related to the management and use of the blood resources of the United States. The effects of these diseases on the American population, its resources, and its economy are enormous. Forty million Americans suffer from diseases of the heart and blood vessels, and about 450 of every 100,000 die from these diseases. This number accounted for more than 50 percent of all deaths in 1980. Among the 16 million afflicted with chronic obstructive pulmonary disease (COPD) and asthma, 25 of every 100,000 die. In 1979, some 9,460,000 units of whole blood and packed red cells were used in the United States in the treatment of 2,700,000 patients. In that same

year, additional hundreds of thousands of Americans received one or more of some 20 special products made from human blood. The use of whole blood and packed red cells will continue to increase each year. In addition, more rapid expansion of the use of blood components, factors, and derivatives is to be expected.

The latest figures measuring morbidity and mortality related to diseases of the heart, lungs, and blood are presented in this chapter. Compared with figures for the same areas in earlier years, the data illustrate historical trends in illness and death attributable to these disorders.

Diseases of the Heart and Blood Vessels

Even though heart disease continues to overshadow all other causes of death in the United States, the sharp decline since 1970 in coronary and cerebrovascular disease is encouraging. In figure 2, death rates for cardiovascular diseases are compared with those for other causes of death between 1960 and 1980. While the rate of death from heart disease varies among age groups, coronary disease ranks first as a cause of death among all other disorders of the heart. Among those people between 25 and 44 years old, heart disease deaths have declined to rank third among all causes of death but remain the leading cause of death at ages 45 to 54 (figure 3).

The death rate from stroke is 20 percent higher in men than women, although more women than men die from this disease, but the death rate from heart disease is twice as high in men. Stroke death rates for nonwhites are up to 2.5 times the rates for whites, and death rates from heart disease for white women are half those for nonwhite women (figures 4 and 5).

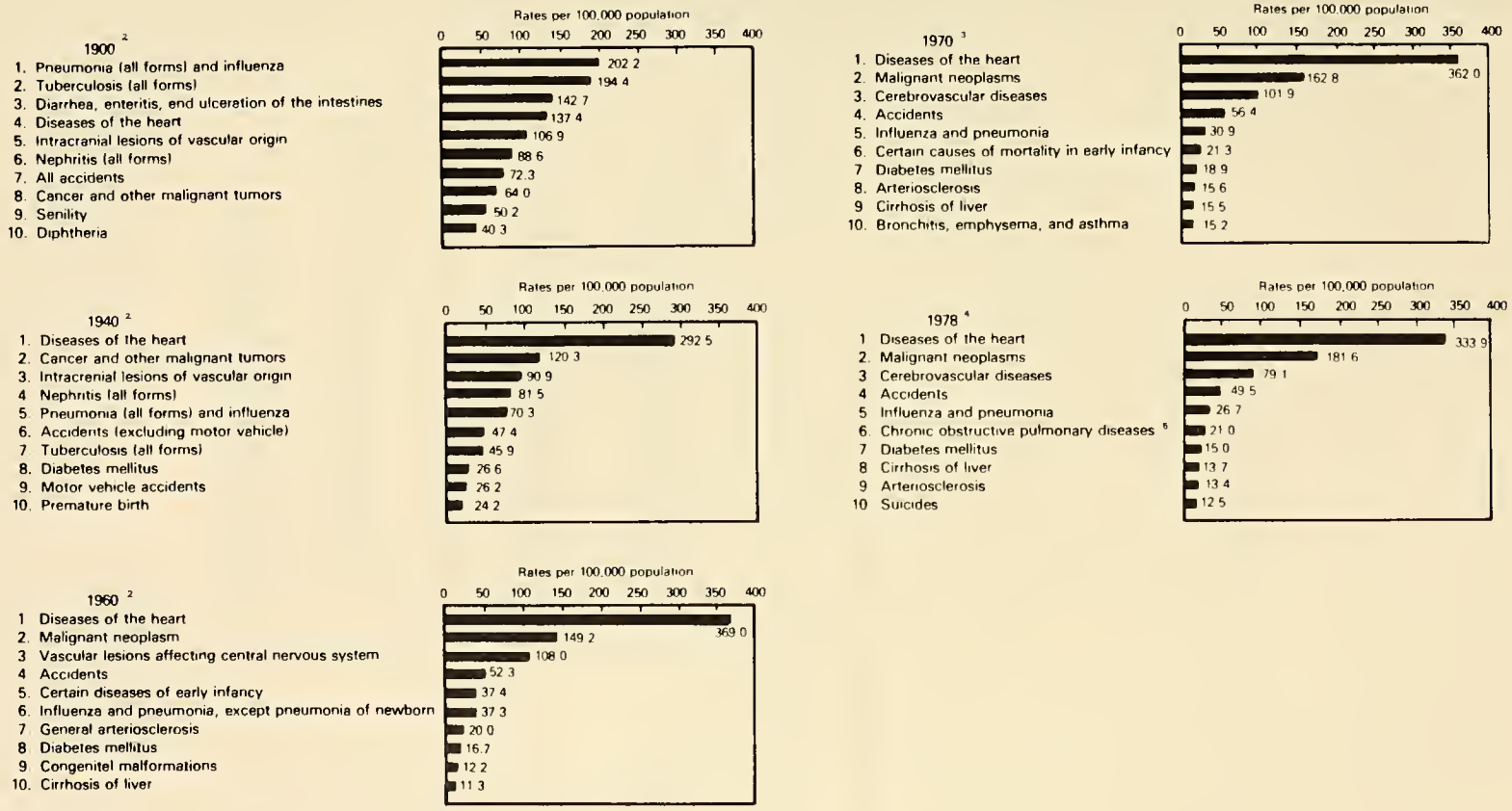
Among the factors that most greatly influence the risk of death from heart disease are age, sex, blood pressure, smoking habits, plasma cholesterol levels, and blood glucose. Diet, physical activity, obesity, water softness, heredity, personality type, and stress also affect the prevalence of death from heart ailments. Individuals who are at high risk from these factors suffer twice as many coronary events (myocardial infarction, coronary death, coronary insufficiency) as others. Recent downward trends in cigarette smoking are an encouraging sign that the prevalence of this risk factor is declining (figures 6 and 7). Smoking in adult men has fallen from 55 percent to 37 percent in recent years, and although teenagers show a similar trend, the concern remains that they are giving up the smoking habit more slowly than is the adult population.

Table 1. Mortality From the Ten Leading Causes of Death, United States, 1980*

Cause of Death	Number of Deaths	Rate per 100,000 Population	Percent
Total	1,986,000	892.6	100.0
1. Heart disease	765,063	34.0	38.4
2. Malignant neoplasms	414,320	186.3	20.9
3. Cerebrovascular diseases	170,420	76.6	8.6
4. Accidents	106,550	47.9	5.4
5. Chronic obstructive pulmonary disease	55,810	25.1	2.8
6. Influenza and pneumonia	52,720	23.7	2.7
7. Diabetes	34,230	15.4	1.7
8. Cirrhosis of the liver	31,330	14.1	1.6
9. Atherosclerosis	29,830	13.4	1.5
10. Suicides	28,290	12.7	1.4
All other causes	299,437	134.4	15.0

*Based on a 10 percent sample of death certificates for the 12 months of 1980. Causes of death were coded to the Ninth Revision of the International Classification of Diseases.

Source: National Center for Health Statistics, *Monthly Vital Statistics Report* 29:13, September 17, 1981.



[1] Terminology is that used in the edition of International List of Causes of Death in effect at that time.

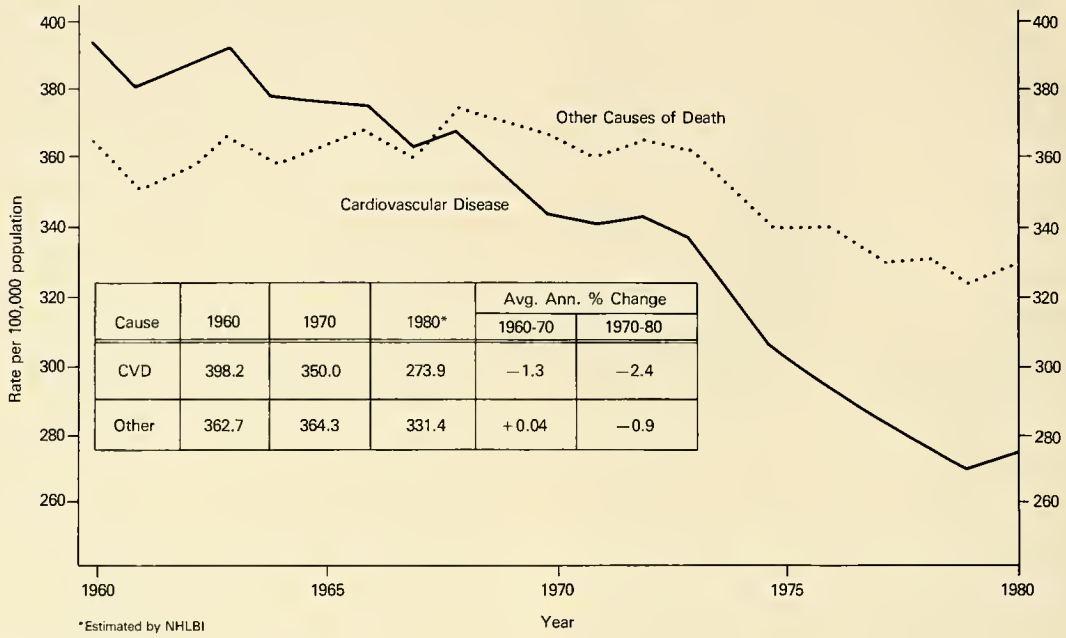
[2] Source: *Vital Statistics Rates in the United States 1900, 1960*. National Center for Health Statistics, PHS Pub. No. 1677.

[3] Source: *Monthly Vital Statistics Report*. Vol. 22, No. 11 (February 22, 1974), NCHS.

[4] Sources: Provisional Statistics, *Monthly Vital Statistics Report*. Vol. 27, No. 13 (August 13, 1979), NCHS and NHLBI Estimates.

[5] This category supplants "bronchitis, emphysema, or asthma" and anticipates the use of "chronic obstructive pulmonary diseases" in the ninth revision of the International Classification of Diseases, because of current increase in use on death certificates of the term "COPD" rather than a specific disease term.

Figure 1. Ten Leading Causes of Death Among Americans in 1900, 1940, 1960, 1970, and 1978[1]



Cause	1960	1970	1980*	Avg. Ann. % Change 1960-70	Avg. Ann. % Change 1970-80
CVD	398.2	350.0	273.9	−1.3	−2.4
Other	362.7	364.3	331.4	+0.04	−0.9

Source: Prepared by NHLBI. Data from the National Center for Health Statistics.

Figure 2. Death Rates for Cardiovascular Diseases and Other Causes of Death,* United States, 1960 to 1980

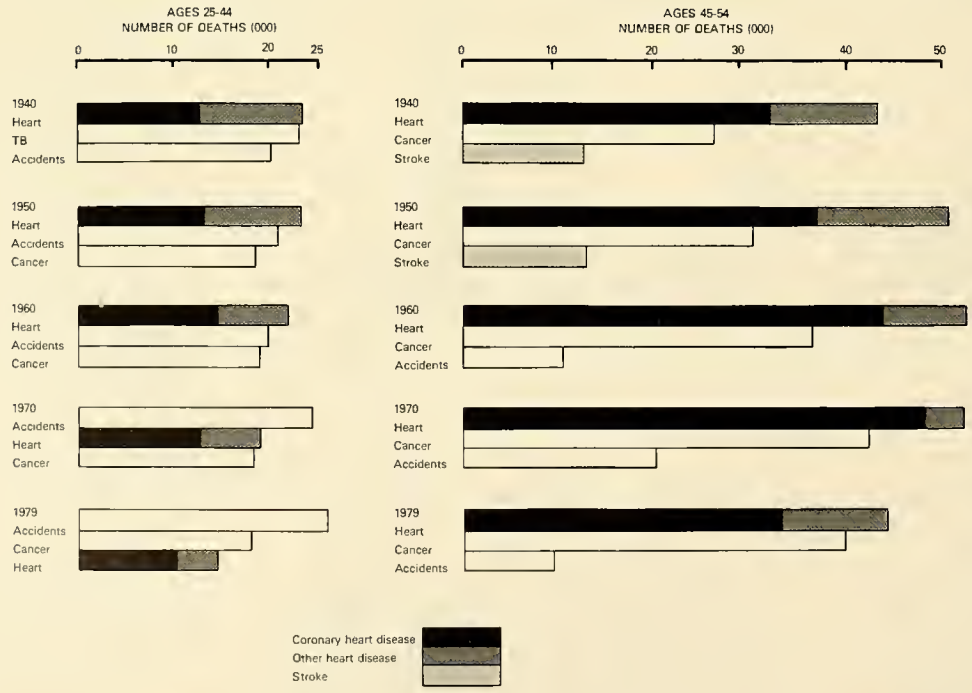
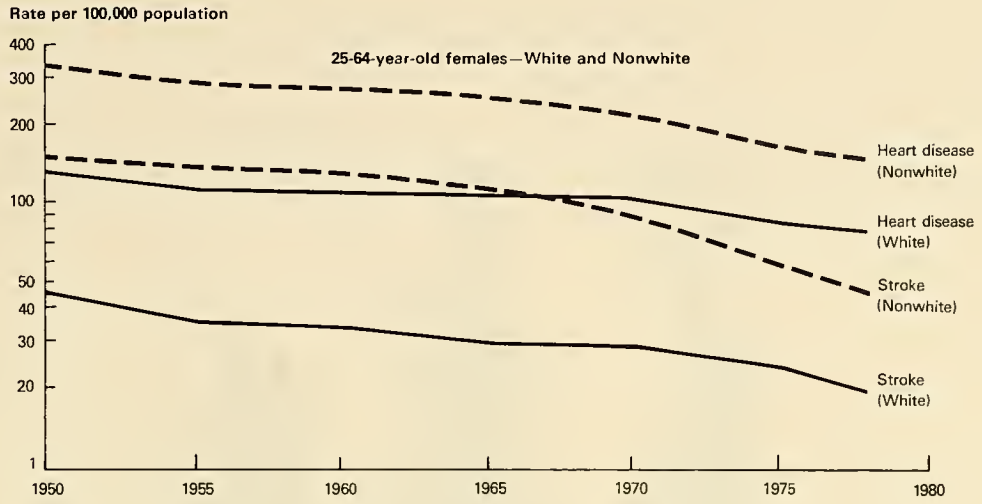


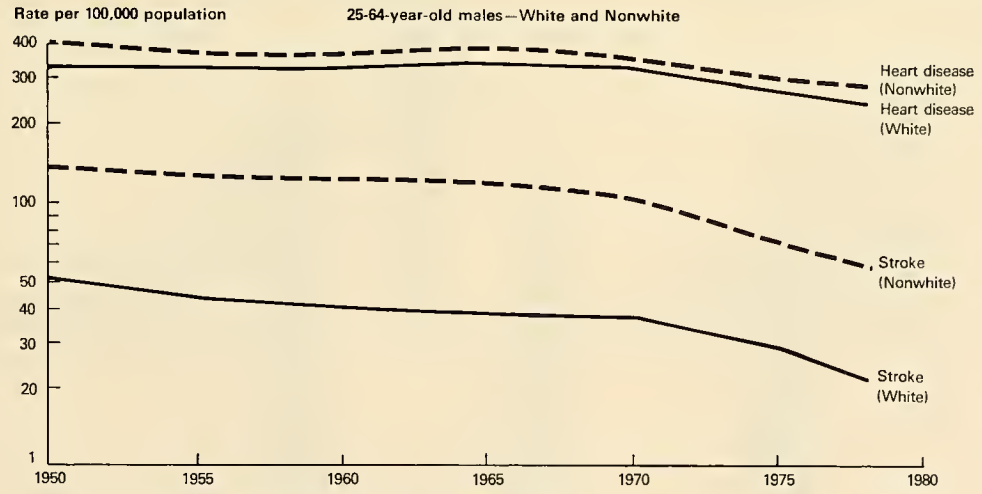
Figure 3. Number of Deaths From the Three Leading Causes of Death (Ages 25 to 44 and 45 to 54) in the United States in 1940, 1950, 1960, 1970, and 1979



Note: The selected years are 1950, 1955, 1960, 1965, 1970, 1975, and 1978.

Sources: NCHS, *Health United States, 1980,* December 1980; NCHS, "Final Mortality Statistics, 1978"; *Monthly Vital Statistics Report* 29(6) Supplement 2: September 17, 1980.

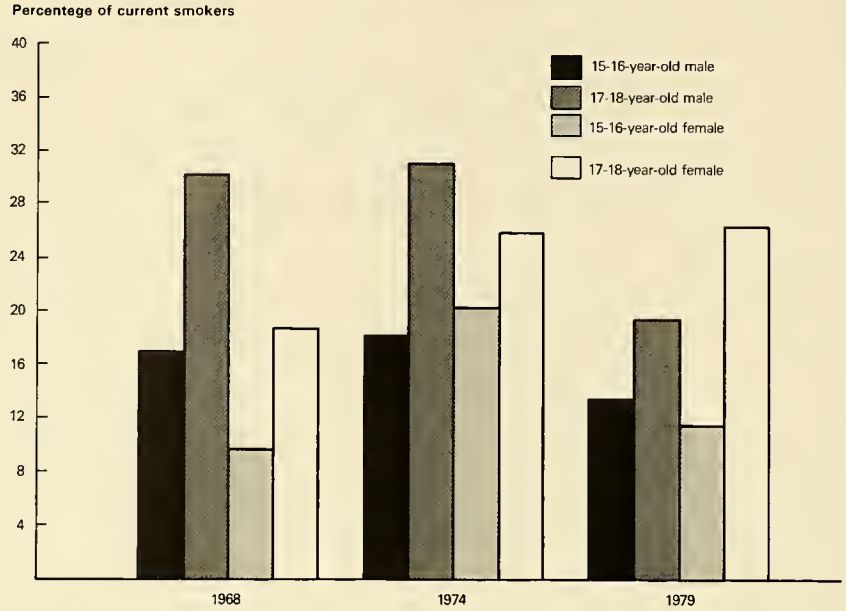
Figure 4. Trends in Death Rates for Heart Disease and Stroke Among Adult Females: Selected Years, 1950 to 1978



Note: The selected years are 1950, 1955, 1960, 1965, 1970, 1975, and 1978.

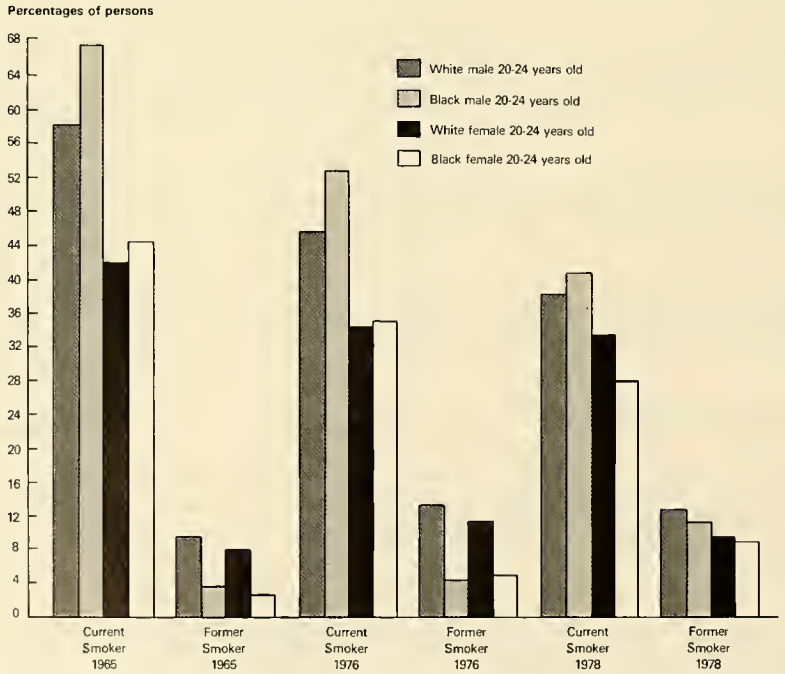
Sources: NCHS, *Health, United States, 1980,* December 1980; NCHS, "Final Mortality Statistics, 1978"; *Monthly Vital Statistics Report* 29(6) Supplement 2: September 17, 1980.

Figure 5. Trends in Death Rates for Heart Disease and Stroke Among Adult Males: Selected Years, 1950 to 1978



Sources: National Clearinghouse for Smoking and Health: Patterns and Prevalence of Teenage Cigarette Smoking 1968, 1970, 1972, and 1974; DHEW, Health Services and Mental Health Administration; DHEW, National Institute of Education: unpublished data.

Figure 6. Cigarette Smoking Among Teenagers, by Age and Sex: 1968, 1974, and 1979



Sources: Data from the Health Interview Survey. Division of Health Interview Statistics, National Center for Health Statistics (NCHS).

Figure 7. Cigarette Smoking Among Young Adults, by Age and Sex: 1965, 1976, and 1978

The data presented in figure 8 differentiate among stroke, other cardiovascular diseases, and coronary disease, and they designate percentages of total deaths from these and other causes for 1970 and 1980. The increase in percentage of deaths from cancer is mainly the result of the decreases in heart disease and of deaths from other causes, except for deaths from chronic obstructive pulmonary disease. The actual cancer death rates for 1970 and 1980 are 129.9 and 135.4 per 100,000.

Morbidity from heart and vascular diseases also places a great strain on our society. Table 2 gives data for the number of discharges from and days spent in hospitals resulting from different cardiovascular diseases. Total ambulatory visits to physicians' offices for this group of diseases was over 49 million in 1979 (table 3). A comparison of direct and indirect costs of medical care by disease categories shows circulatory diseases producing the largest proportion of the burden in the country (table 4).

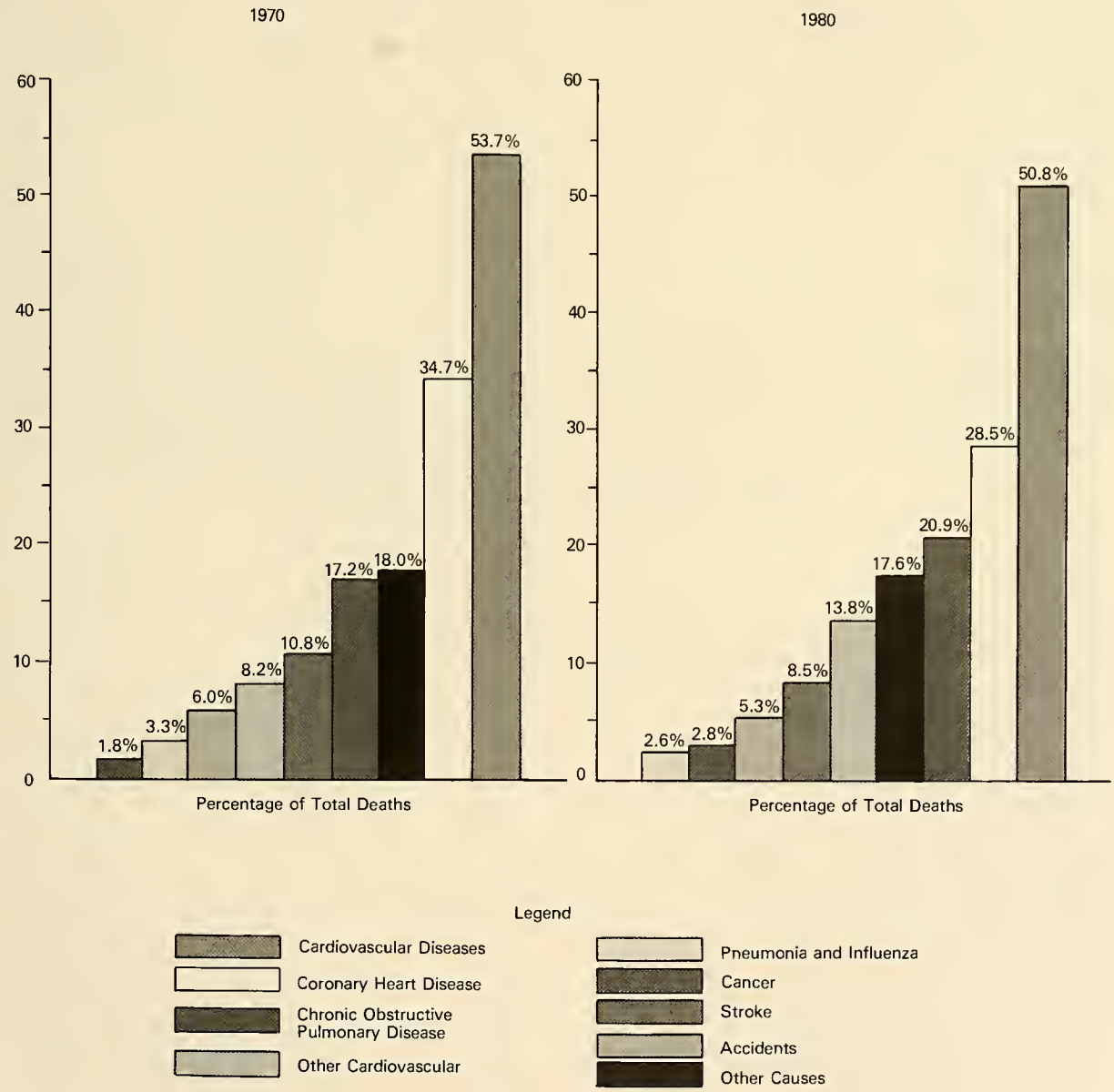


Figure 8. Deaths by Cause and Percentage of Total Deaths, 1970 and 1980

Table 2. Number of Hospital Discharges and Days for Patients With Cardiovascular Diseases, United States, 1979

First-listed Diagnosis and ICDA Code	Number of Discharges (000)	Average Length of Stay in Days	Number of Days (000)
Total cardiovascular 390-398, 401-405, 410, 411, 413, 414, 420-429, 430-438, 440-459, 746, 747	4,851	9.8	47,572
Rheumatic fever and rheumatic heart disease 390-398	66	9.1	600
Acute myocardial infarction 410	433	12.6	5,457
Other ischemic heart disease 411, 413, 414	1,280	8.6	11,008
Hypertensive disease 401-405	454	7.7	3,506
Cerebrovascular disease 401-405	746	12.4	9,226
Congenital heart disease 745, 746, 747	57	7.7	437
Other cardiovascular diseases 420-429, 440-459	1,815	9.6	17,338

Source: Unpublished data from the National Hospital Discharge Survey, National Center for Health Statistics (NCHS).

Table 3. Number of Physician Office Visits for Diseases of the Circulatory System and for Selected Principal Diagnoses, United States, 1979

Diagnosis and ICDA Code	Number of Visits (000)
Rheumatic fever and rheumatic heart disease 390-398	504
Hypertensive disease 400-404	25,535
Essential benign hypertension 401	23,607
Ischemic heart disease 410-413	3,275
Acute MI and other acute IHD 410-411	1,189
Chronic IHD 412	646
Angina pectoris 413	1,440
Other forms of heart disease 420-429	5,406
Symptomatic heart disease 427	1,822
Cerebrovascular disease 430-438	1,770
Diseases of arteries, arterioles, capillaries 440-448	2,290
Arteriosclerosis 440	952
Diseases of veins and other circulatory 450-458	3,985
Phlebitis and thrombophlebitides 451	963
Varicose veins of lower extremities 454	724
Hemorrhoids 455	1,907
Total circulatory 390-458	49,607

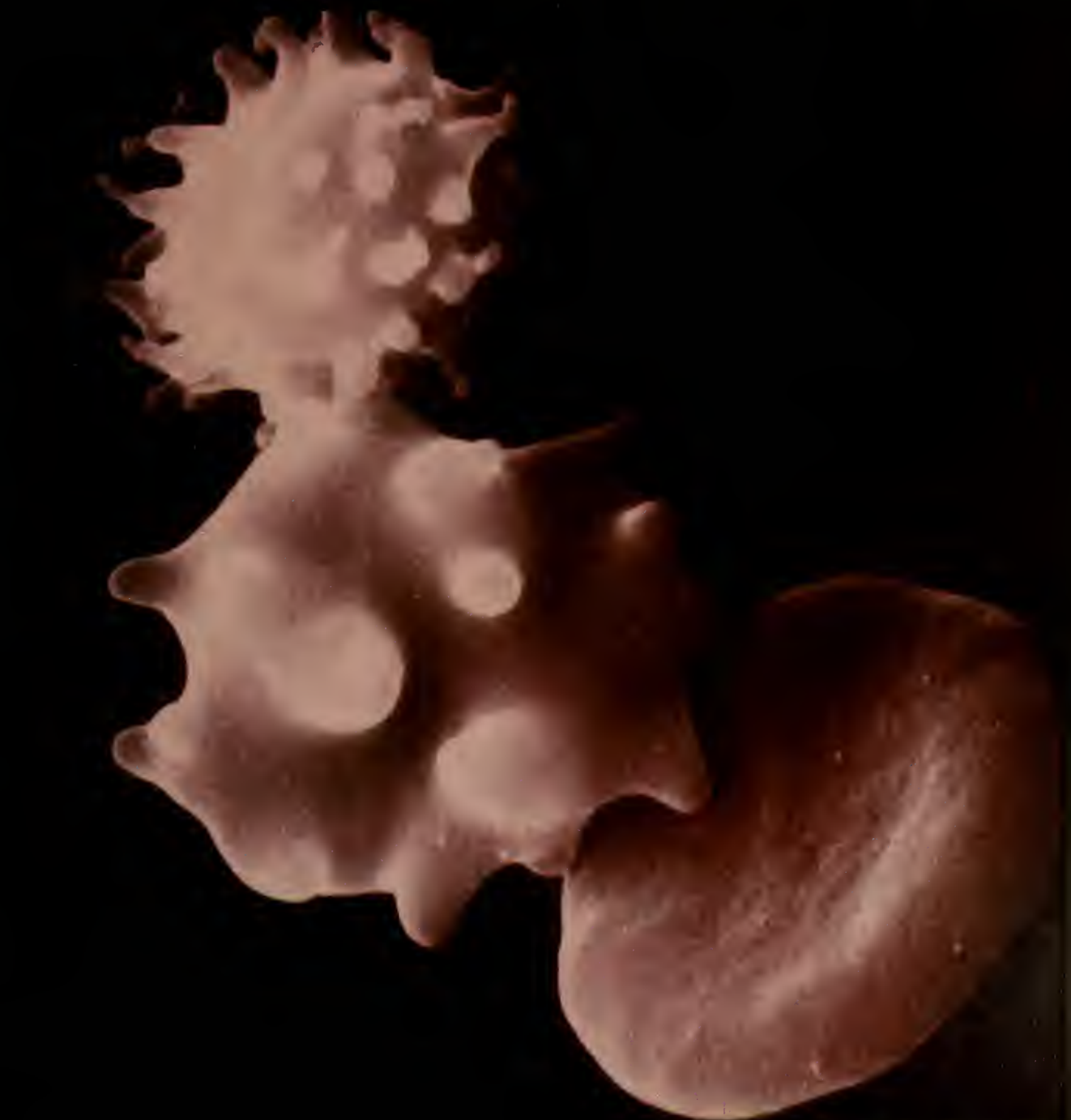
Source: Unpublished data from the National Ambulatory Medical Care Survey, National Center for Health Statistics (NCHS).

Table 4. Economic Cost of Selected Diseases, 1975

Diagnosis	Direct Costs		Indirect Costs				Combined Costs	
			Morbidity		Mortality			
	($ in millions)							
	$	%	$	%	$	%	$	%
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 disease	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.

2. Description of the National Program



A scanning electron microscope reveals the variety of shapes that can be adopted by red blood cells.

2. Description of the National Program

Historical Account of Relevant Public Law

For over 30 years, the National Heart, Lung, and Blood Institute has been responding to national health problems and to the need for research to improve health conditions. The Institute has focused on diseases affecting the heart, lungs, and blood. As a result of a series of legislative mandates, the scope of the Institute's biomedical research and professional and public education activities has grown significantly.

The National Heart Institute was established in 1948 by authority of the National Heart Act (P.L. 80-655). Since then, Congress has reendorsed the Institute's authorization and expanded its mandate four times. In 1969, the mandate was enlarged to encompass research and training in respiratory diseases; hence, the name changed to the National Heart and Lung Institute. In 1972, Congress directed the addition of a plan to address blood vessel and blood diseases. Public Law 92-423 specified the development of a National Program to coordinate the attack on these diseases. In 1976, the Health Research and Health Services Amendments (P.L. 92-278) were adopted, which provided for the continuation of the National Program efforts in heart, lung, and blood disease and added expanded responsibilities for research in blood, blood products, and management of the Nation's blood resources.

The amount and allocation of the budget have also changed noticeably during the Institute's history. In 1948, the first budget for the National Heart Institute was $1.6 million; in 1972, the National Heart and Lung Institute's budget was $232.6 million; and in 1981, the NHLBI's budget totaled $549.7 million (figure 9).

Since the Institute's establishment, significant advances have been made in the areas of prevention, detection, diagnosis, and treatment of heart, lung, and blood diseases. Through continuing research, the Institute is now better equipped to respond actively to the national need.

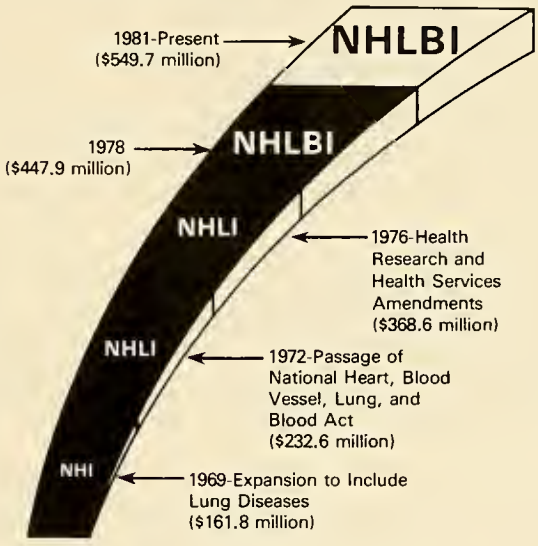


Figure 9. Growth of NHLBI Budget During the Institute's History

Legislative Expansion of NHLBI Mandates

1972 LEGISLATION

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

To meet these responsibilities effectively, the Institute required a new program strategy. Thus, the law mandated that the Director of the Institute, with the advice of its National Advisory 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 advice 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 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
- 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 it is updated each year. A provision of the 1972 legislation 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 on plans for the next 5 years.

The act also mandated an annual report from the National Advisory Council to the President for transmittal to Congress, and 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 advising on heart diseases to advising on heart, blood vessel, lung, and blood diseases.

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

- Established the 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 diseases of children, 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
- Specified the utilization of a minimum of 15 percent of appropriated funds 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 the Public Health Service Act, Section 301, which has 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; reauthorization was required 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. During this period, the start of the fiscal year was shifted from July 1 to October 1 through an act of Congress.

The significant thrust of the 1975-1976 legislation was to emphasize, clarify, and expand the Institute's role in blood-related areas. These actions took several forms 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 coordinate blood research programs and research on the management of blood resources.

Other 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 to recommend 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
- 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.

The Congress held hearings on several substantive issues in the conduct and management of biomedical research while legislation was kept to as simple an extension as possible. In the 1977 legislation, the 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 Council membership space (formerly allocated to 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 mandates to disseminate information, 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 to have information programs for the public. Additional technical amendments included a reimbursement provision for experts and consultants.

Authorizations of appropriations in the 1978 law expired on September 30, 1980. During the winter and spring of 1980, Congressional committees considered bills to continue the activities and programs of the National Heart, Lung, and Blood Institute. The outcome was reauthorization of the Institute's activities through September 1982.

Program Goals and Planned Activities

The scientific staff of the Institute, with extensive participation by NHLBI advisory committees and task forces, develop program goals and planned research activities. Other leading research experts contribute their specialized knowledge in the technical refinement of proposed goals and activities. After agreement is reached, the program goals and planned activities are presented to the National Heart, Lung, and Blood Advisory Council for its consideration.

The current program goals indicate areas of research priority.* The activities that are listed give areas of major emphasis and are not all-inclusive. New areas are continually being evaluated, as the Institute seeks to maintain the flexibility to fund research in promising new areas. Throughout this process, the NHLBI gauges investigative pursuits according to its potential for advancing the state

*The plans and goals presented here reflect the attitudes and priorities of NHLBI as of 1981. The Institute is currently undertaking an intensive review of its past priorities and achievements to develop a revised program plan. During this process, the goals and activities related here may undergo some revisions or expansions. These changes will be reported in the Ten-year Review and Update of the National Heart, Blood Vessel, Lung, Blood Disease, and Blood Resources Program Plan, to be completed in 1983.

of the science; for making effective use of available personnel, facilities, and funding; and for producing results "important to mankind."

The current program goals and planned activities for each of the 20 areas that comprise the three major Institute programs are discussed in this section: heart and blood vessel diseases; lung diseases; and blood diseases and blood resources. These goals will be reviewed and new recommendations will be developed by panels of scientists over the period of 1981 to 1982.

Heart and Blood Vessel Diseases

The National Program concerns itself with 10 major research areas related to heart and blood vessel disorders: arteriosclerosis, hypertension, cerebrovascular diseases, coronary heart disease, peripheral vascular diseases, arrhythmias, heart failure and shock, congenital and rheumatic heart diseases, cardiomyopathies and infections of the heart, and circulatory assistance. The program also stresses a major effort in prevention, control, and education in the areas of hypertension (or high blood pressure), arteriosclerosis, coronary heart disease, congenital heart disease, and rheumatic fever. This effort focuses on demonstrations, communications programs, and training in areas of high impact where the state of the art is sufficiently advanced to allow meaningful clinical applications of research findings.

Extra- and intramural research programs in heart and blood vessel diseases support investigator-initiated basic, applied, and clinical projects in all 10 program areas. Contract-supported research is being carried out in promising areas of research and demonstration that have highly specified objectives and require accelerated implementation.

ARTERIOSCLEROSIS

Program Goals

The Institute's mission is to improve the prevention, diagnosis, treatment, and cure of arteriosclerosis and arteriosclerotic disease. 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

During the next 5 years, program activities are planned in the following areas:

- Etiology and pathogenesis of arteriosclerosis and studies of the diabetes-atherogenesis connection
- Biology of blood vessels
- Prevention and regression of arteriosclerotic lesions
- Discovery of new risk factors
- Basic, clinical, and population aspects of arteriosclerosis
- Completion of the Multiple Risk Factor Intervention Trial and the Lipid Research Clinics Coronary Primary Prevention Trial
- Development and testing of noninvasive methods of detection and monitoring of arteriosclerosis.

HYPERTENSION

Program Goals

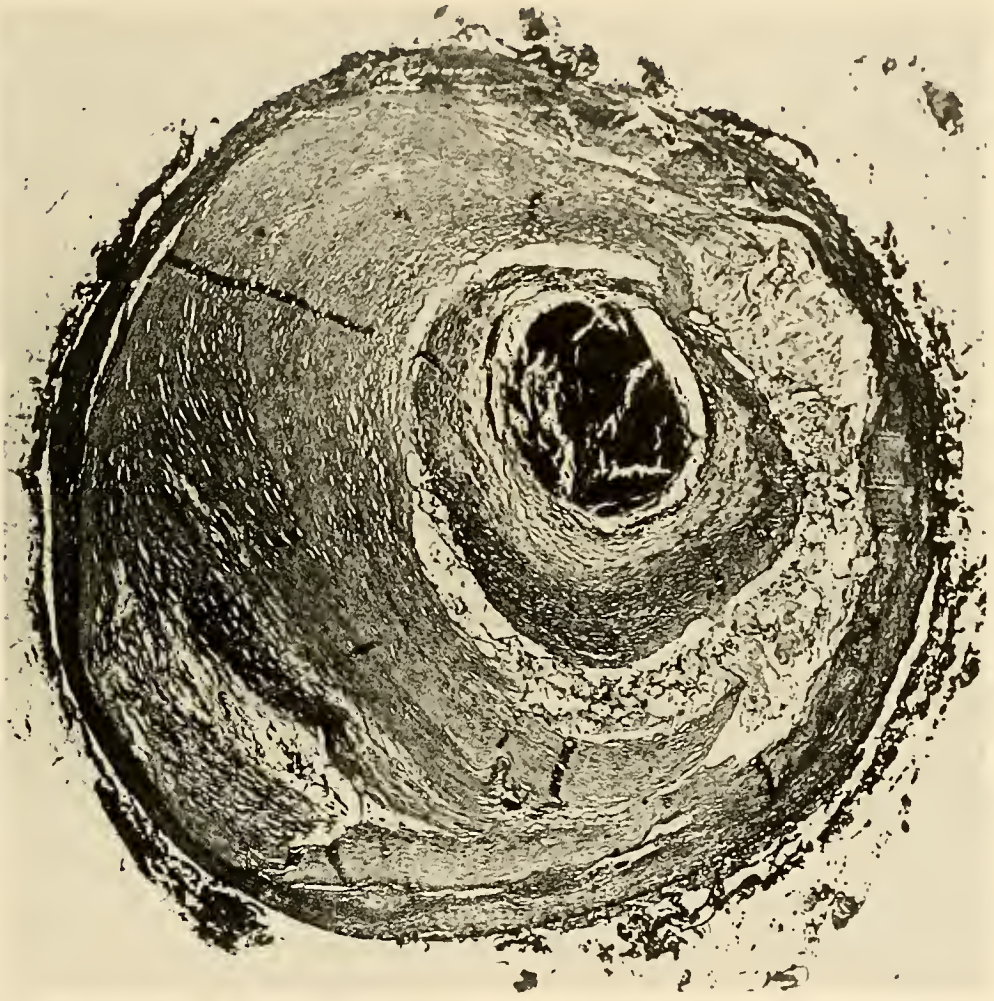
The Institute is working to reach a better understanding of the physiological systems that control blood pressure and the means by which these systems can initiate or exacerbate the development of hypertension. Improvement of therapy for those already afflicted will help to reduce side effects that are still associated with antihypertensive drugs. The following are basic goals 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
- Evaluate the basic and clinical research implications of the Hypertension Detection and Follow-up Program (HDFP), and implement appropriate actions to improve patient care
- Implement effective models of high blood pressure control on a community-wide basis.

Planned Activities

During the next 5 years, program activities are planned in the following areas:

- Research on inhibitors of renin-angiotensin, 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



Severe and progressive blockage of an artery is seen as atherosclerotic deposits restrict the flow of blood to the heart.

- Fundamental investigations toward improved diagnosis, treatment, and prevention of hypertension
- 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. 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 monitoring of disorders of the large vessels supplying the brain.

Planned Activities

During the next 5 years, program activities are planned in the following areas:

- Intensive study of the etiology and pathogenesis of cerebrovascular disease
- Development of animal models for future use in research.

CORONARY HEART DISEASE

Program Goals

The Institute's objective for the next 5 years is to decrease even further the mortality from coronary heart disease. Already established programs as well as ongoing evaluation activities will be continued. The specific goals are the following:

- Improve the recognition and assessment of latent coronary artery disease and overt coronary heart disease
- Monitor trends of incidence of fatal and nonfatal coronary heart disease in relation to changing risk factors
- Improve the therapy of patients with acute myocardial infarction and of 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 damaged irreversibly 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 coronary angioplasty (PTCA) in the management of ischemic heart disease.

Planned Activities

During the next 5 years, program activities are planned in the following areas:

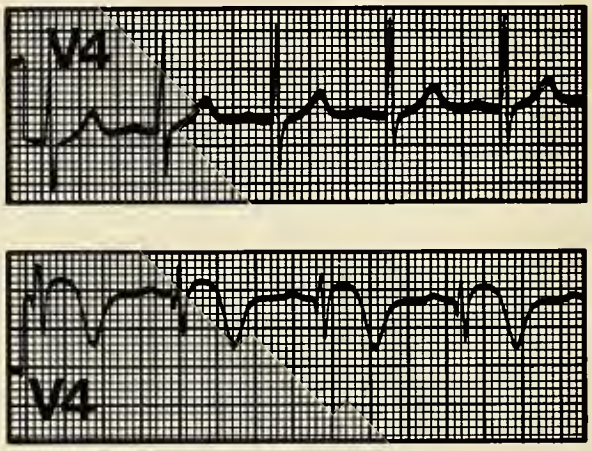
- Studies to limit the myocardial damage due to coronary events
- Development and testing of new techniques of emergency cardiovascular diagnosis and therapy
- Investigation of the mechanisms and factors that precipitate acute coronary events
- Completion of major clinical trials including the Beta-Blocker Heart Attack Trial (BHAT), Multicenter Investigation of Limitation of Infarct Size (MILIS), and Coronary Artery Surgery Study (CASS), to improve the management of coronary heart disease.

PERIPHERAL VASCULAR DISEASES

Program Goals

The Institute's broad goal in the area of peripheral vascular diseases 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 disease that are suitable for the assessment of symptomatic patients, for the recognition of latent arterial disease, and for research assessment of new modes of therapy designed to retard or reverse atherogenesis
- Improve management of patients with peripheral arterial disease with particular attention to the long-term effects of arterial grafts and to the improvement of graft techniques for smaller arterial vessels
- Encourage greater research effort on the causes and treatment of peripheral venous diseases.



The signal from one of the chest leads (V4) of an electrocardiograph (ECG) is here charted in a patient before (above) and after (below) a heart attack.

Planned Activities

During the next 5 years, program activities are planned in the following areas:

- Diagnosis, therapy, and rehabilitation of peripheral arterial, venous, and lymphatic diseases
- Research on the natural history of occlusive venous disease with and without surgery
- Effectiveness of various therapeutic procedures and drugs
- 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 improved understanding of lethal arrhythmias and the means to prevent

them. The Institute's current goals are to define the fundamental processes of electrical rhythm and conduction disorders and to develop methods of acute and chronic preventive therapy. Specific goals over the next 5 years are the following:

- Develop improved understanding of the mechanisms whereby arrhythmias arise
- Develop methods of chronic prophylactic therapy, using pharamacological 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 extended, electrocardiographic monitoring of heart rhythm of ambulatory patients to permit clinical management
- Develop more effective methods for the recognition of those at heightened risk of sudden cardiac death.

Planned Activities

During the next 5 years, program activities are planned in the following areas:

- Fundamental understanding and prevention of arrhythmias
- 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 ischemic mechanisms more fully, improve diagnostic techniques, and develop methods for the prevention and treatment of heart failure and cardiogenic shock. Specific 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

During the next 5 years, program activities are planned in the following areas:

- 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
- 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. New diagnostic and surgical techniques have prolonged the life of afflicted individuals and improved its quality. New means to prevent rheumatic heart disease have been developed, but only a few causes of congenital heart disease 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. During the next 5 years, the Institute's research program will be directed toward the following goals:

- Understand more fully the etiology of congenital heart defects
- Improve surgical techniques for the repair of defects and improve noninvasive techniques for diagnosis and treatment of patients with congenital and rheumatic heart defects
- Seek a better understanding of the developmental biology of the heart and the causes of, and susceptibility to, congenital and rheumatic heart diseases.

Planned Activities

During the next 5 years, program activities are planned in the following areas:

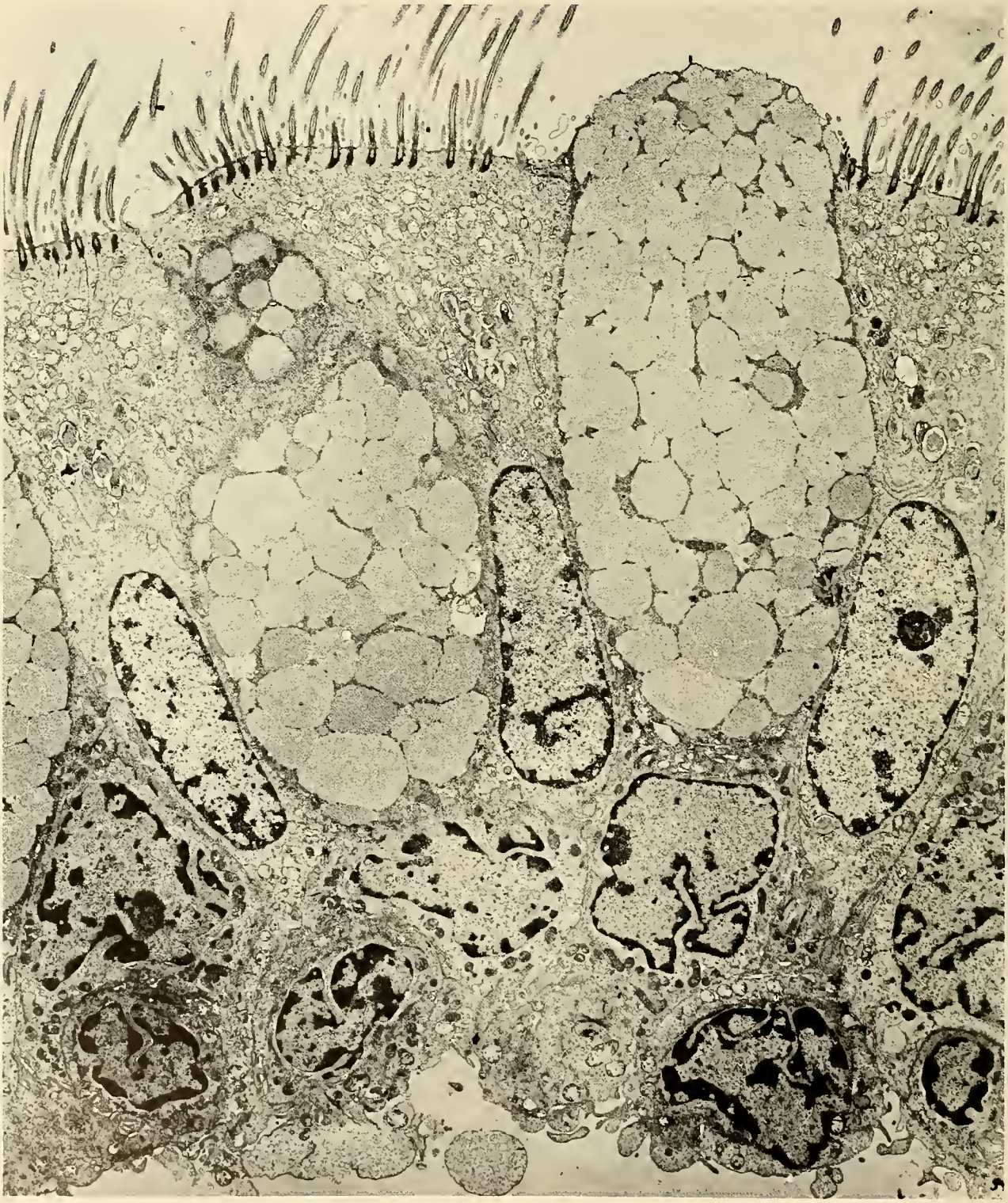
- Understanding the etiology of congenital heart disease
- Research on animal models
- Immunological problems in heart disease and their management, specifically related to rheumatic heart disease.

CARDIOMYOPATHIES AND INFECTIONS OF THE HEART

Program Goals

The goals of this program area were established in response to the problems posed by diffuse congenital infections and by conditions of environmental etiology (including diet). The Institute plans to achieve the following goals:

- Encourage greater research effort on the causes and treatment of cardiomyopathies and infections of the heart



Cells lining the airways of the lung of the cat are seen in thin sections in the electron microscope.

- Develop more effective methods for diagnosis and treatment.

Planned Activities

In order to reach its goals, activities are planned in the following areas:

- Experimental work to study cardiomyopathies and infections of the heart
- Investigations 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 can 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 are suitable depend not only on the degree of cardiac function that must be restored, but also on the period of time for which such lifesaving support is required. 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 test circulatory assist devices on the bench and in animals, particularly of the left ventricular assist type
- Conduct clinical evaluations after satisfactory animal testing, to assess the efficacy of, and define the clinical indications for, left ventricular assist devices.

Planned Activities

During the next 5 years, activities planned for this program area include:

- 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

Lung diseases and diseases of the respiratory system are a severe health problem. They account for over 5 percent of the years of life lost to illness and exact a great toll in sickness, requirements for treatment, and lost workdays. Respiratory diseases are the most frequent reasons that people seek a physician's attention; they account for more than 20 percent of all physician contacts and 12 percent of all short-term hospital stays. Moreover, there are more lost workdays from respiratory disorders than from any other category of illness.

The National Program is concerned with six major areas related to respiratory disorders: structure and function of the lung, emphysema and chronic bronchitis (chronic obstructive pulmonary diseases), pediatric pulmonary diseases, fibrotic and immunologic interstitial lung diseases, respiratory failure, and pulmonary vascular diseases. These areas are addressed through the support of investigator-initiated research grants, contracts, intramural studies, and research training in lung diseases.

STRUCTURE AND FUNCTION OF THE LUNG

Program Goals

The 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 the adult normal respiratory system, and to determine how these events 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

- Improve understanding of gas exchange and transport, and of alterations associated with exercise, high altitude, hyperbaria, and disease states
- Elucidate the respiratory mechanics in normal breathing, during physiological adjustments to exercise and altered environments, and in disease states
- Increase 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

- Elucidate the roles of lung cells, enzymes, hormones, and immunological reactions in the defense of the lung against insults, both exogenous and endogenous, and disease
- Improve 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

- Characterize the structural and functional features of various types of lung cells, interrelationships among

different cell types, and modifications associated with lung injury and disease
- Characterize the chemical and structural features of lung connective tissue components and alterations in the course of pulmonary disease.

Lung Growth and Development

- Increase 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

Specific activities planned for the next 5-year period include:

- Development of methods to separate major types of lung cells and 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
- 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 PULMONARY DISEASE (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 for the next 5-year period are as follows:

Chronic Obstructive Pulmonary Diseases

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

Asthma

- Elucidate the underlying mechanisms in bronchoconstriction, and develop more effective measures to ameliorate or prevent the bronchoconstrictor response.

Planned Activities

Future activities of the program will focus on:

- Studies of the natural history of PiZZ emphysema (a rare genetically related form of emphysema)
- Studies to correlate biochemical and physiological alterations in early stages of chronic obstructive pulmonary diseases.

PEDIATRIC PULMONARY DISEASES

Program Goals

The Institute's goal is to prevent pediatric pulmonary diseases through increased knowledge of the underlying disease process. During the next 5 years, the following specific goals are planned:

Neonatal Respiratory Distress Syndrome

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

Bronchiolitis

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

Cystic Fibrosis

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

Planned Activities

During the next 5 years, program activities are planned in the following area:

- 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.

FIBROTIC AND IMMUNOLOGIC INTERSTITIAL LUNG DISEASES

Program Goals

The 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:

- Elucidate 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
- Prevent interstitial lung diseases and improve the management of them through identification of etiologic agents and other risk factors, early detection of disease, and development and improvement of therapeutic regimens.

Planned Activities

Future program activities include investigations of:
- Specific agents responsible for fibrotic lung diseases in occupational environments, with specific attention to dose-response relationships
- Immunological and biochemical responses to organic and inorganic dusts that lead to fibrotic lung diseases and hypersensitivity pneumonitis.

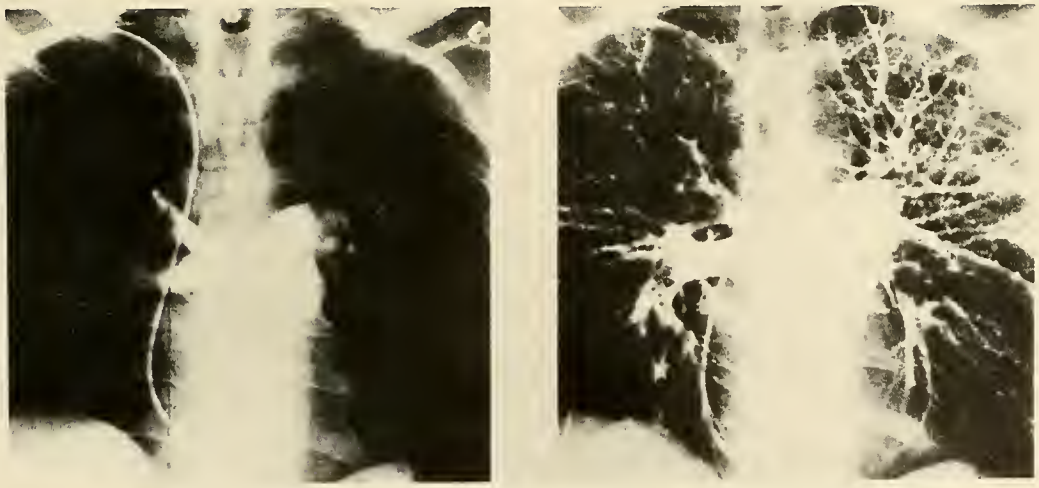
Planned Activities

Studies to be initiated during the next 5 years address:
- Basic mechanism of the adult respiratory distress syndrome
- Determination of how degenerative changes in the lung can be arrested or reversed.

PULMONARY VASCULAR DISEASES

Program Goals

In pulmonary vascular diseases, early detection is the key to effective patient management, and fundamental knowledge of pulmonary circulation is the key to effective disease prevention. The goals of the Institute are to elucidate the mechanisms that regulate normal and diseased pulmonary circulation; to improve understanding of the pathogenesis of pulmonary edema, pulmonary hypertension, cor pulmonale, and pulmonary embolism; and to improve the diagnosis and treatment of these disorders. Specific goals for the next 5 years are as follows:
- Attempt to prevent pulmonary edema through understanding the mechanisms involved in the hydrostatic and permeability changes that affect fluid and electrolyte exchange in the lung
- Elucidate the mechanisms that control the normal pulmonary circulation and their relationship to the pathogenesis of pulmonary hypertension
- Improve the management of pulmonary vascular diseases through development of noninvasive diagnostic techniques and more effective therapeutic regimens.



A looping catheter delivers the anticoagulant urokinase to a blood clot in the lung; two hours later, the clogged blood vessels are open again.

RESPIRATORY FAILURE

Program Goals

To reduce death and disability from respiratory failure, the Institute seeks to improve the prevention, diagnosis, and management of adult respiratory failure through better understanding of the structural, biochemical, immunological, and physiological mechanisms of acute lung injury and repair. Specific goals directing the Institute's program during the next 5 years are as follows:
- Elucidate the intrinsic mechanisms involved in lung injury, and analyze progressive changes that result in respiratory failure
- Improve the therapeutic management of respiratory failure, and develop measures that identify, arrest, or reverse degenerative changes accompanying lung injury.

Planned Activities

During the next 5 years, program activities are planned in the following areas:

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

Blood Diseases and Blood Resources

Disorders of the blood are closely related to heart, blood vessel, and lung diseases. Blood is the vehicle by which oxygen, nutrients, and other substances are carried to every part of the body to be exchanged for carbon dioxide, waste products, and chemicals that need to be transported away from the tissues to other body organs where they are metabolized or excreted.

The National Program is concerned with four major areas related to blood: bleeding and clotting disorders, disorders of the red blood cell, sickle cell disease, and blood resources.

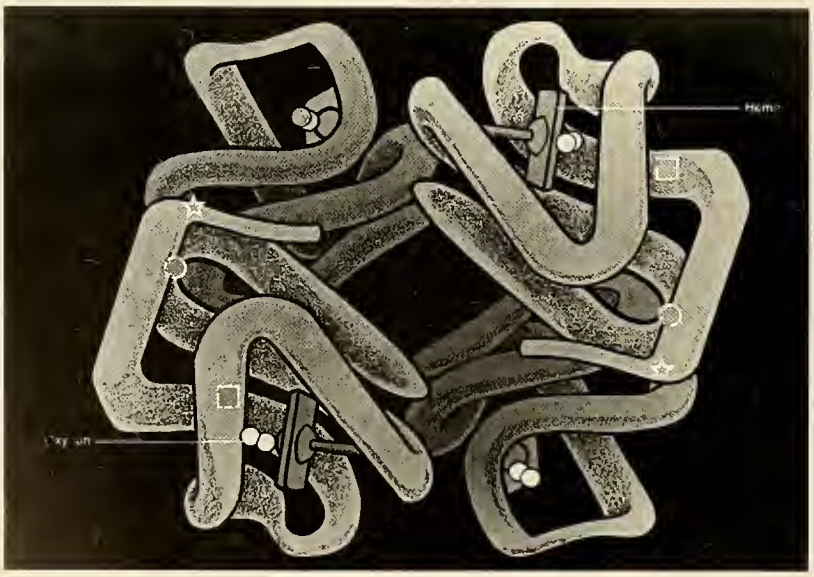
The National Program addresses these problems through investigator-initiated research, Specialized Centers of Research, contract studies in special areas of research and development, training programs, and programs to communicate the most current advanced knowledge to the public and to the practitioner.

BLEEDING AND CLOTTING DISORDERS

Program Goals

Advances in basic understanding of the coagulation system are critical to the 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 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 the understanding of the pathophysiology of arterial thrombosis to bring about its ultimate prevention
- Increase the knowledge of the basic mechanisms of venous thrombosis to encourage 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



An artist's conception of the hemoglobin molecule, which carries oxygen in the red blood cells. Sites are shown where slight chemical changes in the molecule can result in serious illnesses such as sickle cell anemia.

- Explore the pharmacology of agents such as the prostaglandins, aspirin, and oral contraceptives that affect platelet interactions, endothelial function, and cellular reactivity to a variety of stresses.

Planned Activities

During the next 5 years, program activities are planned in the following areas:

- 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
- Studies to understand the thrombotic process and improve ability to prevent and treat thrombotic disorders
- Studies to understand and clinically manage hereditary bleeding disorders.

RED BLOOD CELL DISORDERS

Program Goals

The overall goal of the program for the next 5 years is the acquisition of knowledge that will lead 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, and devote major efforts to the development and testing of techniques for prenatal diagnosis
- 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 that 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 preparations of erythropoietin (one of the prime regulators of red blood cell production) suitable for use in controlling human diseases.

Planned Activities

Future program activities include:

- Studies of the molecular and clinical aspects of thalassemia
- Purification and characterization of erythropoietin
- Studies of the red blood cell plasma membrane
- Investigations into bone marrow physiology, pathology, and regulation.

SICKLE CELL DISEASE

Program Goals

To fulfill its mission to reduce morbidity and mortality due to sickle cell disease, the Institute has 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 approaches to patient management based on the latest scientific advances
- Provide accurate, up-to-date information to providers and consumers of health care
- Evaluate the effectiveness of education, testing, and counseling programs.

Planned Activities

During the next 5 years, program activities are planned in the following areas:

- Studies of the switch from fetal hemoglobin synthesis to adult hemoglobin production
- Molecular studies of globin gene expression at the alpha, beta, and gamma loci
- Studies of the metabolism of sickled cells and the role of coagulation in vaso-occlusive crises
- Collaborative studies to identify and evaluate the factors that determine the clinical course of sickle cell disease and the presence or absence of complications
- Development of new drugs for the treatment of sickle cell disease
- Activities in educational, diagnostic, and counseling services in sickle cell disease, training, and community demonstrations.

BLOOD RESOURCES

Program Goals

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

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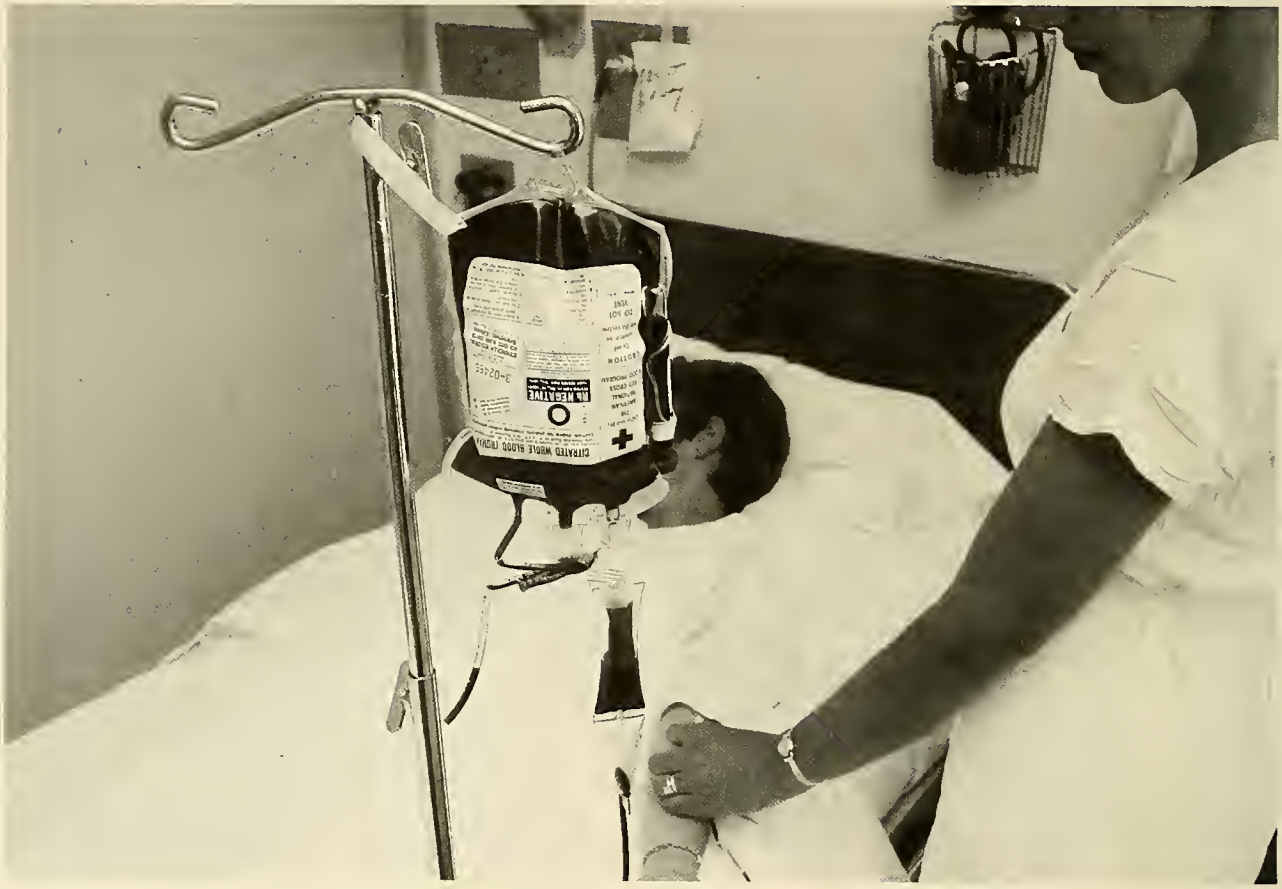
* The National Blood Policy was issued in 1973 by the Secretary of Health, Education, and Welfare (later Health and Human Services). It calls for cooperation of the blood-banking community and other agencies with the Government in meeting U.S. needs in blood resources.



For blood, the gift of life, there is at present no substitute.

Blood Resource Management

- Foster the efficient use and assure an adequate supply of high-quality blood and 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 sharing of blood resources both regionally and nationally.

Blood Safety

- Prevent morbidity and mortality from posttransfusion 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
- Support studies to improve the safety and efficiency of selective removal of blood components.

Blood Substitutes

- 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 therapeutic applications.

Blood Component Therapy

- Develop definitive guidelines for the clinical use of blood components for transfusion, including packed red cells, granulocytes, and platelet concentrates
- Determine and clarify parameters for collection and storage of platelets and stem cells 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 components; support clinical trials to establish the effects and role of these new components and methods
- Promote research into the appropriate use of blood component removal, now being employed in the treatment of many disorders.

Planned Activities

During the next 5 years, program activities are planned in the following areas:

- Implementation of a national blood data center
- Evaluation of the impact of the new preservative 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
- Development of improved methods for producing human leukocyte interferon
- Support of various research and demonstration projects at regional blood centers.

The Interagency Technical Committee

In 1972, Congress established the National Heart and Lung Institute and the Interagency Technical Committee (IATC) (P.L. 92-423). This Committee comprises representatives of agencies throughout the Federal Government that contribute to research in diseases of the heart, blood vessels, lungs, and blood (figure 10).

Under the direction of the Committee, five working groups direct their efforts toward specific areas:

- Blood Resources and Blood Substitutes
- Cardiovascular Biomedical Engineering
- Hypertension
- Nutrition
- Smoking and Diseases of the Heart, Lungs, and Blood.

At its September 1980 meeting, the IATC heard an extensive presentation on the results of the Hypertension Detection and Follow-up Program. These results demonstrate that systematic treatment of even mild cases of hypertension can reduce the number of premature deaths attributable to high blood pressure.

The cochairmen of the newly formed Working Group on Blood Resources and Substitutes outlined their objectives and proposed activities to the IATC at the January 1981 meeting. At its meeting in July 1981, IATC members were informed about the use of alanine aminotransferase (ALT) as an indirect assay for non-A,non-B viral hepatitis. The working group also discussed recent research accomplishments in the NHLBI hepatitis program.

During FY 1979, the Federal agencies represented on the IATC committed $378,811,000 to 5,092 projects concerning heart and blood vessel diseases. A total of 1,697 research projects in lung diseases were allocated $133,010,000, while the combined funds for research in blood diseases and blood resources amounted to $134,088,000, supporting 2,078 research projects. Overall, in FY 1979 the IATC member agencies funded 8,867 projects related to the 20 areas of the National Program at a cost of $646,709,000.

The four-volume *1979 Report of the Interagency Technical Committee on Heart, Lung, and Blood Diseases* (NIH Publication No. 81-2181) was published in 1981. The first volume is an overview of the IATC—its basis in legislation, its structure, the fiscal support that member agencies provide to research in the National Program areas, and highlights of individual research efforts. Volume II, *Directory of Federally Supported Research Projects in Heart and Blood Vessel Diseases* (NIH Publication No. 81-2182), presents detailed information about Federal projects relating to the National Program and the funds allocated to those projects; and Volume III, *Directory of Federally Supported Research Projects in Lung and Blood Diseases and Blood Resources* (NIH Publication No. 81-2183), contains similar details about these program areas. Volume IV, *Compendium of Federal Projects on Smoking and Heart, Lung, and Blood Diseases* (NIH Publication No. 81-2184), was compiled by the Working Group on Smoking and Heart, Lung, and Blood Diseases to describe the work of more than 200 projects supported by the Federal Government in this critical area.

As the functional arms of the IATC, the working groups presented their current plans to the IATC at its meeting in September 1981 and will continue to examine their areas of responsibility in the coming year.

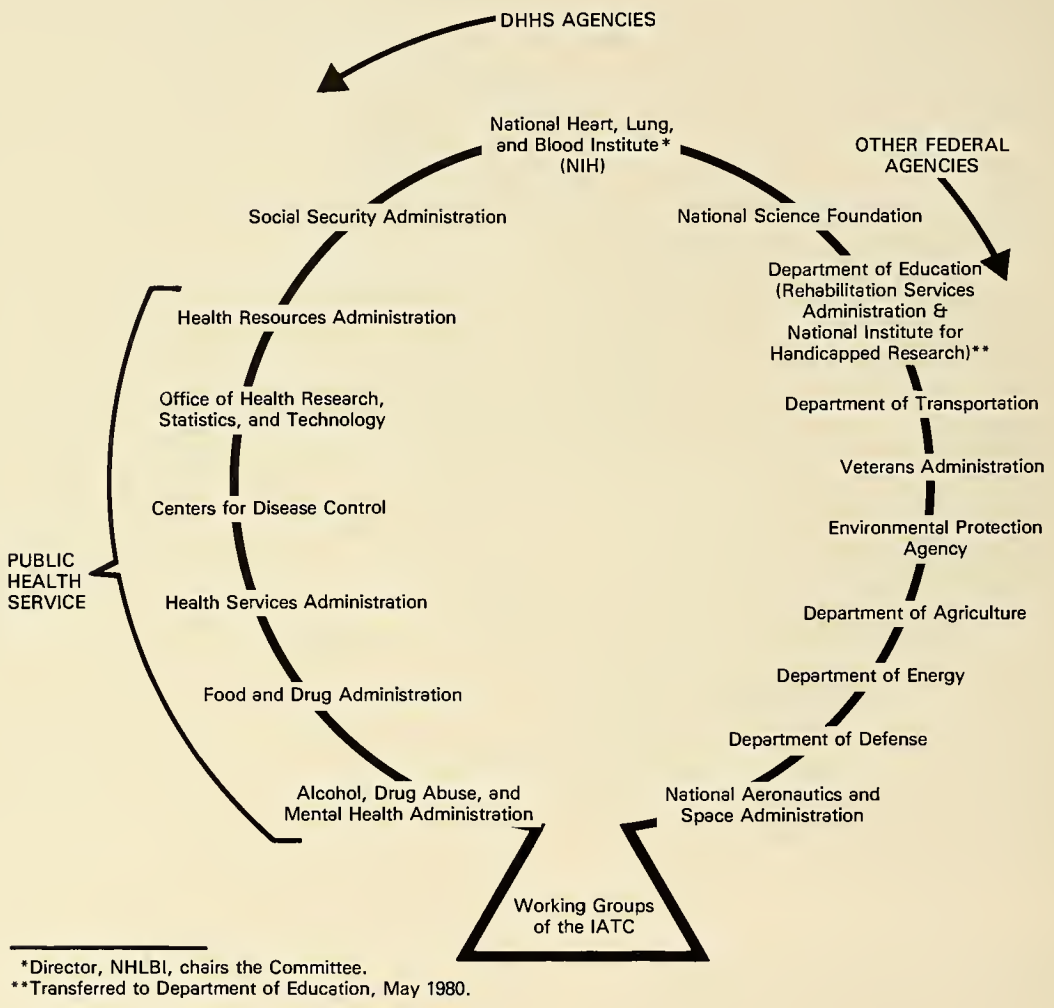
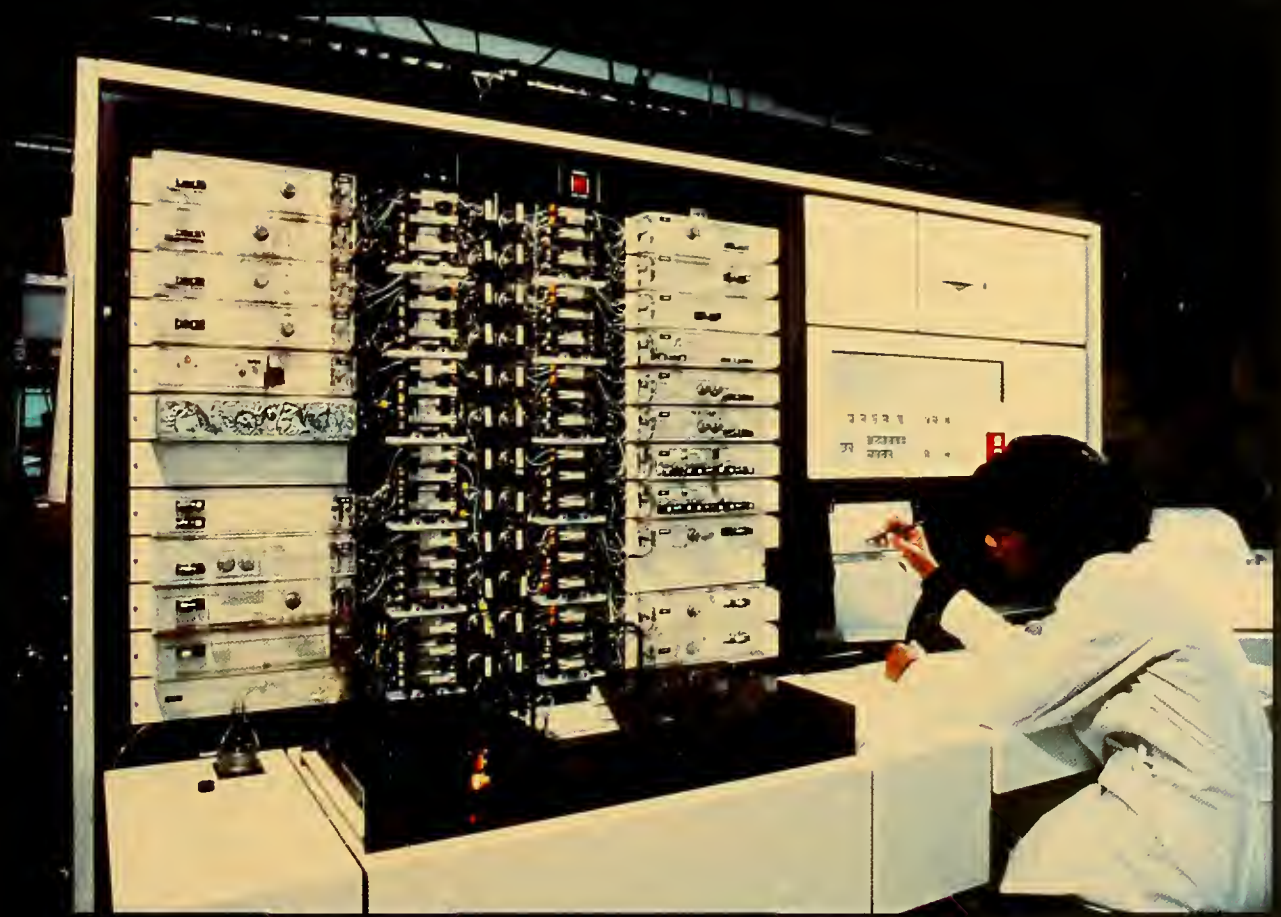


Figure 10. Federal agencies of the Interagency Technical Committee contribute to heart, lung, and blood research.

3. Research Pathways to Modern Medicine



The sequential multiple analysis computer can read the levels of 20 different chemical substances in blood at the same time.

3. Research Pathways to Modern Medicine

With the acquisition of new knowledge and improved diagnostic and therapeutic techniques, prospects for better health care are realized. Biomedical knowledge is constantly advancing through research, and the pace has increased substantially during this century.

Improvements in health care are realized in many ways. New procedures sometimes result from observations made by practicing clinicians. Fresh ideas often result from critical reviews of the state of the art in various areas of medicine. Research that addresses specific issues can lead to better medical practice. In some instances, pure chance has played a part in major advances. Fundamental scientific research, however, is responsible for the greater share of credit. Without the knowledge that comes from experimentation, only instinctive action is possible. A lack of continuing education in new advances in basic and clinical sciences frequently leaves health professionals at a disadvantage and unprepared to handle new medical developments.

Three separate diseases within the scope of the NHLBI have been chosen as examples of the role of research in the evolution of modern medicine. The following sections provide an insight into the past and present achievements and into future goals of research on hypertension, chronic obstructive pulmonary disease, and hepatitis.

Hypertension

Hypertension—chronically elevated blood pressure—has been labeled "the silent killer." A chief contributor to heart and kidney disease and the single greatest cause of stroke, hypertension frequently has no recognizable symptoms. It is estimated that 60 million Americans have high blood pressure.

Black Americans have twice the prevalence of hypertension of whites; men have a somewhat lower prevalence than women; and persons over 65 have about twice the prevalence of younger persons. By 1980, the economic costs resulting from hypertension-affected diseases had amounted to about $8 billion annually.

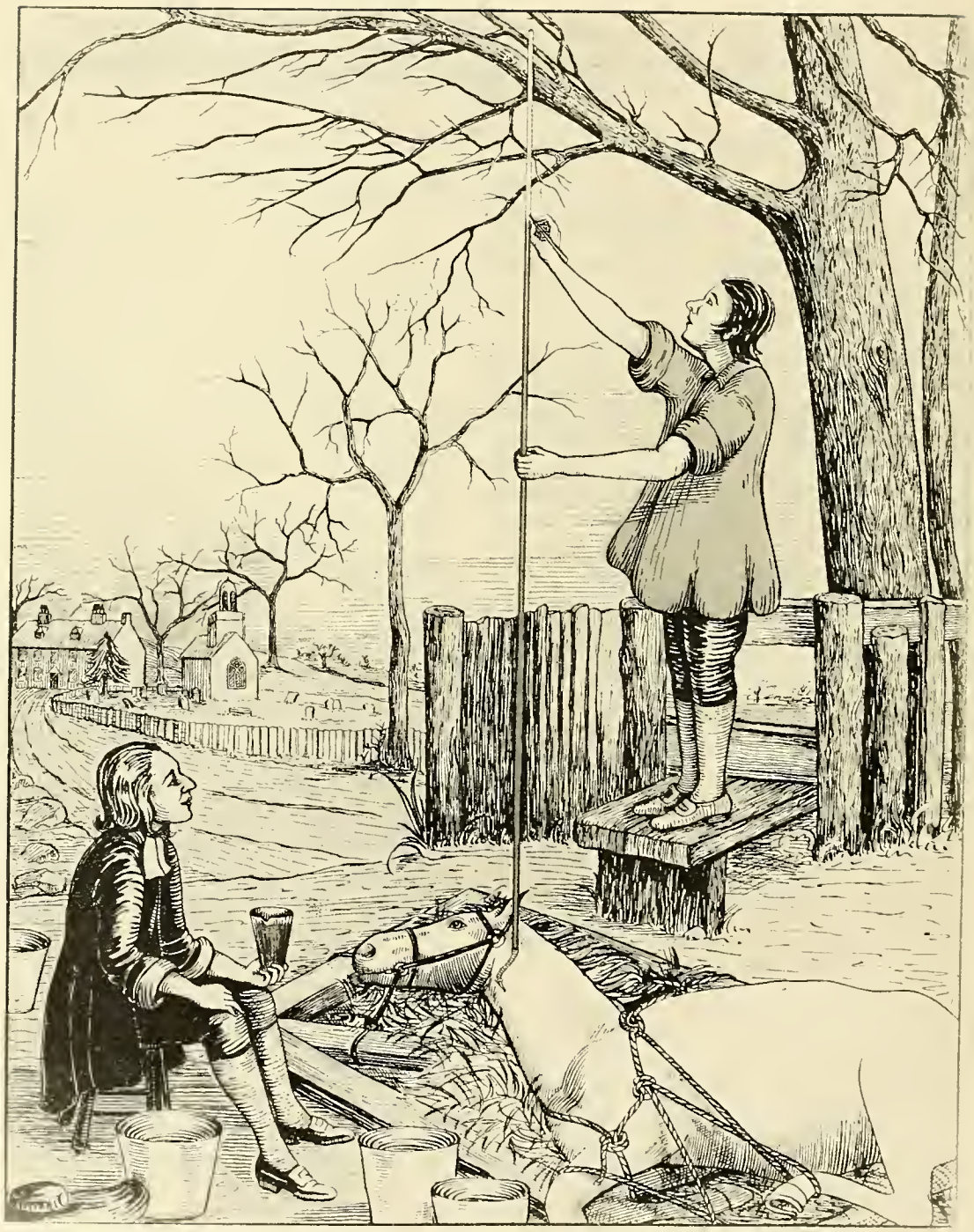
The National Heart, Lung, and Blood Institute has reaffirmed its commitment to research on the etiology and pathogenesis of hypertension, to improving methods and techniques of hypertension research, to encouraging new scientists to contribute to the research, to evaluating and implementing findings of the HDFP, and to implementing community-wide models of high blood pressure control. These measures are the Institute's contribution toward attainment of the national objectives for improving the health of Americans: reduced risks, increased public awareness, improved health services, and systems to monitor the incidence and categories of hypertension and to prevent its sequelae—stroke, heart attack, and heart and renal failure.

Historical Perspectives

DIAGNOSTIC ADVANCES

One hundred years ago, physicians recognized high blood pressure only as a part of Bright's (kidney) disease. In 1827, Dr. Richard Bright published his discovery that, among patients who had died from kidney disease, a significant number had enlarged left ventricles of the heart and diseased aortas. To explain this association, Bright suggested "that the altered quality of the blood so affects the minute and capillary circulation, as to render greater action necessary to force the blood through the distant divisions of the vascular system." Although the idea of arterial blood pressure was implicit, Bright did not refer to it. Like so many early discoveries, Bright's understanding was based on pathologic evidence gained from autopsy studies, and his speculations concerning the relationship between kidney disease and arterial obstruction were limited by a rather rudimentary knowledge of hydraulics. Many other basic studies were to be completed before hydraulics could be applied directly to physiology.

In 1714, before Bright's discovery, Hales performed the first blood pressure measurement ever recorded. A prevailing theory of that time held that under intense pressure, blood dilated muscle fibers and caused the muscle to swell upon contraction. Skeptical of this erroneous thesis, and wishing to investigate the force and velocity of blood "as a likely means to give a considerable insight into the animal economy," Hales began his experiments. After coaxing a white mare to the ground and tying her to a fallen gate, he exposed the animal's carotid artery. He



Hales measured blood pressure of mare he had tied to a fallen gate. Glass pipe inserted into jugular vein showed blood pressure column. It measured 12 inches when animal was quiet, 64 inches when animal stirred and became excited.

The first blood pressure measurement is recorded.

inserted into the artery the end of a simple gauge constructed of brass and glass tubes and the flexible windpipe of a goose. Blood traveling into the device through the windpipe spurted up in the glass tube to a height of more than 5 feet. In a similar experiment, probably performed at the same time, the clergyman-physiologist measured the blood pressure in a horse's jugular vein. Hales later used the findings of these studies to augment his remarkable research on sap movement and pressures in plants.

More than a century elapsed before Poiseuille measured the arterial blood pressure of a dog by using a mercury manometer and a U-tube of a more practical length (6 to 12 inches) than Hales's 9-foot glass pipes. Even in 1828, this type of blood pressure measurement could not be applied safely to human subjects because the technique required inserting a pipe into the artery, and clinical determination of blood pressure had to await the development of a new apparatus. That innovation occurred in 1876, when von Basch invested the first sphygmomanometer. Though crude and not very accurate, this device could be used to measure the blood pressure of a human without breaking the skin. It was a forerunner of the simple instrument introduced by Riva-Rocci in 1896, the first reliable means of measuring arterial pressure in humans. With this accurate, easy-to-apply, portable device, investigators were able to obtain blood pressure readings indirectly by inflating a cuff around the arm and noting the pressure at which the radial pulse disappeared. This measurement was called *systolic* blood pressure because it coincided with the *contraction* of the heart (systole). Korotkoff discovered how to measure both systolic and *diastolic* pressures in 1905, when, using a stethoscope over the brachial artery to monitor the pulse, he noted the pressures at which sounds appeared and disappeared as cuff pressure was decreased, at points roughly in consonance with the relaxation of the heart (diastole).

Further refinements to blood pressure measuring equipment appeared in later years. Lambert and Wood developed a strain gauge manometer for measuring blood pressure in 1947. In 1958, scientists created the first catheter tip manometer with a strain gauge to measure pressures within the heart itself. More recently, automated sphygmomanometers that measure blood pressure by passing ultrasonic waves through the subject's arm have been produced. Without such reliable and convenient devices, researchers and medical practitioners would be handicapped in conducting research and in monitoring treatment for high blood pressure.

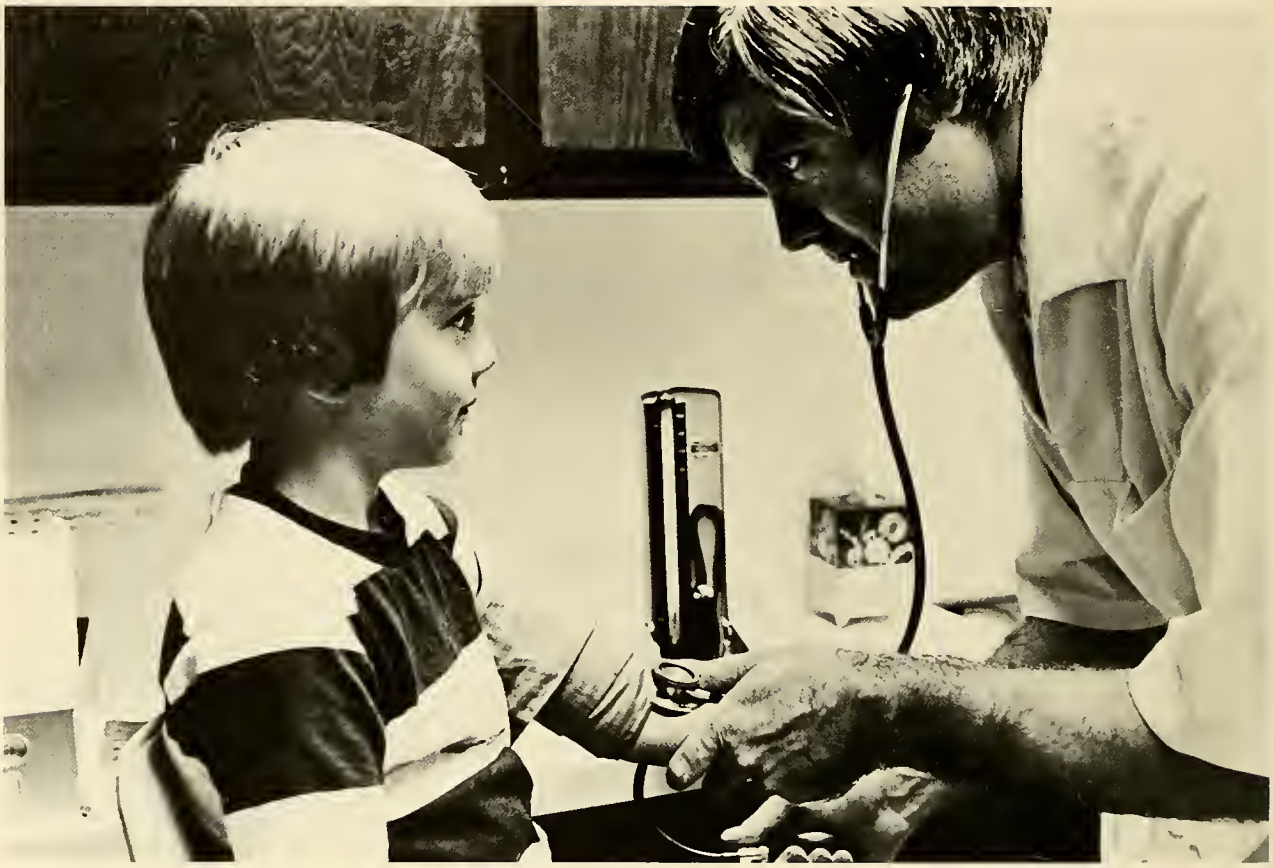
KIDNEY FUNCTION AND BLOOD PRESSURE

Experimental renal artery stenosis (a narrowing of the artery of the kidney) has provided one mechanism to identify the causes of hypertension and understand its underlying mechanisms. Developments in the field of biochemistry augmented early physiological understanding of this condition, but it was not until 75 years later that scientists began to study the hormonal control of blood pressure in its modern sense. Bright's brilliant early observation relating renal disease to excessive growth of the heart and thickening of the arteries was expanded in 1898 by Tigerstedt and Bergman, who made the initial scientific discovery that crude saline extracts of the kidney contain a pressor substance (one raising or tending to raise blood pressure), which they labeled "renin." Their finding, however, attracted little interest, particularly after numerous investigators failed to sustain any reproducible form of experimental hypertension involving the kidney. This lack of confirmation may have been caused by laboratory workers extracting with alcohol or acetone, which destroyed the renin.

It was Goldblatt and his colleagues in 1934 who discovered that a silver clamp applied to a main renal artery, effectively reducing the flow of blood through the kidneys, can reproducibly increase arterial pressure in dogs. A pathologist, Goldblatt observed that high blood pressure was frequently associated with obstructive disease of the renal arteries. The results of his work prompted others to rediscover renin and, through its relation to experimental renal hypertension, to start an entirely new area of renal and adrenal physiology and pathology.

Results of numerous subsequent scientific studies indicated that constricted or obstructed renal arteries of acutely hypertensive dogs created a pressor and vasoconstrictor (inducing a narrowing of the cavity of blood vessels) substance, and extensive investigation ensued to learn more about the substance and how to isolate it. In 1940, Page and Helmer and Braun-Menendez and colleagues reported that renin, which is an active enzyme, formed a substance acted upon in the blood plasma. Page named the substance "angiotonin," and Braun-Menendez named it "hypertensin." In 1958, both agreed to rename the substance "angiotensin." However, the observation of a hormone-like substance acting upon a plasma protein to release the effector of its action was not new. Werle and colleagues had shown in 1937 that the enzyme kallikrein releases kallidin, the peptide responsible for its biological action, from a plasma protein.

Basic investigation has since been directed toward the role of angiotensin in renal hypertension. Gross, who in 1958 reported an inverse relationship among sodium balance, renin content of the kidney, and secretion of the hormone aldosterone from the adrenal gland, suggested a feedback mechanism regulating the secretion of aldosterone and renin. Two years later, Laragh and coworkers found that injections of angiotensin consistently increased the rate of aldosterone secretion; they postulated that the



Regular measurements of blood pressure allow early detection and correction of hypertension, a major risk factor for heart attack and stroke.

renal (angiotensin)/adrenal (aldosterone) system may physiologically regulate blood pressure and sodium balance. In the years since, aldosterone has been shown to induce the kidneys to retain salt and water, an action that increases the volume of blood in the circulatory system and raises blood pressure. Angiotensin is a powerful vasoconstrictor that raises blood pressure in response to renal artery stenosis: The body attempts to overcome the narrowing of the renal artery and to provide the kidney with the blood supply it needs.

This research established a connection between kidney function and blood pressure, and it illustrates the fact that in biological research, the relevancy of basic findings is not always apparent. The discovery that the renin/angiotensin system is involved in the release of aldosterone by the adrenal glands, although a surprise to most investigators in the field, was a significant advance in scientific knowledge.

Hypertension is now considered a disease in which the regulatory mechanisms that control arterial pressure within the normal range are disturbed. Since the discovery by Bayliss in 1902 that swelling of blood vessels acts as a stimulus to the muscle cells of the vessel to "spontaneously" regulate blood flow, physiologists have learned that autoregulation permits an organ to keep blood flowing through it at a satisfactory level when arterial blood pressure is increased or decreased, within limits. It has become apparent that a number of factors—the nervous system, the renal/pressor system, fluid volumes outside the cells, and aldosterone—normally take part in controlling arterial pressure and in some types of hypertension are themselves predominant. Much work remains to show how the mechanisms that safeguard the body against high blood pressure fail to operate in disease.

NEED FOR CONTROL

Hypertension as a disease was studied sparingly during the 19th century following Bright's pioneer work. In the 1886 edition of the widely used *Practice of Medicine,*

Flint observed that in patients with apoplexy, the pulse was "full and hard, the artery striking against the finger like a metal rod." But no one perceived the wide prevalence of hypertension until blood pressure had been measured in thousands of individuals. The first systematic study of hypertensive patients was conducted by Janeway between 1903 and 1912. In 1913, Janeway reported that of 7,872 patients, 11.1 percent had at some time sustained a systolic blood pressure of 165 mm Hg or higher, as measured by the Riva-Rocci method. Although he did not speculate whether hypertension causes cardiovascular changes or results from them, he did use the term "hypertensive cardiovascular disease" to emphasize the threat by high blood pressure to the heart and blood vessels. Janeway also noted that the average duration of life after patients developed symptoms associated with high blood pressure was 4 to 5 years. Major causes of death were cardiac failure, uremia, apoplexy, and angina pectoris. Similarly, Paullin in 1926 observed an increase in mortality from "heart and blood vessel weakness" that did not involve renal disease.

Nevertheless, as late as the 1950's, physicians feared lowering high blood pressure in patients because of the belief, promulgated in 1856 by Traube, that hypertension is compensatory and therefore is required to supply adequate amounts of blood to vital organs. Credibility of this view decreased as evidence grew of the need to reduce high blood pressure. It was demonstrated in 1925, for example, that sympathectomy (surgical removal of a portion of the autonomic nervous pathways) lowered blood pressure and improved the condition of a patient with malignant hypertension; in 1926 that the use of nitrites to lower blood pressure in hypertensive patients did not impair the kidney's excretory function; and in 1934 that the use of thiocyanate to lower blood pressure in patients with malignant hypertension did not decrease urea clearance.

The results of a number of investigations had pictured an unfavorable course and prognosis for patients with untreated essential hypertension (high blood pressure with no known cause), when, in 1959, the Society of Actuaries published reliable quantitative data about the risks of death and disease associated with hypertension.

During the "Build and Blood Pressure" study, based on information from 3.9 million policyholders compiled between 1935 and 1954, investigators found that mortality rates increased with a rise in both systolic and diastolic blood pressures. The impetus for this significant epidemiological study came from members of the field of applied economics. This influence continues as insurance carriers become increasingly conscious of the costs of health care. Demonstrating that preventive care and hypertension control can reduce economic losses has been crucial to gaining support for related research and humanitarian endeavors.

Other epidemiological studies in the 1950's and 1960's, particularly those conducted at Framingham, Massachusetts, and supported by the National Heart Institute, reinforced the findings that any sustained elevation of blood pressure, even though moderate or mild, increases the likelihood of catastrophic illness or premature death. In 1970 and 1971, Framingham data established that hypertension is the most powerful risk factor of stroke and is a main etiologic precursor of congestive heart failure as well as a common and potent contributor to coronary heart disease.

Family studies suggest that both genetic and environmental factors affect the etiology of essential hypertension. Other research results demonstrate that substantial restriction of salt and correction of obesity generally lower blood pressure, that regular, vigorous exercise tends to lower resting blood pressure, and that certain relaxation techniques may lower blood pressure. These techniques, however, do not necessarily lower blood pressure to normal levels.

By the 1950's, a number of investigators had demonstrated the value of lowering the blood pressures of patients with malignant hypertension. It was several years, however, before scientists obtained significant evidence that treatment of milder hypertension effectively reduces the risks created by high blood pressure. In 1964, Hamilton and coworkers showed that reduction of blood pressure from diastolic levels averaging 110 mm Hg and higher helps reduce risk to both men and women. In 1967, the results of the well-known Veterans Administration (VA) Cooperative Studies found blood pressure reduction to be effective in reduction of mortality and morbidity for men with initial diastolic pressures of 115 mm Hg to 129 mm Hg. In 1970, a further report from the VA Cooperative Study Group provided evidence of a significant reduction of mortality and morbidity for men receiving antihypertensive drug therapy with diastolic blood pressure averaging 105 to 114 mm Hg.

Moreover, the 5-year mortality findings of the Hypertension Detection and Follow-up Program, published in November 1979, confirm that systematic, effective treatment of hypertension reduces the number of premature deaths caused by high blood pressure. In 1977, the Public Health Service named treatment of hypertension one of the top 10 clinical advances in cardiovascular-pulmonary medicine and surgery.

THE DRUG REVOLUTION IN THERAPY

As evidence accumulated attesting to the dangers of high blood pressure, research on antihypertensive therapy intensified. Identified causes of hypertension—an inadequately perfused kidney, a tumor of the adrenal medulla, emotional stress, toxemia of pregnancy—can frequently be treated specifically and cured. These cases of "secondary" hypertension, however, account for only

about 5 percent of all hypertension cases. The remaining 95 percent are classified as "essential" or "primary" hypertension. Despite the intensive research into this condition, its causes have eluded discovery as have specific curative or preventive measures.

Nearly 150 years ago, in 1835, Osgood described the apparent blood-pressure-reducing effect of a class of drugs called the veratrum alkaloids. There was no significant progress in treating hypertension with drugs, however, until the late 1940's and in the 1950's, when detailed information appeared about the use of veratrum, rauwolfia alkaloids, hydralazine, and the ganglion-blocking drugs. In 1945, the available drug therapies for hypertension were limited to three medical agents, thiocyanate, kidney extract, and vitamin A, and to two surgical procedures, nephrectomy (removal of a diseased kidney) and sympathectomy.

The ganglion-blocking agents were widely used in the early 1950's and provided effective results in most hypertensive emergencies. Unfortunately, they were difficult to use in chronic hypertensive therapy because of their severe side effects and frequently erratic levels of control.

The introduction in 1957 of chlorothiazide, the first practical diuretic (a drug tending to increase the excretion of sodium and flow of urine) for hypertension, was an important advance in therapy. Interestingly, investigations leading to the development of diuretics stemmed from a search not for an antihypertensive drug but for a substance to relieve edema in patients with congestive heart failure. When used alone, chlorothiazide not only controlled blood pressure in many hypertensive patients but also made the antihypertensive effect of other agents more potent, continuous, and predictable. Chlorothiazide and the subsequently developed thiazide derivatives produced the same beneficial result when used in combination with the more potent antihypertensive drugs, particularly guanethidine and alphamethyldopa (which were introduced into clinical practice in 1959 and 1960 and which largely replaced their predecessors), and also when used in combination with the still newer beta-blockers, clonidine, and vasodilators.

Development of these drugs was based on a variety of principles discovered by biochemically trained pharmacologists who had become interested in the biosynethesis, storage, and metabolism of vasoactive compounds. The drug industries, in turn, had committed considerable research effort to routine screening for antihypertensive drugs, to the logical synthesis of new compounds, and to the purification and synthesis of the active principle of drugs discovered empirically, such as reserpine. To complete the process, clinical physiologists and clinical pharmacologists had become expert in controlled clinical trials of new drugs. Elsewhere in this report, there is a description of a recently completed program that has demonstrated the effectiveness of drug therapy for hypertension.

SALT RESTRICTION

Since the beginning of this century, theories about the value of dietary salt restriction as a remedy for hypertension have varied. In 1904, Ambard and Beaujard first perceived a relationship between chloride balance and blood pressure and advocated a salt-free diet for persons with hypertension. In 1909, Blum noted that the sodium rather than the chloride in salt is the chief factor in water retention. Actual proof of this contention was finally achieved in 1920 through the work of Blum and Magnus-Levy. Shortly thereafter, Allen and Sherrill rediscovered the salt-free diet, and Kempner's 1944 rice diet heightened interest in reducing salt intake to lower blood pressure. The popularity of this treatment eventually succumbed to antihypertensive drug therapy, and in 1972, a team of investigators recommended salt restriction only for hypertensive patients with kidney failure.

Recently, however, a number of scientists have argued persuasively in favor of salt restriction for all hypertensive patients. This change in attitude appears to have resulted from a recognition that the typical sodium intake is much greater than the body needs, from an increased awareness of the potential dangers of lifelong antihypertensive drugs, and from improved evidence that reduced sodium intake can reduce some side effects of diuretics. This evidence has stimulated a search for alternative treatments such as low-salt diets, which are used as adjuncts to most forms of antihypertensive therapy today.

In 1979, the NHLBI-commissioned Task Force on Hypertension recognized the relationship between dietary sodium and hypertension and agreed that sodium restriction is important in the treatment of some hypertensive patients. In its report, however, the task force noted that it is not known whether limiting sodium intake will prevent high blood pressure. Until more facts are available, the group recommended restraint in advocating reduced sodium consumption for the general public. Basic, clinical, and epidemiological investigations are expanding the understanding of sodium intake and other risk factors, but until the mechanisms of hypertension are better understood, antihypertensive drugs will remain the mainstay of therapy.

HIGH BLOOD PRESSURE CONTROL IN THE WORKSETTING

The NHLBI supported three 24- to 30-month studies to determine the feasibility of high blood pressure control

in the worksetting. Subjects were screened, referred to medical care, and followed up with emphasis on recording changes in their health status and cost of care. These studies indicate that age and weight influence the incidence of hypertension, that control status is not affected by race, and that control is more effective for women than for men. Among those subjects who received treatment, blood pressure control was greater in proportion to aggressive followup procedures. Results of the three projects indicate that short-term hypertension control in the worksetting is indeed feasible. Although all three projects concluded in 1981, two of the three groups plan to continue their efforts.

INFLUENCE OF HYPERTENSION DETECTION AND FOLLOW-UP PROGRAM

Despite the virtual revolution in hypertension therapy since the Second World War, resistance to widespread clinical acceptance of antihypertensive therapy existed as late as 1974, when Fry asserted that the dangers of untreated hypertension in older patients are so minimal that treatment is not warranted. The incidence of the predominantly atherosclerotic complications of hypertension—including coronary heart disease and atherothrombotic strokes—was not reduced significantly in the 5 to 7 years of the VA and U.S. Public Health Service trials of treating mild to moderate hypertension. The small number of participants and low number of events did not allow an adequate test of the efforts of therapy. Proger noted in 1972 that these "nonfindings" blunted some of the enthusiasm for antihypertensive drug therapy.

Moreover, although the VA trials had demonstrated that drug therapy was effective in preventing stroke, renal failure, and heart failure in men with moderate to severe hypertension, the VA findings were not representative of hypertension found in the general population, women, minorities, the young, or individuals with "mild" hypertension (those with a diastolic pressure between 90 and 104 mm Hg).

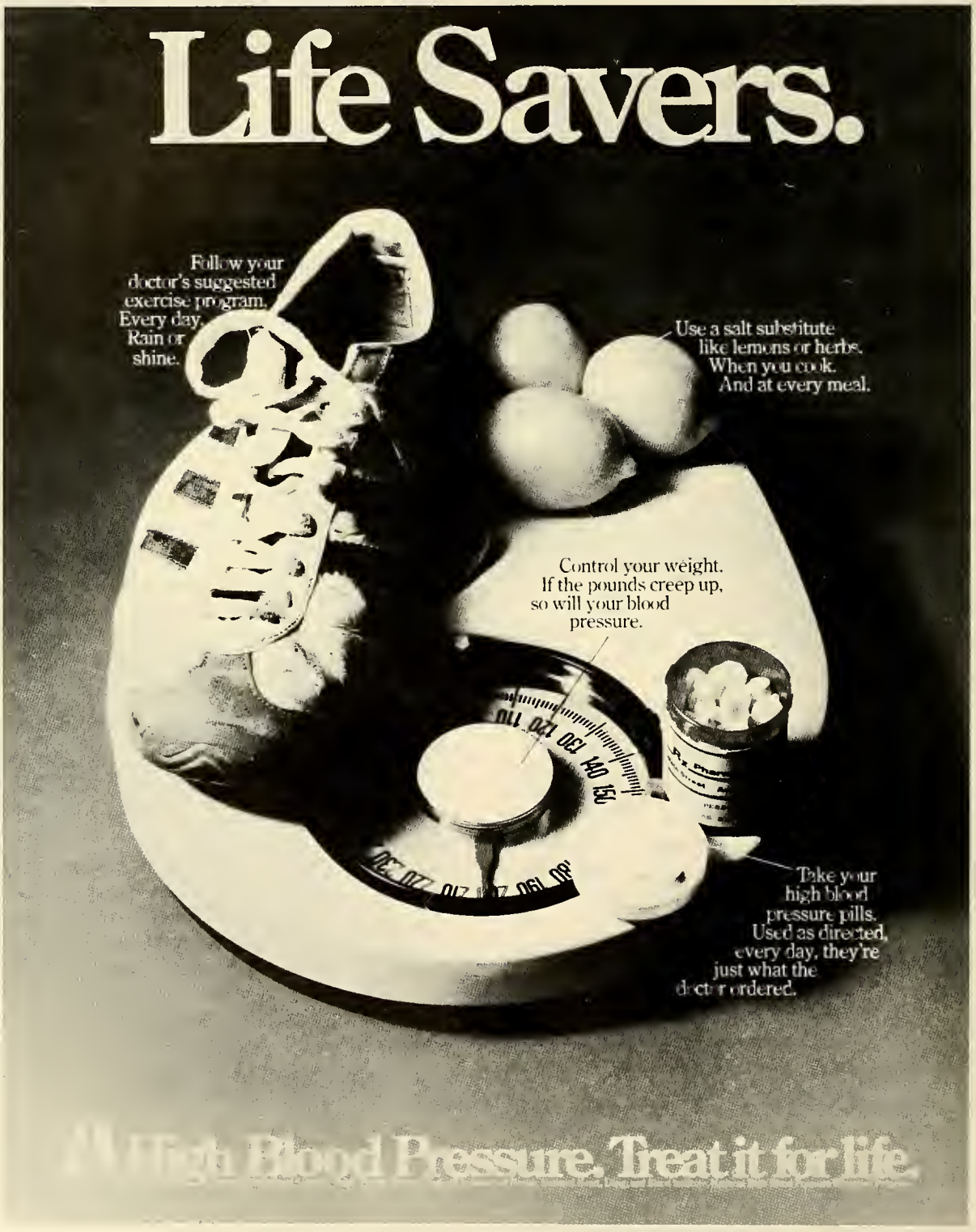
In light of the major problems with these studies, the NHLBI appointed a panel of experts in 1970 to assess the need for additional trials on control of hypertension. After reviewing the results of the VA trials, along with other studies, the panel made the following recommendation: A study to assess the effectiveness of antihypertensive therapy in reducing morbidity and mortality from hypertension in the general public should include both sexes, all races in a community, and younger adults as well as middle age ranges. A study of this type should not use a placebo group but should allow randomization of subjects for comparison of optimum drug regimens versus the customary medical care in the community.

The NHLBI launched the massive HDFP in 1972. The results of the completed study demonstrated among a general population the need to prescribe a vigorous, well-controlled, systematic treatment program for hypertensive patients to reduce their blood pressure levels to normal regardless of the level of elevation. For the first time, a significant reduction in incidence of premature deaths as a result of treating even mild hypertension was demonstrated. Of 10,940 persons with high blood pressure, one-half (randomly selected) were assigned to stepped care (SC) and offered 5 years of free followup care at the program clinical centers. The other one-half of the participants were directed to private physicians for referred care (RC). For the SC patients, blood pressure goals were established and therapy with antihypertensive drugs was increased stepwise to achieve and maintain diastolic blood pressure at or below the set goals. Staff of the program centers prescribed only FDA-approved antihypertensive agents; new drugs approved by the FDA during the trial period were made available for the later portions of the study. As specified by the protocol, the drug dosage and regimen were adapted to minimize side effects and maintain control of blood pressure. Every effort was made to facilitate and encourage adherence to the regimen.

The results of the study were positive and significant:

- After 5 years, the SC program had placed a larger proportion (78 percent) of patients on continuing antihypertensive treatment than had the RC program (58 percent).
- Sixty-five percent of the persons in the SC group reached or exceeded blood pressure goals at 5 years compared to the RC group, of which only 44 percent attained these blood pressure levels.
- The overall death rate for SC participants was 17 percent lower than that for the RC group.
- Of those with mild hypertension, death rate for the SC group was 20 percent lower than that for the RC group.
- Deaths from stroke were 45 percent lower for the SC group than for the RC group.
- A reduction in deaths of 18.5 percent for black men and 27.8 percent for black women has important implications for future benefits from treatment of hypertension in the black population.

It is important to remember that the control group in this study was *not a placebo group*. Rather than comparing good care with no care, this study compared systematic care directed to uniform blood pressure goals with the typical care offered in American communities. The improved routine care of high blood pressure that has been provided in communities in recent years considerably heightens the significance of this study and of its basic finding that systematic care of even mild hypertension does indeed


Life Savers.
Follow your doctor's suggested exercise program. Every day. Rain or shine.
Use a salt substitute like lemons or herbs. When you cook. And at every meal.
Control your weight. If the pounds creep up, so will your blood pressure.
Take your high blood pressure pills. Used as directed, every day, they're just what the doctor ordered.
High Blood Pressure. Treat it for life.

improve the length and quality of life. Health professionals and the millions of persons who have high blood pressure now have a greater incentive to improve the management of high blood pressure.

Activities of the HDFP will continue for another 2 years, during which time the NHLBI will analyze morbidity and mortality data related to the subjects of the study and will publish these findings for the health profession and for the public. As SC participants in the study transfer to community health care, the NHLBI will monitor a representative sample of SC and RC patients over the 2-year period to assess the effects of this transfer of treatment on SC patients.

Future Directions

The HDFP obviously would not have been possible had not scientists from many disciplines and many vantage points contributed knowledge leading to an improved understanding of treatment of hypertension. The accomplishments highlighted here only hint at the magnitude of the scientific enterprise undertaken to date.

The use of antihypertensive drugs for patients with heart failure is a prime example of the contribution of hypertension research to medicine. For years, doctors recognized that vasoconstriction accompanies heart failure, but the knowledge of its significance in pathophysiology was not applied. In recent years, however, vasodilator drugs that were developed for the treatment of hypertension have proved lifesaving for many people with heart failure. Moreover, drugs developed for treatment of hypertension have been used to effect the controlled lowering of blood pressure, a particular aid to many types of neurosurgery.

Recognition of the importance of the renin/angiotensin system in regulating aldosterone production is a result of hypertension research. Related fundamental information has increased the understanding of certain types of heart failure, liver disease, and kidney disease.

Development of the field of prostaglandin (a hormone-like fatty acid) biochemistry and physiology followed upon the observation that seminal fluid lowers arterial pressure. Already, research efforts in this field have affected diverse topics, such as obstetrics, blood clotting, and certain digestive diseases. Similar effects occurred for the kallikrein/kinin system.

Hypertension has enormous social and economic implications and accounts for a major share of death and disability in the United States. Research in the last four decades has enhanced understandings of hypertension considerably, but further knowledge is needed to develop safe and effective preventive measures and improved treatment. In addition to providing important clinical advances in the management of high blood pressure and associated diseases, basic research on hypertension will likely produce "spin-offs" such as those described above that will have a major effect on controlling other human diseases.

The Institute will continue to support fundamental research on inhibitors of kinins, kallikreins, and prostaglandins to better understand the physiological actions of these hormones; basic and clinical activities to examine the effects of restricted salt intake and weight control; efforts toward improved diagnosis, treatment, and prevention of hypertension; and a broadly focused hypertension education program directed toward the general public and the medical community.

Chronic Obstructive Pulmonary Disease

Respiratory diseases are among the leading causes of death and disability in the United States. About one in every five people in this country experiences some chronic respiratory problem, and chronic obstructive pulmonary diseases are the fastest rising among the leading causes of death in the United States.

The two most prevalent forms of COPD are chronic bronchitis and emphysema. COPD involves progressive, disabling conditions affecting approximately 9 million Americans, severely limiting their lifestyles and shortening their lives. This disease accounts for almost 49,000, or 2.5 percent, of all deaths every year, the fifth leading cause of death in the United States (table 5). Although the mortality rates for other leading causes of death have declined over the last 10 years, mortality from COPD has rapidly increased by about 1.4 percent per year. The cost associated with this disease category in health care and in wages and time lost from work now exceeds $19 billion annually.

When the National Heart, Lung, and Blood Institute program was developed in 1972, very little progress had been made in understanding the processes and characteristics of COPD. The goal was to identify common factors among COPD patients to predict and perhaps control the course of the disease. It was also necessary to examine existing treatment and seek new methods of treatment to improve lifestyles and prolong lives. Over the past 10 to 15 years, research has progressed; however, more basic and epidemiological research is needed. The Institute's present and long-range objectives for COPD lie within three major areas of research: identification of factors that control the risk of developing COPD so that preventive measures can be initiated; investigation to develop methods to detect structural and functional abnormalities, which will help to delay the onset and progression of the disease by means of early diagnosis; and assessment of current

Table 5. Numbers of Deaths From Chronic Respiratory Diseases, United States, 1978

Cause of Death	Number of Deaths
Emphysema	15,627
Bronchitis, chronic and unqualified	4,376
Other obstructive lung diseases	28,613
Subtotal	48,616
Asthma	1,872
Cystic fibrosis	505
Sarcoidosis	284
Acute bronchitis and bronchiolitis	756
Pneumoconiosis	1,422
Other chronic interstitial pneumonia	3,146
Bronchiectasis	653
Pulmonary heart disease	1,412
Pulmonary embolism and infarction	10,941
Acute edema of lung	238
Hyaline membrane disease	2,671
Respiratory distress syndrome	3,341
Asphyxia of newborn	2,965
Immaturity, unqualified	3,679
Total chronic respiratory disease	82,501

Source: Division of Vital Statistics, National Center for Health Statistics, *Vital Statistics of the United States*, Volume II, Mortality, 1978.

therapeutic measures and development of more effective regimens to improve the management of patients currently suffering from COPD.

Chronic obstructive pulmonary disease is one of the most devastating and expensive health problems faced by all Americans and medicine today. Solving this problem in the future will require an even greater and more concerted effort linking basic, clinical, and epidemiological research, training, and patient care.

Historical Perspectives

The term chronic obstructive pulmonary disease refers to those chronic diseases characterized by increased resistance to flow in the airways of the lungs, generally resulting in shortness of breath, wheezing, and cough productive of sputum. This term includes such entities as chronic bronchitis and emphysema.

Chronic bronchitis is characterized by inflammation of the walls of the airways, which triggers the production of mucus. A patient with the disease coughs and produces sputum. Eventually, the inflammation and the mucus partially obstruct the airways and cause shortness of breath.

Emphysema, on the other hand, is defined as a disorder of anatomy—the permanent enlargement of any part of the acinus (terminal part of the airway), and is accompanied by destructive changes. Emphysema destroys the walls of the air sacs, which help support the airways, and thus impedes airflow just as in bronchitis. This destruction of tissue in the airways results in a loss of lung elasticity and in decreased lung surface area available for gas exchange. The ability of the lungs to absorb oxygen and release carbon dioxide is disrupted.

Chronic bronchitis and emphysema commonly coexist, and the majority of COPD patients suffer from a combination of the two (figure 11). Recognizing these entities separately or determining their relative importance may be difficult or impossible in the living patient and at

autopsy. Today, COPD is the most common chronic pulmonary disorder and appears to be increasing in prevalence. In addition, COPD is now the fifth leading cause of death and the second leading cause of disability in the United States.

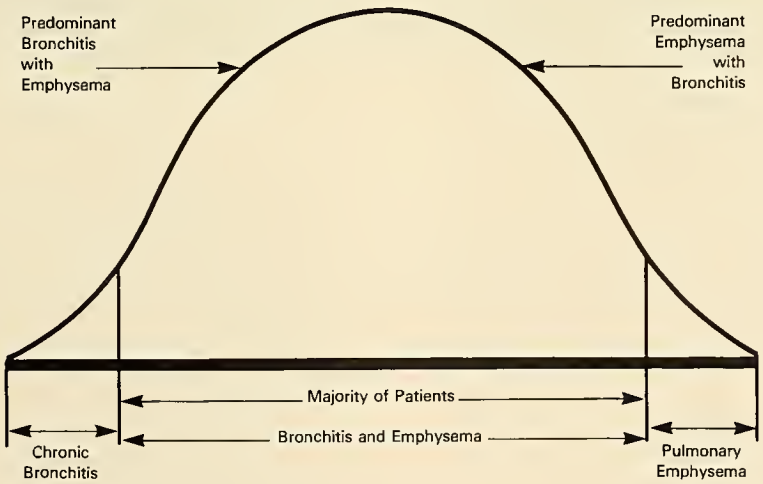
The first known reference to COPD in medical history was made as early as 1713 by Ramazzini. At that time, chronic lung diseases were just beginning to be recognized as serious threats to human health and be linked to occupational conditions. In describing diseases of tradesmen, Ramazzini noted that glassmakers, like other industrial workers, were "subject to the diseases of the breast (and are so exposed) so that Nature, tho' strong and robust, can't long bear such violent and sudden changes; but must needs sink under pleuresies, asthmas, and chronical coughs."

The term bronchitis was first used in a clinical account by Badham in 1808, and in 1819, Laennec gave the first anatomical description of pulmonary emphysema. The illustration accompanying Laennec's description follows. In industrialized Europe, where COPD has been a major cause of fatal illness for at least two centuries, little attention was given to this complex of diseases until the end of the first half of the 20th century. Collis, who undertook in 1923 a detailed review of mortality and morbidity statistics in Great Britain, stated:

> The trite observation that familiarity breeds contempt is essentially true with regard to the outlook on chronic bronchitis: those afflicted are inclined to accept the complaint as inevitable, as something troublesome but not serious. Those called upon to treat it do not find it sufficiently interesting to study closely. At a hospital it tends to be disregarded with an out-patient mixture yet . . . records in England and Wales show that when mortality and morbidity are taken together, bronchitis is the most important of all diseases and further . . . it is at the same time a most preventable disease.

There was little medical attention until 1951, when the Association of Physicians of Great Britain and Ireland held a symposium on chronic bronchitis. In 1953, Oswald and colleagues published an account of the clinical features of 1,000 cases, and Goodman and coworkers, impressed by the predominance of chronic lung disease as a cause of severe disablement, reviewed the data on mortality and morbidity. They drew attention to the large excesses of mortality among men in the lower social classes, in urban areas, and in certain industrial occupations.

It was not until 1953 that the British Medical Research Council established a committee to advise on research on



Spectrum of the emphysema-bronchitis complex. There are relatively few patients with pure bronchitis or pure emphysema, and most patients have combination of both diseases. (Modified from Rodman, T., and Sterling, F.H.: Pulmonary emphysema and related lung diseases, St. Louis, 1969, The C.V. Mosby Co.)

Figure 11. Spectrum of the emphysema-bronchitis complex: Chronic bronchitis and emphysema commonly coexist.

Many occupations pose a high risk for the development of lung diseases.

chronic bronchitis. The sudden interest in studying this pulmonary disease was probably due to an increased death rate linked to a dense, cold fog that hung over London between December 5 and 9, 1952, resulting in approximately 4,000 deaths predominantly of people already suffering from chronic respiratory or cardiovascular disease. In the United States and other nations, interest in COPD was also renewed following this event.

EARLY LUNG INVESTIGATIONS

Galen recognized the need for fresh air and believed that it reacted with the blood in the left heart and arteries to produce the "vital spirit." The absence of a visible communication between the pulmonary artery and the pulmonary vein led him to suggest that blood passed through invisible pores between the two sides of the heart; he therefore failed to appreciate the true function of the lung.

The "invisible" passage of blood was finally recognized as false in the 17th century when Harvey and Malpighi independently proposed that blood passes from the pulmonary artery through the lung to the pulmonary vein. In the mid-1600's, Harvey demonstrated the circulation of blood through the lung, and Malpighi indicated the proximity of the capillaries to the smallest air spaces.

The discovery of oxygen by Priestley was made in 1775, but work during the previous century clearly demonstrated the role of ventilation by the lungs in maintaining life. A number of discoveries, including Lower's observation that the uptake of air in the lung causes the blood to change color, provided the foundations for subsequent studies of gas exchange, but their importance was not immediately apparent. The confusion was noted by Samuel Pepys, who, after a meeting of England's Royal Society on the subject of respiration, in 1666 wrote in his diary, "it is not to this day known, or concluded on among physicians . . . how the action is managed by nature, or for what use it is."

Information about the lung, which was necessary for the development of the field of respiratory physiology,

increased at different rates, and it reflected immediate scientific interest and the techniques available for investigation. The stroke output of the lung bellows, or the amount of air that a person can inhale during a single deep breath, was the first aspect of function to be investigated. Stroke output was measured by Borelli in 1679 and used as a lung function test by Hutchinson in 1846. Hutchinson defined the "vital capacity" as "the greatest voluntary expiration following the deepest inspiration," and he designed a spirometer for estimating it. He showed that vital capacity is related to a person's height so that "for every inch of height (from 5' to 6') eight additional cubic inches of air at 60°F are given out by forced expiration." Hutchinson further showed that the vital capacity decreases with age and is reduced by excess weight and by disease of the lung.

During the early 1800's, there was interest in the mechanical properties of the lung, but because of the absence of suitable techniques for measurement, progress was slow. Intensive studies of gas exchange in the lung were initiated around 1890. The studies led to a broader understanding of the respiratory function of the blood and of the implications for gas exchange between lung ventilation and perfusion.

MECHANISMS OF PATHOGENESIS

Soon after Hutchinson developed the spirometer for measuring forced expiration, Donders demonstrated in 1849 the role of the elastic recoil of the lung in causing expiration. In 1915, Rohrer applied the concepts of Newtonian mechanisms to explain the relationship between the force exerted by the respiratory muscles and the rate of airflow. Neergaard extended this work and also demonstrated the role of surface forces in the lung by comparing the relationship of lung volume to retractive force when the air in the lung is replaced by water. Between 1939 and 1946, several investigators extended these studies of the viscoelastic properties of the lung. The results led to the discovery of lung surfactant (surface-active substance).

That pioneering discovery was made in 1964 by Eriksson, who associated emphysema with a markedly decreased ability in the body fluids of some persons to inhibit a specific enzyme (trypsin) that can "dissolve" lung tissue. This disorder, severe alpha$_1$-antitrypsin (A_1AT) deficiency, is due to a rare genetic trait that occurs in approximately 1 in 2,000 people. Less severe reductions of this protease inhibitor are found in approximately 2 to 10 percent of the population. In individuals with this genetically related form of emphysema, the disease begins earlier, is more severe, is characterized by difficulty of respiration rather than cough, and frequently is unassociated with a prior history of bronchitis.

Although severe deficiency of A_1AT is thought to account for less than 5 percent of all emphysema cases in the United States, research has contributed greatly to the current concept of the pathogenesis of emphysema. This concept explains that progressive destruction of alveolar tissue in the lungs results from an excessive enzyme activity (proteases, especially elastase) that destroys lung tissue and also destroys inhibitors such as A_1AT that act to keep this destruction in check. If the inhibitors are deficient, or if the proteases are in excess, the equilibrium is disturbed. The disturbance provides the conditions for degradation of tissue, especially of elastin, which is a structural protein that makes up 25 to 30 percent of lung connective tissue and gives the lung its elastic properties.

Fig 7.

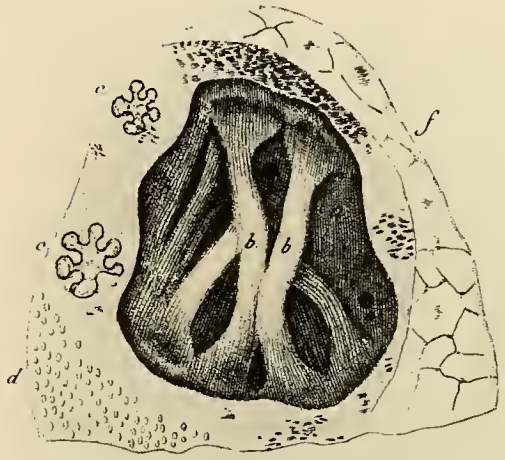
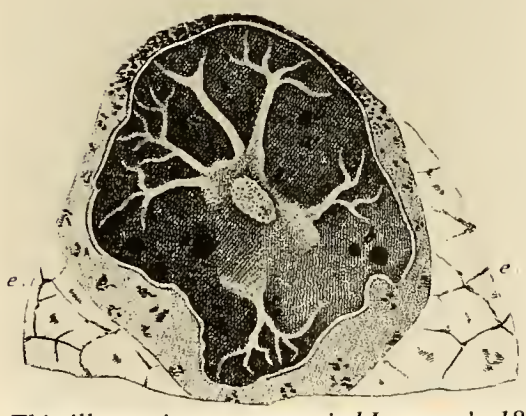


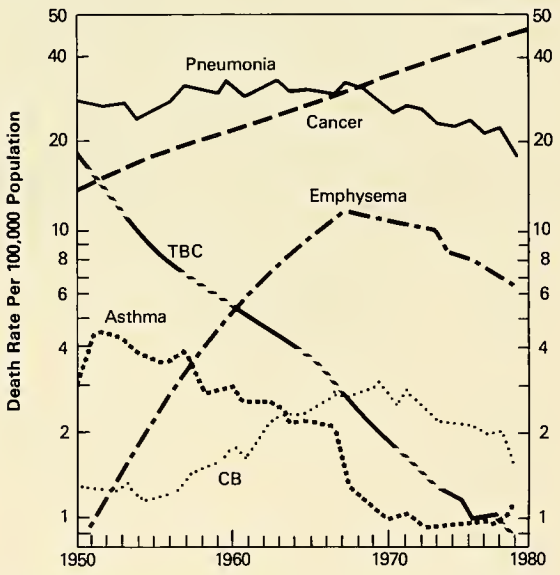
Fig. 8.



This illustration accompanied Laennec's 1819 anatomical description of pulmonary emphysema and notes the destructive enlargement of the tiny airways in the lungs.

Recent investigations have found that several of these proteases are made by the cells that defend the lung against bacteria and other foreign agents, such as particulate matter from cigarette smoke. When these defending cells—leukoctytes and macrophages—ingest such foreign matter, they may spill their enzymes onto the surface of the lung. Thus, the total protease activity in the lungs is increased considerably in cigarette smokers and enhances the prospects for lung damage.

Other recent fundamental studies show that oxidants in cigarette smoke inactivate the inhibitors that ordinarily prevent the enzymes from degrading lung proteins. Experiments show that the addition of antioxidants prevents the inactivation of the protective material. If this finding is confirmed in animal and human studies now in progress, it would demonstrate one possible explanation for the strong association between cigarette smoking and the occurrence of emphysema. It is also of potential clinical value, since drugs may be used to block some of the adverse effects of cigarette smoke.



Death rate among U.S. populations from leading respiratory diseases in the years 1950-1979, showing sustained rise of mortality from neoplasms of the respiratory system (CA) and from emphysema, and the decreasing mortality from tuberculosis of the respiratory system (TBC); there is a slower rise for chronic bronchitis (CB) and a decline for asthma; pneumonia has been stable for the past 10 years. (Data reproduced by permission from: *Vital Statistics of the United States*, Vol. 11, Mortality, 1950 through 1979, Washington, U.S. Government Printing Office.)

Figure 12. Death rate among U.S. populations from leading respiratory diseases, 1950 to 1979: Overall incidence of COPD has increased.

RISK FACTORS—Smoking

The increase in reported incidence of COPD over the past 30 years (figure 12) is attributable in part to improvements in techniques for its detection. There is also a real increase because of greater environmental and occupational exposure to agents implicated in the pathogenesis of COPD.

Epidemiologists are making significant advances in the understanding of risk factors for COPD. Over the past 25 years, studies have been made of the prevalence and correlates of mucus hypersecretion, chest illnesses, airflow obstruction, and death rates from chronic respiratory diseases. The broad conclusion that can be derived from all these studies is that cigarette smoking is now the most important cause of COPD.

Results from six major prospective studies conducted from mid-1950 to mid-1960 related smoking to mortality from COPD (table 6). These studies represent more than 13 million patient years of observation and about 270,000 deaths from all causes. The number of deaths related to COPD is probably underestimated, since some of the deaths attributed to pneumonia or myocardial disease may be due to complications of COPD. These mortality figures also do not include a sizable number of individuals for whom COPD may have been a major contributory cause of death. It is not uncommon, for example, for individuals to have COPD and lung cancer at the same time.

In addition to an increase in deaths from COPD, cigarette smokers have an increased prevalence of respiratory symptoms and diminished performance on testing for pulmonary function compared to nonsmokers. The adverse effects on the lungs of smokers have been demonstrated in very young, working-age, and elderly populations. Doll and Peto recently reported their 20-year followup of 34,440 British male physicians. The data demonstrate an increased mortality ratio in all current smokers and a dose-response relationship to the number of cigarettes smoked. They also found a 1.5-fold higher death rate in smokers who inhaled as compared to smokers who did not inhale.

RISK FACTORS—Pollution

The relationship of COPD to air pollution remains controversial. The difficulty in determining this relationship lies in the problem of controlling other potential risk factors such as socioeconomic class, degree of crowding, ethnic differences, and age distribution, and of determining the exact types and amount of individual exposure to pollution. Smoking as a form of individual air pollution must also be taken into careful consideration. Measuring individual exposure, even within a small area, is difficult, since both amount and type of exposure can vary dramatically from one area to another.

Table 6. COPD Mortality Ratios of Current Cigarette-Only Smokers in Six Prospective Epidemiological Studies

Study (date)	Mortality Ratio*		
	Emphysema and/or Bronchitis	Emphysema Without Bronchitis	Bronchitis
British doctors (1956)	24.7		
Men in 25 States (1966)			
Age 45-64		6.55	
Age 65-79		11.41	
U.S. veterans (1966)	10.08	14.17	4.49
Canadian veterans (1961)		7.7	11.3
Men in 9 States (1958)	2.30		
California occupations (1960)	4.3		

* Ratio of nonsmokers = 1.0

Two basic approaches in study design have been utilized in an effort to control as many of these variables as possible. The first is to find areas where different pollution levels are measured carefully and then to select comparable populations in these areas. Thus, a population in a low-pollution area can be compared with a similar population in a high-pollution area. The second approach is to select a reasonably uniform population, such as twins, to measure individual responses to different pollution exposures.

The Community Health and Environmental Surveillance System (CHESS) in 1970 to 1971 used the first approach to evaluate excess COPD in subjects from two communities having different levels of air pollution: Salt Lake City (high), and the Rocky Mountain area (low). Results showed that smoking and exposure to air pollution have a synergistic effect and that smoking is the most important risk factor in developing abnormal pulmonary function.

The second study design was used in a survey of telephone repairmen and installers in 1962 and 1967. The survey revealed no relation between pulmonary symptoms and degree of urbanization of place of work or place of residence. It can be speculated that the lack of positive evidence linking urbanization with pulmonary symptoms is a result of the crude estimation of exposure to pollution. The investigators were able, however, to establish a strong correlation between smoking and pulmonary symptoms. These and a variety of other studies indicate that if air pollution increases the risk of COPD, it is small compared to the risk of cigarette smoking. The possibility remains that the two kinds of exposure may interact to increase the total effect beyond that which each kind of exposure separately contributes. Similarly, an increased prevalence of COPD has been found due to exposures to coal, granite dust, and cotton fiber, but in none of these studies is the relationship of COPD to occupational environments as strong as that to smoking.

DETECTION

A particularly difficult problem in the treatment of COPD is that the disease is insidious. Many victims are unaware of their condition until symptoms appear and irreversible lung damage has occurred. For this reason, emphasis is placed on early detection of structural, physiologic, and biochemical abnormalities that precede the development of symptomatic, irreversible diseases.

One promising biochemical method for early detection is the measurement of elastin-breakdown fragments in the urine. Desmosine has been identified as a degradation product especially useful in research because it is not absorbed by the digestive tract and is not utilized by the body. The amount of this substance present in urine is a true measure of tissue degradation. This recent line of research is being pursued actively in many laboratories.

Confirmed and validated results would permit monitoring the effect of interventions in COPD as well as detecting the pathological process long before changes in pulmonary function tests can be observed.

TREATMENT

Nearly two centuries ago, Beddoes and Watt developed a means to treat asthma by instructing the patient to inhale oxygen through a face piece of oiled silk. Other therapies for patients with asthma and COPD have long been recognized: oxygen administration by a face mask (1917); oxygen tents (1921); oxygen administration by a nasal catheter (1929); inhalation of a mixture of 80 percent helium and 20 percent oxygen (1936); inhalation of nebulized solutions (aerosols) of bronchodilator drugs (1940); and intermittent positive pressure breathing (IPPB) with air (1978).

Unfortunately, the present therapy for COPD is largely palliative and treats only symptoms. A recently completed clinical trial undertaken by the NHLBI concluded that 12-hour (nocturnal) oxygen therapy is not as beneficial as 24-hour (continuous) low-flow oxygen therapy in extending the lives of patients with severe respiratory impairment. Earlier investigations indicated that nighttime administration of oxygen, which is less costly and more convenient than round-the-clock oxygen therapy, appeared to prevent complications of oxygen deficiency such as increased numbers of circulating red blood cells and elevated pressures in the pulmonary artery. Results of this study, however, indicated that mortality was twice as great among patients in nocturnal oxygen therapy than among those in continuous therapy. Another NHLBI-sponsored clinical trial seeks to establish the efficacy of intermittent positive pressure breathing as a therapy for ambulatory COPD patients. Results of these trials are expected to have substantial impact on home care and treatment.

Important new contributions are also being made to alleviate discomfort experienced by COPD patients by teaching them to condition their ventilatory muscles through exercise training. This type of therapy is a result of extensive research into the role of the diaphragm and the respiratory and ventilatory muscles in the breathing process.

Future Directions

The natural history of most chronic diseases, especially of emphysema and other obstructive pulmonary diseases, is represented by figure 13. During the 135 years following the first post-mortem observation of emphysema in 1819, investigators learned to identify emphysema through clinical and x-ray examinations. That knowledge, however, did not provide a control. Since the mid-1950's, research has broadened understandings of the functional consequences of emphysema through development of refined pulmonary function tests and correlations with alterations in lung anatomy.

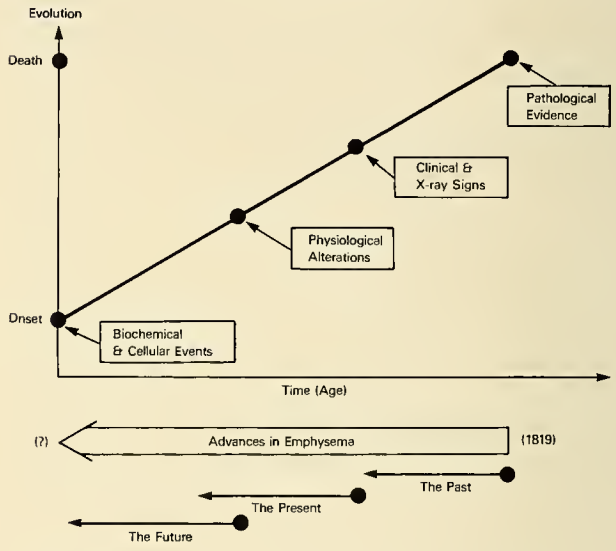


Figure 13. The natural history of emphysema is represented, from onset to death.

Despite the importance of this knowledge, the opportunity to apply it comes too late in the course of the disease to prevent or interrupt irreparable structural damage. The goal of scientists is to discover and understand the events that occur prior to physiological destruction. The disease must be recognized through its biochemical and cellular manifestations. If the results of steady research on COPD during the past 26 years are any indication, that goal may indeed be within reach.

Over the past three decades, research has advanced fundamental knowledge of the physiological behavior of the lung and its derangement in disease. Although the research has provided many useful clinical insights into the patterns of physiological disorders of the lung, it has not determined the precise basis of the disease. Such disorders of respiratory function are usually the result of pulmonary diseases and are frequently life threatening. Continuing detailed study of normal lung tissue and function is a prerequisite to the study of pulmonary disease states.

The lack of an adequate base of information about the structure and function of the lung in relation to health

and disease is an obstacle to finding solutions to many specific lung disease problems.

The lung is no longer viewed as a simple mechanical organ alternately expanding and contracting to draw in or expel air. Rather, it is now known that in addition to its ventilatory function, the lung is a complex organ comprising many different types of cells, acting and interacting in concert, and accomplishing a variety of hormonal and metabolic functions that may affect not only the lungs but the entire body.

Any subtle change in structure or function of these interrelated parts may cause disease. For this reason, it is essential that research on fundamental mechanisms involving molecular biology, biochemistry, immunology, endocrinology, and cell biology be emphasized in order to understand more about the etiology and pathogenesis of all of the major lung diseases. The insights gained from fundamental research are necessary in order to open new possibilities for prevention, early diagnosis, and treatment.

Viral Hepatitis

Historical Perspectives

If indeed the "Huang-ti nei-ching su-wen"—the most revered medical textbook in China—was compiled by Emperor Huang-ti in the year 2697 B.C., hepatitis is as old as man himself. An entry in chapter 19, translated by I. Veith, refers to "a disease called numbness of the liver. . . .The liver passes the disease to the spleen. . . . The influences of the spleen create . . . weariness . . . and the complexion will turn yellow." Whether or not this account is almost 5,000 years old, most early descriptions of hepatitis stressed the dramatic appearance of jaundice. Aretaeus the Cappadocian (circa A.D. 120) gave this account: "For it is a dire affliction, the colour being frightful in appearance, and the patients of a golden colour; for the same thing is not becoming in a man which is beautiful in a stone."

Although the epidemic character of the disease was well known, even to the Greek writers of the 5th century B.C., it was not until the 8th century A.D., in a letter from Pope Zacharias to the Archbishop of Mainz, that the contagious nature of hepatitis was first suggested. However, despite the many outbreaks of hepatitis that were recorded subsequently, especially those occurring in military campaigns, only in the early part of the 20th century was it widely accepted that hepatitis could be infectious.

From the Middle Ages onward, "campaign jaundice," as it came to be known, was frequently reported during wartime. Conditions characterized by warfare, such as crowding and poor hygiene, seemed to provide an environment that favored development of the disease. The troops of the American Revolution were not to escape it. Surgeon James Tilton, of the Delaware Regiment in George Washington's army (see illustration), afterward wrote of his experiences: "In the year 1776 . . . our raw and undisciplined condition at that time subjected the soldiers to great irregularity. . . . The camp became excessively filthy. All manner of excrementitious matter was scattered indiscriminately. . . . Flour was served to the troops instead of bread. We could only make sodden bread and dumplings. . . . Many were afflicted with the jaundice. . . . I shared the fate of the rest, and I shall never forget my fatiguing march from the North River to Brunswick, with the jaundice on me." Some 70,000 Union troops were disabled by hepatitis in the Civil War. In World War II, 250,000 U.S. soldiers succumbed, while 5 million German civilian and military personnel were affected. Indeed, the extent of the disease was so vast as to influence the strategy of the war.

During the late 1800's, the idea gradually developed that hepatitis is brought about by an infectious agent, and many investigators spent fruitless years searching for a bacterium as the possible cause. The first hint that a virus might be involved came from Scotland in 1890, when S. McDonald wrote: ". . . it may be that the typical condition is only produced when some special virus acts on a previously damaged liver." The greatest impetus to the idea that a virus might be responsible came in 1918 from C. J. Martin, who in writing about jaundice occurring in Egypt commented that "Professor Kartulis, using various microscopical and bacteriological methods, searched for the pathogenic agent in both classes of infectious jaundice, but hitherto in vain. He suggests that it must be invisible, like that of yellow fever." This analogy, drawn by a trained scientific mind, was enough to start a serious hunt for hepatitis viruses.

Episodes of *infectious* hepatitis (now known as hepatitis A) have always been distinguished from outbreaks of *serum* hepatitis (now known as hepatitis B), which was first recognized in the late 1800's in shipyard workers in Bremen. Several cases of smallpox led to large-scale vaccination of these workers, using human "lymph." Some 1,300 were vaccinated, of whom 191 later developed hepatitis. The information obtained in the report of this incident, published in 1855, is a good example of the result of careful scientific appraisal, for it was determined that those who contracted jaundice all received the same batch of vaccine, which was seen to be the culprit.

Similar outbreaks were associated in the 1920's, 1930's, and 1940's with venereal disease clinics, where various forms of treatment, such as injections of arsenic or acriflavine, were performed, often with unsterilized syringes. During World War II, the incidence of hepatitis rose to 30 percent (60 percent in some centers) in syphilitic soldiers

James Tilton was a military surgeon in the army of George Washington.

receiving weekly intravenous injections of arsenic when a few drops of blood were drawn into the syringe before the injection was made, to make sure that the needle was in a vein. In short-staffed and hard-pressed circumstances, blood-contaminated syringes were merely washed in running water. It soon became clear that hepatitis was being transmitted by the act of intravenous injection itself.

Hepatitis B was found under many other circumstances in which injections were involved—for example, in diabetes clinics (before the time of self-administration of insulin) and with measles and yellow fever immunizations. British scientists observed in 1937 that jaundice "may be due to some organism injected with the vaccine or serum." This idea was reinforced in 1939 by the observation that 27 percent of 304 people inoculated with one batch of yellow fever vaccine developed jaundice 4 months after the injection. The most dramatic evidence came in 1942, when 28,585 American soldiers inoculated with yellow fever vaccine developed hepatitis, of whom 62 died. A subsequent discriminating analysis by scientists showed that the most likely source of hepatitis was the human serum used to prepare the yellow fever vaccine. Thereafter, no serum was used from donors with a previous history of jaundice.

In that same year, Winston Churchill planned to visit Stalin in Moscow. He was to fly by way of the Middle

East and needed a yellow fever vaccination. Because the visit was to take place before a vaccine inoculation would have had time to work, the medical authorities decided against it. Several months later, the Director General of Medical Services for the RAF revealed that he had contracted hepatitis from the batch of yellow fever vaccine that would have been used by Mr. Churchill. The course of world events might well have taken an entirely different direction had the Prime Minister become infected with hepatitis at this crucial stage of the war.

The final establishment of a viral cause of hepatitis came from a series of experiments employing human volunteers, first in Germany, then with British and American troops in the Middle East, and finally among the civilian populations of Great Britain and the United States. These were careful experiments, conducted in accordance with the provisions of the Code of Ethics for Human Experimentation of the World Medical Association. They established information about the mode of transmission of hepatitis and some of the physical and chemical properties of the responsible viruses. By 1960, the scientific world, alert to the existence of hepatitis viruses, stood poised on the brink of major advances that in the 1980's hold promise of the virtual elimination of the disease.

AUSTRALIA ANTIGEN

When foreign material, notably protein, is introduced into the blood and the body reacts by producing antibody against the material in an attempt to eliminate it, the material is called an antigen. Viruses, including those of hepatitis, or even pieces of the coat of the virus can act as antigens. The science of immunology deals with this type of situation, and basic research has provided increasingly sensitive and sophisticated laboratory methods for the detection of antigens and antibodies. In 1961, B. S. Blumberg and his colleague A. C. Allison, using a newly developed immunological technique, systematically examined blood of donors from different geographical areas. They sought to determine whether patients receiving blood transfusions would develop antibodies against proteins found in the units of blood they had received. Having had some success, Blumberg continued the search and in 1963 found that certain sera from American hemophiliacs who had been transfused many times reacted with an antigen in serum obtained from an Australian aborigine. It was consequently named "Australia antigen." Subsequent studies by Blumberg showed that the Australia antigen was frequently found in the blood of patients with acute leukemia, and it was postulated at first that the antigen might represent a virus involved in producing this malignancy. In 1966, however, one of Blumberg's patients with mongolism, who did not carry Australia antigen on initial examination, suddenly produced the antigen in a later test. Further examinations showed the patient to have developed hepatitis. A little later, a technician in Blumberg's laboratory working with Australia antigen herself showed symptoms of the disease.

Other workers using techniques similar to Blumberg's then began to demonstrate Australia antigen in patients suffering from posttransfusion hepatitis. Eventually, Australia antigen was shown to be a part of the hepatitis B virus. What started out as an academic exercise in basic immunology eventually led to the award of the Nobel Prize to Blumberg in 1976 for the discovery of Australia antigen, which opened up a new era in hepatitis research. It was impossible to predict this vital development at the time Blumberg began basic studies.

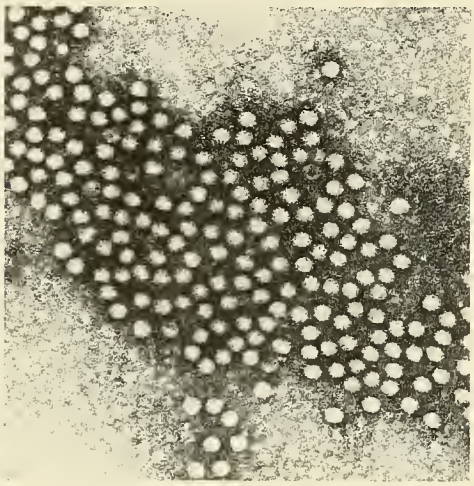
Rapid advances made since the discovery of Australia antigen have relied, to a considerable extent, on the electron microscope. The evolution of this instrument into the powerful analytical tool it now represents has depended greatly on the work of physicists and engineers working in conjunction with biologists. The enormous powers of magnification now available make it relatively easy to visualize particles as small as viruses. The first electron microscope studies of serum containing Australia antigen showed small, spherical particles with knob-like surface structures. Subsequently, examination of the blood of two heroin addicts, who contracted acute hepatitis after sharing syringes, showed tubular structures in many shapes and sizes. Hepatitis B virus is now known to exist as a double-shelled structure, with the small particles and tubular forms found in most sera being noninfectious, surplus, virus surface protein. The illustration on page 46 shows electron microscope photographs of hepatitis viruses magnified 126,000 times.

A, B, AND NON-A,NON-B HEPATITIS

In recent years, immmunologists have marshaled a veritable arsenal of sensitive techniques for the detection of various antigens and antibodies. Several of them have resulted from a combination of methods and ideas from separate disciplines. For example, the technique known as radioimmunoassay (RIA)—the development of which secured yet another Nobel Prize—uses antibodies raised in experimental animals following injection of purified and concentrated virus antigen. The antibodies are isolated, and radioactive atoms are chemically coupled to them. The resulting radioactive antibodies latch on to virus antigen present in a test serum, and this uptake of radioactivity, which can be accurately determined by a suitable detector, is a measure of the amount of virus antigen present in the sample under test. Basic scientific developments in physics, chemistry, and biology, dating back to the discovery of radioactivity by Becquerel in 1895, have made this particular method possible. By

using techniques such as RIA, it has been possible to distinctly separate the viruses of hepatitis A and B. Purified virus suspensions examined in the electron microscope confirm that they are quite different, as shown in the illustration.

(A)



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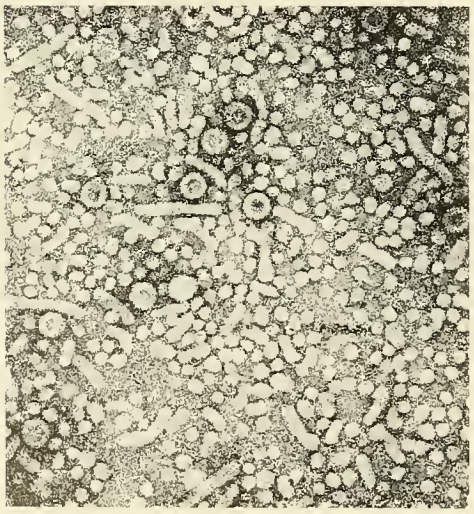


(A) Hepatitis A virus

(B) Hepatitis B virus and Australia antigen. The infectious virus particles appear as double-shelled spheres.

(Zuckerman, A.J., and Howard, C.R., 1979, Hepatitis Viruses of Man. *London: Academic Press.)*

Electron microscope photographs of hepatitis viruses are magnified 126,000 times.

These sensitive tests have also made it possible to eliminate blood donations from carriers of hepatitis B antigen from the transfusion supplies. Yet posttransfusion hepatitis remains, and a whole class of patients with hepatitis exists where no evidence for A or B virus can be found. Such observations have led to the conclusion that a third form of the disease exists, called non-A,non-B (NANB) hepatitis. Furthermore, this condition may be caused by more than one virus. As yet, the viruses have not been properly characterized, and no specific laboratory test to detect NANB hepatitis can be developed until this characterization has been made. This area of active immunological research is of great importance.

A serious drawback to research on all forms of hepatitis is that so far, it has proved nearly impossible to grow the causative viruses in laboratory cultures of tissue. Recently, in 1979, one group of investigators reported that they were able to propagate hepatitis A virus in cells derived from marmoset liver and rhesus monkey kidney. This development may represent the beginning of an important new advance. For the time being, however, the successful utilization of nonhuman primates, especially the chimpanzee, as realistic sources of hepatitis viruses will continue to facilitate research into the disease.

PROSPECTS FOR VACCINES

The elimination of disease and disability is the ultimate goal of modern medicine, and the prevention of disease is of far more concern than is treatment. Smallpox has been removed from the face of the earth, and poliomyelitis has been brought under effective control. In both cases, vaccines were responsible. In order to make conventional vaccines, however, it is necessary to grow large quantities of the agent of the disease for subsequent inactivation and inoculation. In the case of the hepatitis viruses, such large-scale propagation is feasible only in tissue culture, and, as has been pointed out, this activity is not yet possible.

There are unconventional approaches likely to carry considerable promise. Since Australia antigen, which is a portion of the coat protein of the hepatitis B virus, leads to the production of protective antibody, it may well be feasible to use the purified material as a vaccine. Experimental vaccines of this kind have already been prepared using plasma from apparently healthy carriers of Australia antigen, and they have proved safe and effective in chimpanzees. Although two successful small-scale human clinical trials recently took place in France and the United States, this type of vaccine, which is derived directly from human carriers, is a new departure in medical practice, and great caution must be exercised. Concern remains that infectious hepatitis B virus might be inadvertently transferred by the vaccine. A further step in the direction of

safety has been taken by breaking down the Australia antigen into its component parts and then using them after separation and concentration. In this way, the likelihood of intact, infectious virus being found in the resulting vaccine is much reduced.

Hematologists have joined forces with genetic engineers to produce vaccine material in a completely new approach recently reported from France. The gene carrying the message for the production of Australia antigen was removed from hepatitis B virus and placed into another unrelated virus called a phage, which is a virus that causes lysis of the common bacterium *Escherichia coli*. The newly tailored phage was then allowed to infect cultures of the bacterium. The infected bacteria began to manufacture proteins. On examination, one of the proteins was found to include the Australia antigen in its makeup. The genetic message carried by the phage had been used by the infected bacteria to provide this unique protein. Bacteria can be grown in huge quantities in "fermenters," and so the possibility now exists for the production of large amounts of Australia antigen using *Escherichia coli*. The antigen would be completely free of intact hepatitis B virus, and a vaccine made from this material would be safe and probably highly effective. This type of manipulation of genetic material—commonly called recombinant DNA technology—has resulted from many years of basic research by geneticists and biochemists working with bacteria. Here again is an example of an unexpected medical advance resulting from apparently unrelated scientific investigation, with a real prospect for the prevention of a serious disease.

As protein chemists and x-ray crystallographers continue to refine their methods for determining the submicroscopic structure of proteins and for determining the sequence of the amino acid subunits of which they are built, the hope for a synthetic vaccine increases. If the part of the hepatitis B virus coat that is responsible for conferring immunity can be fully characterized in this way, it might be possible to manufacture chemical copies devoid of the slightest risk of infectious virus content or untoward side effects. Such future prospects for the ultimate vaccine depend on continuing and increased support of the basic research necessary to provide the appropriate techniques and materials.

THE COST OF VIRAL HEPATITIS

Viral hepatitis is a disease of major public health concern in the United States and has been classified as a reportable disease since January 1952. All age groups are susceptible and the incidence of the disease appears to be on the increase. Despite considerable scientific and medical interest, especially during the past decade, viral hepatitis continues to take its toll.

A list of direct and indirect costs of viral hepatitis (table 7) shows a conservative estimate of the economic impact of the disease. The figures are adjusted for inflation only. They take no account of increased incidence of disease or more costly laboratory techniques developed during the 10 years since they were first calculated. Even so, the total cost in the United States of this single problem in 1980 is shown to be $1.3 billion, well over 100 percent more than the total operating budget of the National Heart, Lung, and Blood Institute in the same year. Clearly, the prevention of this widespread and debilitating disease would be cost effective.

The increase in knowledge acquired during research on viral hepatitis in the past decade has been substantial. Most of the advances have derived directly from basic scientific research, which is also providing ideas, techniques, and approaches for many other diseases of viral origin for which the conventional approach has proved unsuccessful.

Accomplishments of the NHLBI Hepatitis Research Program

HEPATITIS B SURFACE ANTIGEN

The importance of Australia antigen, or hepatitis B surface antigen (HBsAg), as it is now known, has already been stressed. Blumberg's discovery of the antigen was followed by Prince's observations, made on multiple-transfused hemophiliacs at the New York Blood Center, which finally and unequivocally linked HBsAg to hepatitis. Since that time, improvements in serological methods have made it possible to detect HBsAg and its antibody on a routine basis, to the extent that all donor blood is now tested before being used for transfusion. As a result, hepatitis B has virtually disappeared in the United States, although it remains a serious problem elsewhere in the world.

HEPATITIS B IMMUNE GLOBULIN

Availability of serological tests for the detection of HBsAg led to the speculation that antibodies in highly concentrated form might be useful in preventing, or at least in mitigating, the severity of hepatitis B. Through the collaborative efforts of Prince and Woods in 1970, the first hepatitis B antibodies (HBIg) were produced. A small clinical trial at New York University showed HBIg to be effective in preventing the transmission of hepatitis B by blood. Following this study, two large-scale, national multicenter clinical trials supported by the NHLBI showed HBIg to be effective in preventing hepatitis caused by accidental needle sticks, direct mucous

membrane contact, and oral ingestion of infected materials. HBIg is now a licensed product available throughout the world. A new use for HBIg has recently emerged from studies in Taiwan. In areas where 5 to 15 percent of the local population are chronic carriers of HBsAg, such as Africa, Asia, and Latin America, much of the transmission of the virus is vertical, from mother to child during delivery. The Taiwan study demonstrates that the administration of HBIg within minutes of birth can prevent infection in the baby for 3 to 6 months, during which time conventional vaccination can be expected to confer complete immunity.

THE EPIDEMIOLOGY OF HEPATITIS A AND HEPATITIS B

A series of classical studies on the incidence and spread of hepatitis B, conducted over a period of 8 years by Szmuness and his colleagues, resulted in the delineation of the risk factors involved in the transmission of the disease. These studies also revealed the worldwide prevalence of hepatitis B and the remarkably high levels found in Asia, Africa, and Latin America. A further important finding was that hepatitis B is the major risk factor in the development of hepatocellular carcinoma, an extremely widespread cancer of the liver constituting 2.5 percent of all cancers in the United States. Following the identification of the hepatitis A virus by Feinstone and Purcell at the National Institutes of Health in 1973, Szmuness undertook a study of the prevalence of the disease. This led to the knowledge that the disease had no carrier state and therefore had little association with posttransfusion hepatitis. With the elimination of hepatitis B as a posttransfusion hazard in the United States, what remains as transfusion-transmitted disease is caused by viruses as yet unidentified and not yet isolated, which produce the condition known as NANB hepatitis.

NHLBI CHIMPANZEE FACILITY

Hepatitis B and NANB are found only in man and in the great ape. Realizing that the number of chimpanzees available for hepatitis B research would soon decline (the animal having been designated an endangered species), a task group sponsored jointly by the National Institute of Allergy and Infectious Diseases (NIAID) and the NHLBI recommended in 1973 that a survey of existing chimpanzee resources be made and that steps be taken to assure a

Table 7. Estimated Economic Costs of Viral Hepatitis in the United States, 1980*

	($ in millions)
Direct Costs	
Preventive	$32.0
Curative	
Physician, office care	18.2
Physician, hospital care	32.4
Laboratory	64.4
Hospital	215.2
Total direct costs	$362.2
Indirect Costs	
Time lost from work for treatment and convalescence	$356.0
Lost earnings, premature death	584.2
Total indirect costs	940.2
Total costs	$1,302.4

**Pro rata* from Tolsma, D. D. and Bryan, J. A., 1976 *Public Health Reports* 91:349.

stable, continuous supply of uninfected animals for hepatitis research. In 1974, the NHLBI established a chimpanzee breeding colony to supply animals for use on a selected basis by the scientific community. These chimpanzees, currently housed in a facility at the Southwest Foundation for Research Education in San Antonio, Texas, have been used in studies of the assessment of methods to remove hepatitis B virus from such blood products as factor XIII and factor IV, in tests of the safety of the hepatitis B vaccine, and in the evaluation of maternal-fetal hepatitis transmission to simulate the process that occurs in the human population.

DEVELOPMENT OF A HEPATITIS B VACCINE

Following the demonstration by Krugman in 1971 that a hepatitis B vaccine was feasible, Hilleman of Merck Sharp & Dohme developed the first product for clinical use. It was utilized by Szmuness in definitive clinical trials sponsored by the NHLBI in which high-risk populations were examined both with and without the vaccine. The results of these trials, published in 1980, showed that the vaccine had little or no side effects and that within 2 months 77 percent of those vaccinated developed protective antibodies against HBsAg. This proportion increased to 96 percent after the administration of a booster dose and remained that way for the duration of the trial. In the first 18 months of followup, only 1.4 to 3.4 percent of those vaccinated developed hepatitis B, compared to 18 to 27 percent of those in the unvaccinated group. A second trial, which includes patients and staff of 44 Kidney Dialysis Centers, is well underway, and additional trials with children in Taiwan and Africa are also being conducted. It is expected that the vaccine will be licensed and available for all high-risk populations within 2 years.

NANB HEPATITIS

The NHLBI-supported Transfusion Transmitted Virus (TTV) Study Group is currently analyzing risk factors associated with posttransfusion hepatitis. Findings published in April 1981 described an attack rate of 10.3 percent for NANB hepatitis in five major centers involving 1,513 recipients of transfused blood, each of whom received an average of slightly less than four units of blood. Included in this study were 1,500 nontransfused control subjects and 5,000 donors. There was also an indication that the incidence of NANB hepatitis was associated with elevated levels of an enzyme released from the liver, alanine aminotransferase (ALT), which appeared in the blood of those afflicted. The TTV findings show that testing for ALT in blood donors may be an effective way to identify blood capable of causing posttransfusion NANB hepatitis, although further information is required before this finding can be fully established.

The NHLBI continues to support high-quality research in a number of areas likely to increase knowledge of posttransfusion hepatitis and eventually to bring it completely under control.

4. Accomplishments and Highlights

A left ventricular assist device, seen here at the right of the backbone, takes over the work of pumping blood from a failing heart.

4. Accomplishments and Highlights

Progress has been achieved in many areas of heart, blood vessel, lung, and blood research since the initiation of the National Program in 1972. The following pages contain examples of the research that has led to some of the past year's many accomplishments. These activities represent the achievements of scientists at the Institute and throughout the Nation, who work cooperatively to improve understandings of the causes of diseases and methods for diagnosing, treating, and preventing diseases.

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.

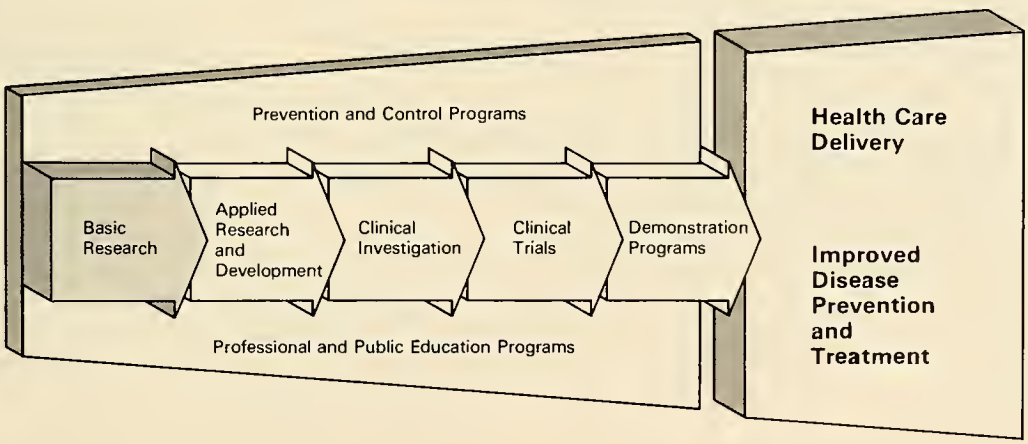
As the foundation of the Institute's program, basic research on disease etiology and pathogenesis receives the major portion of Institute resources. This research has resulted in a number of significant concepts, theories, and discoveries that have become the foundation for further research, refinement,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

Plasma Lipids in Diabetic Patients

. . . Poor Control of Blood Glucose Leads to Increases in Blood Lipids and Accelerated Atherosclerosis

Accelerated atherosclerosis is a major complication of juvenile-onset, insulin-dependent diabetes mellitus. A prospective study of young, insulin-dependent diabetic patients has now shown that statistically significant increases in blood levels of total cholesterol, total triglyceride, and lipoprotein subfractions (except for high-density lipoprotein cholesterol) are associated with increasingly poor control of blood glucose. Diabetic patients in best control had blood lipid levels similar to those of their nondiabetic siblings. These results lend credence to the hypothesis that poor control of blood glucose is linked to accelerated atherosclerosis as a consequence of associated deleterious elevations in plasma lipid levels.

Studies of long-term intervention in insulin-dependent diabetics will now be necessary to establish whether the specific lipid components examined in these studies can be brought to, and maintained at, normal levels and whether this action will ultimately decrease the progression of atherosclerosis.



Measurement of Glycosylation in Diabetics With Abnormal Hemoglobin Traits

. . . New Test Allows Diabetics With Sickle Cell and Other Abnormal Hemoglobin Traits to Be Monitored Accurately

Glycosylation of the hemoglobin molecule is increased in diabetic patients as a result of elevated blood glucose levels, and estimates of its extent can be used as a measure of long-term blood glucose control. Variant hemoglobins, with altered charge properties, are found in individuals with abnormal hemoglobin traits, such as sickle cell trait, and they produce misleading estimates of glycosylation in standard chromatographic assays. A new procedure, the thiobarbituric acid method (TBA), has been developed in which a direct measurement of hemoglobin glycosylation is possible. The measurement is uninfluenced by the charge on the hemoglobin molecule.

Studies have shown that the TBA method is capable of producing reliable and accurate information about the extent of hemoglobin glycosylation—and hence blood glucose control—in all diabetic subjects, including those with abnormal hemoglobin traits, whose progress can now be monitored in a fully dependable fashion.

Diabetic Cardiomyopathy

. . . Degenerative Changes in Heart Muscle in Diabetic Patients

Many diabetics are susceptible to changes in heart muscle that may lead to cardiac enlargement, potentially lethal arrhythmias, or congestive heart failure. This damage is thought to stem, at least in part, from preliminary, diabetes-induced damage to the smallest blood vessels, or microcirculation, of the heart. Baseline studies have been performed on a group of some 100 insulin-dependent patients with diabetes, of mean age 15 years. A high prevalence of echocardiographic abnormalities has been found, together with a constellation of structural changes. This study is now proceeding to examine the relationship of these changes to the development of microvascular disease, using a variety of techniques including stereocolor retinal photography, fluorescein angiographs, peripheral nerve electrophysiology, and renal function studies.

Data from this investigation will enable a relationship to be made between blood glucose control in diabetic subjects and the development of microvascular complications leading to severe damage to the heart.

Arteriosclerosis

. . . Macrophage-derived Growth Factor

Recently, investigators demonstrated that cultured macrophages, isolated from several sources, secrete a growth-promoting agent that stimulates *in vivo* DNA synthesis and cell proliferation in vascular smooth muscle and endothelium under conditions in which platelet-derived growth factors are not present. These researchers consider that macrophage-induced smooth muscle proliferation deserves special consideration in the context of arteriosclerosis, since several laboratories have demonstrated that macrophages are present in the aortic intima in both experimental and human atherosclerosis. Smooth muscle cell proliferation is considered to be a central event in the development of the atherosclerotic plaque, and further study of the mechanisms controlling production of macrophage-derived growth factor may provide new insights into the pathogenesis of arteriosclerosis.

Cardiovascular Dynamics

. . . Adenosine, a Natural Coronary Vasodilator

This project tests the hypothesis that endogenous adenosine participates in the physiological regulation of coronary blood flow.

A recently completed study examined the relationship between cardiac oxygen usage (MVO_2), cardiac adenosine levels (Ado), and coronary vascular resistance (CVR). When MVO_2 was experimentally changed over a fivefold range by atrial pacing, paired ventricular pacing, aortic constriction, or beta-adrenergic blockade (propranolol), Ado varied directly and CVR varied inversely with the changes in MVO_2.

The most important original observation resulting from this work established a quantitative relationship between MVO_2, Ado, and CVR[1] based on direct tissue analysis for Ado. That beta-adrenergic stimulation changes these relationships may support the hypothesis to be tested in this year's work—that is, that cyclic AMP is a natural precursor of adenosine.

The growing evidence for an intracellular adenosine compartment may be the most significant development in this field, not only because adenosine data are now interpreted in terms of a one-compartment adenosine model, but also because adenosine is known to modulate the activity of important enzymes such as adenylate cyclase. This project helps in the understanding of the metabolic control of coronary blood flow and the mechanism controlling cardiac muscle function.

Cardiovascular Dynamics

. . . Increased Cardiac Sensitivity to Nicotine in Transplantation Cases

Recent animal studies suggest that intrinsic cardiac nerves (ICN) are potent agents that can indirectly modify the inotropic, chronotropic, and dromotropic functions of the heart, especially in individuals whose hearts have been separated from extrinsic neural connection, such as

in cardiac transplantation. The number of cardiac transplantation patients is steadily growing as this operation becomes more available. These studies have pointed out the importance of the ICN in regulating the heart, a component that must be considered in any comprehensive description of the neural control of cardiac function.

The most significant result of this research is the discovery of the large increase in the sensitivity of the atrioventricular (AV) node to nicotine in cardiac-denervated animals. That cardiac denervation can increase the nicotinic sensitivity of this important part of the conduction system to as much as 200 times normal is an important finding. It suggests that cardiac transplantation patients are extremely vulnerable to nicotine exposure, which can produce severe decreases in AV nodal conduction velocity as well as powerful negative inotropic effects.

Cardiovascular Dynamics

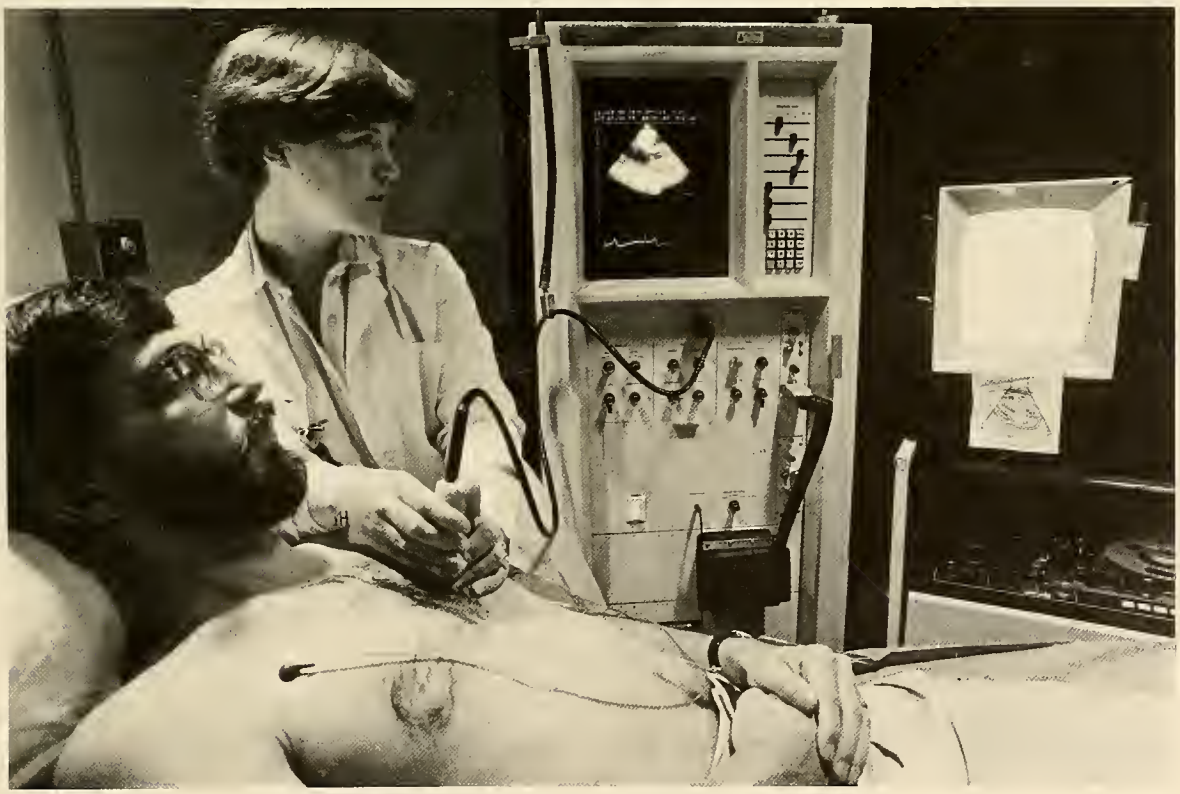
. . . *Stepwise Shortening in Muscle*

Recent studies examined the hypothesis that muscle contraction is considered a stochastic process. Theoretically, cross-bridges make contact with the thin filaments at randomly distributed times; therefore, contraction on a gross scale should be smooth. Three different methods were employed to assess this hypothesis: film analysis of the optical diffraction pattern; on-line measurements of sarcomere length from the striation pattern; and sound measurements. Contrary to the hypothesis, it was found by each method that contraction occurs in a stepwise fashion with sharply defined shortening bursts alternating with long periods of "pause," during which time there is little or no change of sarcomere length. This phenomenon implies a quantal, synchronized shortening pattern. If the finding is further substantiated, it could lead to a model of contraction considerably different from that currently in use.

Cardiovascular Dynamics

. . . *Oxygen Uptake of Isolated Heart Cells*

An investigation of the minimum oxygen requirement of the normal cardiac cell would contribute to understanding the process of myocardial infarction. The knowledge



The echocardiograph uses high-pitched sound waves to produce a picture of various parts of the beating heart.

so acquired would also explain how individual cells contract as distinct from the contraction of the entire heart. Such an investigation would require the preparation of isolated, intact adult myocardial cells in a normal physiological state. The prospects for use of functionally intact isolated heart cells have far exceeded the technical ability to prepare them.

A recently developed technique has enabled the isolation of up to 10 million ventricular myocytes/heart. Of these, 5.5 million cells remain rectangular and quiescent for 1 hour in 1 mM of calcium solution and will contract only in response to electrical stimuli. Electron microscopy has demonstrated that both the cell coat and plasmalemma are intact and continuous in all rectangular cells. The functional integrity of the plasmalemma has been demonstrated by the normal response to electrical stimulation and by normal permeability barriers to extracellular calcium succinate, and ADP. This finding will help define the oxygen gradient required to maintain respiration in resting heart cells. Also, electrical stimulation at definite rates will demonstrate the oxygen gradient required for maintenance of the contractile response. Cellular studies should now be possible using a variety of different disciplines in many laboratories.

Cardiac Hypertrophy

. . . Molecular Stimulus for Cardiac Hypertrophy

Early results of a study using an isolated dog heart model suggested that an extractable substance(s) was involved in the initial response of organ hypertrophy. More recent results of a study utilizing an extract prepared from a dog heart exposed to a hypertrophic stress for 6 hours indicate that the substance is not species specific. That is, when the extract prepared from the dog heart is perfused through an isolated rat heart preparation, the RNA obtained at the conclusion of the perfusion period has a higher translation ability. In more recent experiments, it has been observed that this higher ability of the "experimental" RNA is due to its higher mRNA content. This observation is of considerable significance, since it demonstrates that the molecular response to heart hypertrophy is at the transcriptional level—a process involving gene activation.

Microvascular Permeability

. . . Mechanism of Action of Histamine-like Mediators

Studies are in progress to understand how histamine-like agents facilitate the passage of plasma proteins through the walls of small blood vessels and how these histamine-like substances interact with other naturally occurring agents that either antagonize or potentiate that increase in permeability by a direct action on the vascular membrane.

The object of this study is to examine agents that may further increase protein outflow and edema. Special attention is being paid to the prostaglandins. This project is increasing the understanding of the way in which histamine-like agents mediate such pathophysiological states as inflammation, allergy, arthritis, circulatory shock, and burn injuries.

Respiratory Function

. . . New Evidence of Cadmium Effects on Respiratory Defense Functions

Cadmium is a heavy metal that humans encounter in air, food, water, and soil. It is a component of cigarette smoke and an industrial pollutant that is released into the environment in great quantities. Factory air concentrations have been reported to range from 5 to 250 $\mu g/m^3$. In laboratory animals, levels in this range have been shown to cause cilistasis (failure of cilia to beat), increased infections, and inflammation. Levels above 1,000 $\mu g/m^3$ can cause edema and cell destruction in the lungs. It is apparent that many workers are being exposed to potentially cytotoxic levels of cadmium.

The nature of the cytotoxic response to cadmium in the ciliated respiratory epithelium was the subject of a recent study. The data showed that cadmium severely altered the morphology of treated strips of tracheal epithelium. In addition, cadmium caused significant reductions in ciliary motion and induced cell necrosis. In low concentrations, cadmium induced chemically detectable cell death in 24 to 32 hours. This study is the first to demonstrate both cilistatic and cytotoxic responses in ciliated epithelium. The mechanism by which these cadmium-related alterations in structure and function occur is not clearly understood. It is clear, however, that cadmium salts can induce cell necrosis and a loss of function, which may explain the decreased mucociliary clearance and increased mortality from respiratory infections noted in cadmium-treated animals. This finding underscores the importance of minimizing exposures of humans to high environmental and occupational levels of cadmium.

Depression of Ventilation in Chronic Obstructive Pulmonary Disease Patients

. . . Brain Endorphins May Be Involved

Recently, considerable attention has been paid to a family of natural substances occurring in the brain known as endorphins, which bind to the receptors in the brain to which opium-like drugs also bind. Endorphins mimic the analgesic (loss of pain perception) and catatonic effects of

the opiates. These effects are blocked by naloxone, a potent opiate antagonist.

While the depressant effect of opiate drugs on respiration has long been recognized, it was not known until recently whether the brain's own endorphins have a similar effect. A study of patients with chronic obstructive pulmonary diseases, who retain an excessive amount of carbon dioxide (CO_2), has shown that in some patients there is a definite increase in ventilation when the opiate inhibitor naloxone is administered.

These studies have begun to shed light on mechanisms that might lead to CO_2 retention in COPD patients. For whatever reason, the brain's own natural opiate system appears to act to ease the strain on the respiratory system by decreasing ventilation at the expense of increasing body CO_2 levels. While this action may leave more "reserve" for increasing ventilation with exercise, the excess CO_2 does create problems and, in severe cases, can lead to coma and death.

Pulmonary Endothelial Cells

. . . New Method Makes Long-term Cultures Possible

Enzymes situated along the luminal surface of pulmonary endothelial cells interact with circulating substances in the blood to regulate the hormonal composition of systemic arterial blood. In this way, pulmonary endothelial cells act to clear thrombi and emboli and to regulate blood pressure. Despite recent progress, few, if any, laboratories have succeeded in establishing successful, long-term cultures of pulmonary endothelial cells. An additional problem involves the isolation and culturing of endothelial cells with the use of protease enzymes, such as trypsin, which may yield cells that do not have all of their surface enzymes and other proteins believed to exist on endothelial cells *in vivo*.

A new method for culturing pulmonary endothelial cells has recently been developed that avoids exposure to proteolytic enzymes at both the isolation step and during subculture. This advance may greatly facilitate biochemical studies of the important enzymes of endothelial cells and help to increase the understanding of the many complex processes that these cells may regulate.

Pulmonary Macrophages

. . . Even Moderate Hyperoxia May Cause Injury

Lung macrophages play a crucial role in protecting the lung against foreign particles and bacteria, and they are not uncommonly exposed to a hyperoxic environment, such as during oxygen administration. The extent of injury to cells by high concentrations of oxygen is therefore of clinical importance. Concentrations of 95 percent oxygen produce injury in a variety of experimental animals. In humans, it is generally accepted that oxygen concentrations of 40 percent or less do not produce significant lung injury. Lung function measurements, however, generally do not detect early injury, and presumably, large numbers of lung cells must be injured before such tests become abnormal.

A recent study found that exposure of isolated mouse lung macrophages in tissue culture to 40 and 60 percent oxygen for 48 hours resulted in significant depression of phagocytosis (the engulfing of foreign objects) as compared to air-exposed controls. The impairment of phagocytosis occurred despite significant increases in intracellular superoxide dismutase activity, an enzyme that may play a protective role in oxygen toxicity. Additional studies are needed to determine the biological and clinical relevance of these findings. Whether the increased susceptibility of patients with pulmonary oxygen toxicity to lung infection is related to impaired phagocytosis is still unclear. The results of these studies, however, suggest that lung cell injury may occur at lower levels of oxygen exposure, and they confirm the importance of using the lowest effective levels of supplemental oxygen in therapeutic regimens.

Alpha-1-Antitrypsin

. . . Sugar Side Chains Important in Formation and Breakdown

Alpha-1-antitrypsin (A_1AT) is a glycoprotein that protects the lung against the degradative effect of the enzyme elastase. Glycoproteins are compounds that have a protein core and a small number of side chains made up of different sugars. Structural studies of A_1AT have shown that three side chains are attached to the protein core. Two of these side chains are identical and have two branches (type B). The third chain can be type B or an entirely different type having three branches (type A). These chains bind to specific sites on the protein core. At two of these sites, type B chains are found exclusively; at the other site, the chain can be either type A or B. Thus, there can be at least two types of A_1AT—one with three type B chains and the other with two type B and one type A chains. This finding partially explains why A_1AT appears as several different species when looked at by means of a process called gel electrophoresis.

The presence of sialic acid, which is found on the side chains, is believed to be necessary for the secretion of glycoproteins from the liver. Mutations that result in structural change in the molecule and make it more difficult to attach the sugar side chains also cause a deficiency in the circulating levels of A_1AT and a high risk of developing emphysema.

Chronic Obstructive Pulmonary Disease
. . . Role of Chemotactic Factors

Blood proteins and cells release various factors that attract other cells to sites of injury or inflammation, a process called chemotaxis. The role of these factors in chronic obstructive pulmonary disease has received little attention until recently. It now appears that chemotactic compounds may play an important role in the exacerbation of emphysematous lesions.

These research findings show that alveolar macrophages release at least two distinct chemotactic factors: one of low molecular weight, the other of higher molecular weight. Preliminary evidence indicates that the high molecular weight factor can stimulate these cells to release the contents of granules that contain elastase. In turn, it appears that elastase attracts monocytes to the lesion area through degradation of elastin.

Observations such as these suggest that cigarette smoke causes resident macrophages to release chemotactic factor that attracts neutrophils to the site and causes them to release elastase. As a result of increased local concentration and reduced levels of functional A_1AT (due to oxidation by smoke and phagocytosing cells), this elastase is able to attack elastin and initiate the lesion. In turn, fragments from degraded elastin stimulate the recruitment of additional large numbers of mononuclear phagocytes.

Hypersensitivity Pneumonitis
. . . Development of a Monkey Model

Hypersensitivity pneumonitis, exemplified by such diseases as farmer's lung disease, pigeon breeder's disease, and humidifier lung, is a complex immunologic lung disease that is recognized with increasing frequency across the country. One of the difficulties in studying this disease is the lack of animal models reflecting the human condition. Such a model is now available that may also hold the key to other fibrotic lung diseases.

After repeated immunization with pigeon serum, monkeys are exposed to low-dose, whole-body x-irradiation followed by inhalation challenge with the antigen. The ensuing pulmonary disease is typical of the hypersensitivity pneumonitis suffered by, or found in, man. Irradiation is the key to this model, since animals treated similarly, but without irradiation, show no adverse effects. Not only is it expected that this model will be useful in studying the human disease, but, in the course of developing the model, earlier suggestions were corroborated that a defect in immune regulation may be important in disease production. As it is carried out, irradiation results in dramatically reduced numbers of suppressor lymphocytes, which is an important element in immunoregulation. The objective of this research is to establish the differences between two groups of individuals, the exposed and symptomatic and the exposed but healthy, in hopes of finding a predictive factor that differentiates the two groups and that might lead to better clinical care for diseased individuals.

Immunologic Lung Disease
. . . Blood-borne Antigens Can Enter Pulmonary Lymphoid Tissue

A significant number of pulmonary diseases result from immunologic responses that extend beyond protection and become actively destructive. While most substances that stimulate such responses are inhaled, it has been suspected that a number of diseases result from exposure to agents from the pulmonary vasculature. Recent animal studies provide direct evidence of the ability of antigenic materials injected into the bloodstream to reach and enter the bronchus-associated lymphoid tissue (BALT). In addition, it has been observed that antigenic materials in the bloodstream can enter pulmonary lymph nodes, where they presumably can stimulate the lymphocytes to produce an immune response.

This finding provides a significant insight into an alternate method by which these responses in the lung may be stimulated, and it may lead to a better understanding of immunologic diseases that do not appear to result from inhalation of a pathogenetic agent.

Microemboli-induced Lung Injury
. . . Neutrophils Are Implicated

Pulmonary microvascular injury of varying etiologies often results in pulmonary edema, which is a serious condition with high morbidity and mortality. Clinically, pulmonary vascular resistance is often increased, and a rising resistance suggests a poor prognosis. No specific therapy is available to treat the condition. Because pathologists often find microemboli in the lung in post-mortem examination, it is important to determine the function of microemboli in the process of the microvascular injury.

The number and distribution of neutrophils in normal and embolized lungs were compared to help understand how neutrophils affect microvascular permeability. Experimental pulmonary emboli were produced in sheep by continually infusing air into the pulmonary artery until pulmonary vascular resistance increased two- to three-fold. Post-mortem determinations of neutrophils in the pulmonary vasculature were made. In the embolized sheep, the number of neutrophils in the capillaries, arteries, and veins was significantly higher than in the controls. In addition, almost all of the neutrophils were

intravascular and were absorbed selectively into the air-liquid interface of the air emboli. The determinations suggest that injury induced by neutrophils in embolized lungs is probably mediated through the release of proteases from intravascular neutrophils and does not depend upon their migration into the extravascular lung tissue. Additional studies are necessary to determine whether the neutrophil response can be blocked and whether the neutrophils mediate injuries from other etiologies.

Arachidonic Acid Release From Cell Phospholipids

. . . Potential for New Therapeutic Interventions

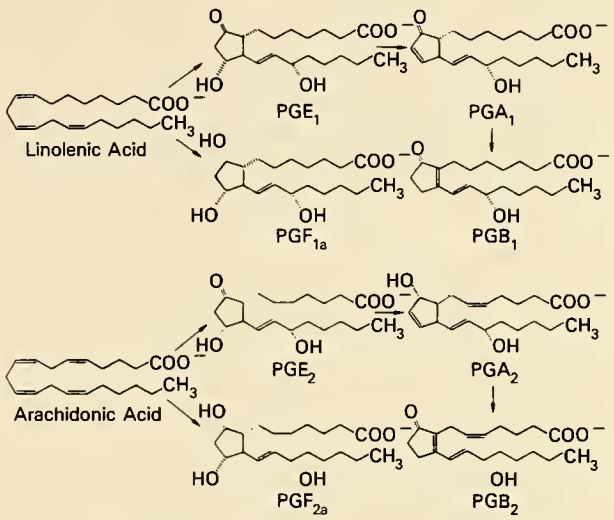
Arachidonic acid metabolites are extremely important mediators of wound healing, atherogenesis, and thrombosis. The active substances are many, including prostaglandins, thromboxanes, prostacyclins, and leukotrienes. The production of all these mediators is controlled by cellular mechanisms that trigger the release of arachidonic acid from cell phospholipids. In the past, it was presumed that the mechanism for this release involved the action of a phospholipase A enzyme. A new and different pathway has been evaluated that involves two steps: hydrolysis of monophosphatidylinositol to yield diacylglycerol and a diacylglycerol lipase that releases arachidonic acid. In the past year, it has been shown that this new pathway can account for arachidonate release from human platelets and appears to be the major mechanism for triggering arachidonate metabolism in cells.

Previous studies have shown that therapeutic interventions involving perturbation of arachidonate metabolism are likely to have a major impact on the problem of thrombosis. Elucidation of the pathway of arachidonate release provides new sites at which therapeutic interventions may be undertaken.

Erythropoiesis

. . . Isolation of a New Species of Erythropoietin

A new species of erythropoietin (Ep) was recently isolated from the urine of leukemic patients. It has been purified extensively and resolved from the conventional Ep. This new erythropoietic activity has been designated Ep-alpha, whereas the conventional species is referred to as Ep-beta. Both are physically present in urine of all types of anemic patients. The activity of Ep-alpha varies significantly according to the cause of the disease. It is active in leukemic patients and inactive in patients suffering from other causes of anemia. Ep-beta is generally active in all types of anemic patients. The existence of a new Ep species and the fact that it can be switched on and off according to the causes of anemia suggest that it may have a regulatory function in erythropoiesis.



A close structural similarity is shown among the family of prostaglandin molecules and their precursors, linolenic and arachidonic acids.

Hementin

. . . A New Fibrinolytic Agent

Pathological disturbances of the coagulation pathways are usually associated with blood clots formed *in vivo* either as thrombi that occlude important vessels, leading to a loss of blood flow, or emboli that circulate in the bloodstream, eventually lodging in important areas of the brain (stroke) or lung (pulmonary embolism). Therefore, agents that dissolve blood clots (fibrinolytic agents) are potentially important drugs for restoring circulation and for preventing damage to valves in veins or to the pulmonary vasculature.

A recently completed study indicates that hementin, a new fibrinolytic enzyme isolated from the salivary glands of the leech (*H. ghilianii*) and partially characterized, carries out a specific proteolytic modification of human fibrinogen. Moreover, hementin represents a new type of fibrinolysin that may prove to be a useful thrombolytic agent for the treatment of thrombotic disease.

Heparin Platelet-binding Sites

. . . Possible Mechanism for Heparin-induced Thrombocytopenia

The nature and extent of heparin-induced platelet aggregation remain a controversial issue. Research findings suggest that the capacity of commercial heparin to bind to platelets, thereby inducing aggregation, may offer some explanation for the thrombocytopenia associated with

heparin therapy. These findings also suggest that an improvement in the safety of heparin therapy may be achieved by using heparin fractions of low molecular weight and high affinity for antithrombin.

Platelet-Vessel Wall Interactions

. . . *Prostacyclin Can Block Interaction in Injured Vessels*

Platelets secrete an alpha-granule mitogenic protein that may initiate myointimal proliferation after vascular injury. Recent NHLBI studies in animals provide the first definitive proof that secreted platelet granule proteins enter the vessel wall and demonstrate that graded infusions of prostacyclin can block platelet adhesion to the vessel wall and subsequent secretion as well as fluid-phase aggregation. The studies provide a means to monitor and prevent the platelet interactions with injured vessels that may ultimately lead to atherosclerotic vascular disease.

Experiments have been undertaken to assess the effect of repeated injury to the endothelium in terms of platelet adherence and the effect of exogenous agents. It was found that a second injury increased the number of adhering platelets and initiated fibrin formation on the vessel wall, which was not seen after the initial injury. Furthermore, prostacyclin alone was much less effective in reducing platelet adhesion and secretion following a second injury. Heparin alone was similarly ineffective; however, a combination of the two reduced platelet adhesion to levels seen after initial injury. These data suggest that an injury in which neointima is damaged results in activation of the coagulation system as well as platelet adhesion, and that combined therapy is necessary to prevent the resulting fibrin formation and platelet adhesion.

Thrombosis

. . . *Further Elucidation of the Sequence of Events in Thrombosis Formation*

Tests to assess *in vivo* clotting currently center on the measurement either of fibrin formation or of platelet activation. In order to fully understand the significance of the measurements, it is important to know the sequence of events in thrombus formation.

Most clinically important thrombi result from both fibrin formation and platelet aggregation. The relationship between these two activities has been studied in an *in vitro* system. Under "normal" conditions, platelet release and fibrin formation occurred simultaneously. However, if either process was inhibited, the other could proceed independently. The findings also suggest that when clotting is initiated by way of the intrinsic pathway, thrombin is also generated on the platelet surface. Simultaneous platelet release and fibrin formation result. On the other hand, initiation by way of the extrinsic system leads to fluid-phase thrombin formation and fibrin formation preceding platelet release. Activation by interaction of blood with collagen causes initial acceleration of platelet release and later acceleration of fibrin formation.

Elucidation of these relationships will lead to more accurate interpretation of test results for patients in whom clotting is suspected.

Thrombosis

. . . *Prostacyclin Can Be Synthesized by Endothelial Cells From Platelet-derived Endoperoxides*

It has been demonstrated that endothelial cells can synthesize prostacyclin from endogenous precursors or from exogenously provided endoperoxides or arachidonate. Last year, experiments were undertaken to determine whether utilization of platelet endoperoxides for prostacyclin synthesis by aspirin-treated endothelial cells might be possible. The production of 6-keto-PGFI-alpha, the stable metabolite of prostacyclin, was measured in systems containing various ratios of endothelial cells to platelets.

The results demonstrate that there are indeed two mechanisms for prostacyclin synthesis by cultured human endothelial cells. The first involves synthesis of prostacyclin from endogenous precursors, and the second, synthesis from endoperoxides to a significant extent derived from stimulated platelets. Endothelial cells can utilize platelet endoperoxides for prostacyclin formation. If an excessive number of platelets are present in the system, large quantities of thromboxane are produced to the detriment of prostacyclin production because platelets "pass" endoperoxides to each other when intervening endothelial cells are outnumbered by the platelets.

The critical nature of the ratio of endothelial cells to platelets may have a clinical counterpart. Patients with high platelet counts may demonstrate a thrombotic diathesis because excessive numbers of platelets exchange endoperoxide for thromboxane formation. The exchange results in platelet stimulation. When platelet counts in these patients are reduced to normal levels, the thrombotic diathesis disappears. It is speculated that in the case of normal platelet numbers, endothelial cells are able to utilize platelet endoperoxides to enhance prostacyclin formation, which may explain why some patients with thrombocytosis can benefit from aspirin therapy.

Protein C

. . . *An Important Regulatory Protein of Hemostasis*

Regulation of fibrin deposition and dissolution is important in maintaining the normal state. Formation of

fibrin can be controlled directly through the inactivation of coagulant enzymes or indirectly through the dissolution of the fibrin clot. A newly described, vitamin K-dependent circulating protein, protein C, fulfills both functions and may turn out to be a potent regulatory protein for the control of coagulation.

Thrombosis and Hemostasis
. . . Purification of Tissue Factor

The process of coagulation, that is, the coupling of stimulus (injury) and response (blood clot), has been the subject of intense research for decades. As the factors involved in clotting have been purified, much knowledge has been gained about the mechanisms and interactions among the coagulation components. The mechanism of initiation of the coagulation cascade at the site of injury, however, has remained obscure because of the lack of purified activator released from the injury site. Current research has found that the putative activation cofactor, which is tissue factor, or "thromboplastin,"can be purified to homogeneity from bovine brain. With the availability of sufficient quantities of this purified material, research can be undertaken to describe the mode(s) of action of the initiation cofactor with the various components of the extrinsic coagulation pathway.

von Willebrand Protein
. . . New Information About Structure-Function Relationships

The von Willebrand protein, a part of the coagulation factor VIII complex, has been fragmented into small peptides by tryptic enzymatic degradation and disulfide reduction. A unique derivative of 116,000 molecular weight was shown to retain von Willebrand factor activity.The larger and smaller molecular weight fragments lack the cofactor activity.

This finding indicates that the 116,000 fragment has unique structural properties that may resemble the active sites of the native von Willebrand molecule. This observation will be useful in elucidating the mode of interaction of the von Willebrand factor with platelets.

Cooley's Anemia
. . . Advances in Gene Switching and Regulation

During the development of most vertebrates, there is a postnatal "switch" from fetal to adult hemoglobin. Adult humans, although having very small amounts of fetal hemoglobin, still retain the molecular and genetic machinery for its production. In Cooley's anemia, the adult hemoglobin is greatly diminished, and in sickle cell anemia it is abnormal. If the production of fetal hemoglobin could be switched back on, people with these diseases could be symptom free.

The mechanism of hemoglobin switching is currently being studied in chickens, and results seem to indicate that the switch may not be controlled at the DNA level. Additional research has enhanced the knowledge of gene regulation in normal and disease states and offers a potential advance in therapy for hemoglobinopathies affecting the beta-globin gene (Cooley's anemia and sickle cell anemia).

Control of Hemoglobin Synthesis
. . . New Insights From Primate Studies

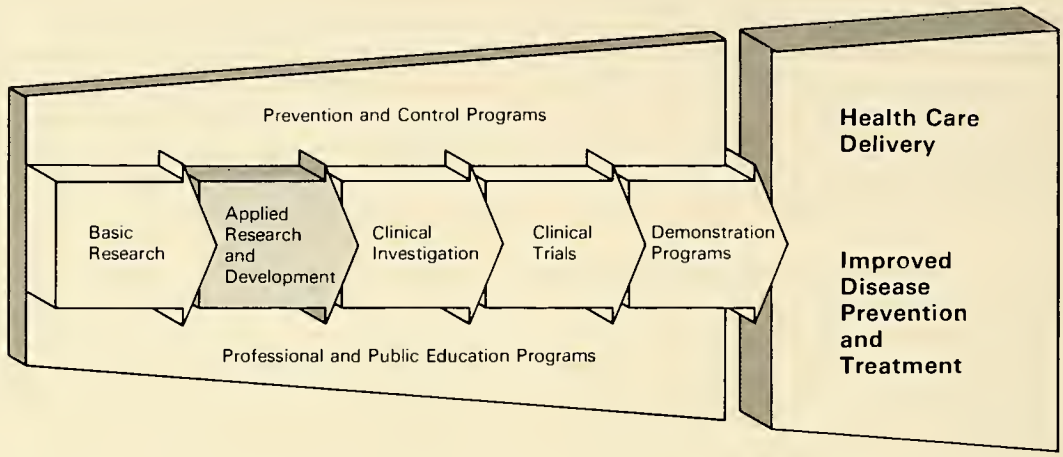
Only a minimum amount of information exists about the regulation of hemoglobin synthesis in the human fetus (HbF), about the normal switch to the synthesis of adult hemoglobin (HbA), and about the conditions of reactivation of HbF synthesis in diseases. A reason for this lack of knowledge is the ethical constraint in experiments using humans. The fact that the baboon has been found to resemble man in many of these respects has offered an opportunity for more detailed studies. Because erythropoietin is known to be indispensable in the stimulation of erythropoiesis in culture, it has been possible to study the synthesis of HbF *in vivo* after induction of hemolysis by phenyl hydrazine or by creation of hypoxia in a hypobaric chamber.

Blood Component Therapy
. . . Preparation of a Therapeutic Porcine Factor VIII Concentrate Using Solid-phase Polyelectrolytes

Porcine factor VIII preparations are useful in the treatment of patients with high-titer factor VIII antibody and low cross-reactivity to animal factor VIII. However, the presence of high concentrations of platelet aggregating factor (PAF) in these preparations causes severe thrombocytopenia. Ethylene/maleic acid anhydride copolymer polyelectrolytes have been employed to remove PAF during purification of the porcine factor VIII. This simple purification procedure produces a porcine factor VIII concentrate lacking in PAF. Clinical studies indicate that this purification procedure permits the production of a product that is clinically useful in humans.

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 seeks first to obtain 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 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. Processes to achieve these goals include design, development, and improvement of prototypes and new processes to meet functional or economic requirements.

Arteriosclerosis

. . . Prevention of High Blood Cholesterol

Alfalfa meal has been shown to reduce blood cholesterol and to diminish the incidence of atherosclerosis in cholesterol-fed monkeys, and the search for the active principle has led to a study of alfalfa saponins. After 6 months on a semipurified diet containing 1.2 mg cholesterol/calorie, 34 Macaca monkeys were divided into control and experimental groups. Both groups were maintained on a diet in which the cholesterol was reduced to 0.32 mg/calorie. The experimental group received in addition 1.2 percent partially hydrolyzed alfalfa saponins. Plasma cholesterol values at 2, 4, 6, and 8 months were consistently high in the control group, but much reduced in the experimental group. Feeding the hydrolyzed saponin did not produce differences in general appearance, body weight, or blood components, except for cholesterol content. No signs of toxicity in cholesterol-fed monkeys were seen as the result of feeding saponins to reduce blood cholesterol.

Hypertension Program

. . . Multifactor Studies in the Development of Hypertension

In recent experimental animal studies, a synergistic relationship between salt and environmental stress has been identified. In unanesthetized free-moving dogs, salt-loading in the presence of stress-producing circumstances produced significantly elevated blood pressures and strokes, whereas there were no strokes in animals exposed to either salt or stress alone. Caffeine and stress have demonstrated a similar synergistic relationship in elevated blood pressures. These data are complemented by another relevant finding that confirms salt preference in offspring of mother rats that were salt-loaded during pregnancy.

These studies confirm the complexity of dietary, developmental, and environmental interactions in the regulation of blood pressure. Meaningful understandings of the development of hypertension can be achieved only by further research into the regulation of blood pressure.

Myocardial Infarction

. . . Perfluorochemicals Reduce Myocardial Ischemic Damage after Coronary Occlusion

Many deaths of patients hospitalized with acute myocardial infarction result from destruction of extensive amounts of myocardial tissue. In a recently completed animal study, a perfluorochemical emulsion consisting of a mixture of perfluorodecalin and perfluorotributylamine was found to reduce myocardial ischemic damage after experimental coronary occlusion.

Although the mechanism by which perfluorochemicals limit infarct size is not clear, perfluorochemicals can increase oxygen delivery because their oxygen-carrying capacity at high oxygen tension is actually better than that

of blood. Also, because the viscosity of perfluorochemicals is less than that of blood, collateral blood flow to the myocardium can be increased.

Congestive Heart Failure

. . . New and Improved Digitalis

There is a narrow margin between an effective dose and a toxic dose of digitalis. As a result, over 20 percent of the patients taking digitalis sooner or later experience digitalis toxicity. A recent finding indicates that one of the aminosugar-containing cardiac glycosides has a greater margin of safety while maintaining a strong cardiac inotropic activity. In fact, the aminosugar type of cardiac glycoside is more effective in enhancing the pumping action of the normal and failing heart than the commonly used neutral sugar cardinolides: digitoxin, digoxin, and ouabain.

Also of interest and importance is the lack of interaction between these substances and the sympathetic nervous system. Rather, it appears that the aminosugar cardiac glycosides may have a positive interaction with the vagus nerve. The mechanism of the therapeutic effect of these agents may be related to their interaction with (Na^+,K^+-ATPase). These interactions make this finding important in the continuing search for a safer drug to be used in congestive heart failure and certain cardiac irregularities.

Cystic Fibrosis

. . . New Understanding of the Reasons for Pseudomonas *Infection*

Patients with cystic fibrosis frequently develop pulmonary infections caused by the *Pseudomonas aeruginosa* (PA) organism. This chronic infection is responsible for most of the morbidity and mortality associated with cystic fibrosis. Recent studies have shed new light on the reasons why individuals with cystic fibrosis are unusually susceptible to this organism.

Moreover, these studies suggest that susceptibilty to *Pseudomonas* infection may be a characteristic acquired during the disease state. They also provide a new understanding of the cellular defects underlying the infections and will possibly lead to improved approaches to the amelioration or prevention of *Pseudomonas* infection in cystic fibrosis.

Neonatal Respiratory Distress Syndrome

. . . Importance of Maintaining Optimal Levels of Carbon Dioxide in the Blood

Around the time of birth, acute stresses on the fetus, such as the loss of blood or lack of oxygen, are important factors in determining the severity of neonatal respiratory distress syndrome (RDS). Although the importance of such risk factors has been recognized for some time, there is considerable controversy about the prevention or amelioration of their damaging influences.

A recently completed study using an animal model of acute hemorrhagic shock was developed in the newborn lamb. In this model, half of the blood volume was removed within 30 minutes while heart and lung functions were recorded continuously. Cardiac output fell to approximately 50 percent of normal, while myocardial (heart muscle) blood flow fell to 40 percent of normal along with a slowing of the heart rate. The animals also increased their rate of breathing, and the carbon dioxide (CO_2) levels in their blood declined. If the lambs were allowed to breathe air that contained 4.5 percent CO_2 (approximately 100 times the concentration normally present in the atmosphere), however, the CO_2 concentrations in their blood remained normal and myocardial blood flow did not fall below normal. In addition, blood flow to the brain actually increased, and the survival rate of the animals improved from 33 percent to 80 percent.

These findings may be of considerable importance in developing improved methods of managing infants with RDS who are also in shock. Currently, such infants receive assisted ventilation without close control of CO_2 levels in the blood, and many of them actually lose CO_2 during aggressive attempts to elevate blood oxygen levels.

Platelet Dysfunction During Cardiopulmonary Bypass

. . . Prevention by Prostacyclin Infusion

Cardiopulmonary bypass in experimental baboons produced transient severe platelet dysfunction as evidenced by prolonged bleeding times in comparison with those of baseline normals. There was an associated release of platelet alpha-granule proteins into the plasma but no significant release of dense granule substances. The infusion of prostacyclin into the bubble oxygenator during bypass prevented the prolongation in bleeding time but did not alter the release of alpha-granule proteins.

These results indicate that transient platelet dysfunction occurring during cardiopulmonary bypass is a result of some activating mechanism that is independent of alpha- or dense granule release. The mechanism is blocked by potent short-acting inhibition of platelet function by the use of prostacyclin infusion into the oxygenating apparatus at optimal therapeutic doses.

Platelet Function Study

. . . A New Videomicroscopic Approach

Collaborative studies have led to a major technological advance in videomicroscopy, which has been applied to NHLBI-supported research. The advance in the AVEC-POL and AVEC-DIC (Allen-Video-Enhanced-Contrast

Red cells, white cells, and smaller platelets of the blood are seen in the scanning electron microscope

Polarization and Differential-Interference-Contrast) methods of videomicroscopy has made it possible to study human platelet motility and the platelet release reaction visually, including the release of dense bodies and the discharge of alpha-granules. Studies have shown that the concept of massive cytoplasmic contraction in the release reaction is incorrect.

The significance of these new and more sophisticated techniques is that certain aspects of platelet function can be quickly quantified by continuous observation of living platelets, and normal and abnormal platelet behavior can be distinguished.

Cooley's Anemia

. . . Noninvasive Measurement of Tissue Iron

One of the most severe consequences in patients with Cooley's or other anemias who require transfusion therapy is the increasing iron buildup in the heart and other vital organs. Patients usually die of cardiac failure as a result of iron overload. Research findings so far have led to the development of two new techniques to assess the severity of this condition and to monitor the efficacy of iron chelation therapy. A noninvasive method of *in vivo* measurement of tissue iron is highly desirable.

Direct noninvasive measurements of human hepatic iron stores and initial observations of human cardiac magnetic fields have been made with two different techniques. Further refinements on the limits of detection are necessary for the measurement of cardiac iron.

Anemia

. . . Diagnosis by Automated Methods

Variations in the size and shape of red blood cells are important in the diagnosis of anemia. Measurement of mean cell volume, assuming that the blood specimen is a single population of cells, has become standard. Measurements of individual cells have been so tedious in clinical studies that they have not been applied routinely to characterize abnormal populations. Advances in computerized image analysis of red cells could change this situation and provide new aids in the diagnosis of anemia.

Fetal Hemoglobins

. . . New Micro Techniques Found Useful

The development of new micro procedures for the separation of the three types of gamma-chains has opened new avenues of study, particularly of the relative amounts of synthesis of the different gamma-chains in subjects having various inherited disorders.

Experimental observations have proven useful for evaluating genetic conditions involving variations in the production of different types of gamma-chains in fetal hemoglobin.

External Quantification of Perfusion

. . . Results Suggest Accurate Measurement of Myocardial Perfusion

A technique has been developed and evaluated using the exponential infusion of positron-emitting diffusible tracers to quantitate myocardial perfusion. The approach employs a parameter that rapidly reaches a constant value as a function of tracer delivery rate, isotope decay constant, and the monotonically increasing tissue radioactivity. Isolated rabbit hearts with controlled flow were used to evaluate the approach because tracer kinetics in such preparations mimic those *in vivo*. In addition, the required exponentially increasing arterial tracer concentrations were shown to be attainable *in vivo* in dogs and rhesus monkeys after intravenous exponential administrations of tracer. The results suggest that the approach employing exponential tracer infusion permits accurate measurement of myocardial perfusion and that such an approach should prove useful in the noninvasive measurement of regional myocardial perfusion *in vivo* by positron emission tomography.

Human Sickle Erythrocytes in Primate Animals
. . . *Search for an Animal Model*

Despite advances in the past 10 years, understandings of sickle cell disease at the molecular and cellular levels and understandings of the pathophysiology of sickling *in vivo* have not improved significantly, because humans are not subject to many experimental conditions. Animals with a naturally occurring homoglobin abnormality that causes comparable hemolytic anemia or vascular occlusion have not been identified. Deer erythrocytes sickle readily *in vitro,* and this phenomenon is associated with the polymerization of B-chain hemoglobin variants. Sickling of deer erythrocytes, however, occurs under conditions (oxygenation and increased pH) that are exactly the reverse of the conditions that determine sickling in human red blood cells. *In vivo* sickling of deer erythrocytes has not been observed, nor have any pathologic consequences been found in animals that exhibit the phenomenon. For these reasons, sickling in deer has not been applicable as a practical model for human sickle cell disease.

Studies utilizing a rat model required the simultaneous blockade of the animal's reticuloendothelial and complement systems and provided only limited data. More recent investigations with chimpanzees have shown that human sickle erythrocytes, transfused to untreated animals, have a lower recovery rate and shorter survival time than do normal red cells similarly transfused. This outcome is also seen in human recipients. In primates, it is possible to measure simultaneously the survival of normal and sickle red cells and thus circumvent problems that result from differences in sizes of the microvasculature between recipients. The usefulness of the model for studying the pathophysiology and treatment of sickle cell disease is therefore strongly suggested.

Hepatitis
. . . *Steps Toward Screening Blood Donors for Non-A, Non-B Hepatitis*

When the NHLBI-supported study of transfusion-transmitted viruses began in 1974, it was recognized that not all cases of posttransfusion hepatitis were being prevented, even when blood banks used sensitive methods to detect hepatitis type B surface antigen-positive donors.

The recognition in 1974 of a previously unknown form of hepatitis, non-A,non-B posttransfusion hepatitis, led to a search for methods by which donors could be screened so that blood that carried the NANB hepatitis virus(es) could be discarded. Because the virus(es) that cause NANB hepatitis were then unknown, as they are now, indirect methods for screening were investigated.

Systematically collected data for the period 1974 through 1979 now provide substantial evidence that the concentration of alanine aminotransferase (ALT) in donor blood may be correlated with the occurrence of NANB hepatitis in transfusion recipients. The extent of the association is sufficient to raise the question of whether ALT screening of donors should be considered. Many questions remain unanswered about the need for, or advisability of, instituting ALT testing as a routine screening procedure for blood donors at this time.

Cooley's Anemia
. . . *Development of Improved Drugs for Iron Removal*

The treatment of certain genetic diseases, such as Cooley's anemia, requires chronic transfusion therapy. This produces a secondary hemochromatosis that causes buildup of iron in the tissues. The buildup eventually results in the failure of vital organs and in the death of most patients by early adulthood. Because there are limited physiological mechanisms in man for the removal of iron, the treatment of iron overload must rely on chelating agents that can affect iron excretion.

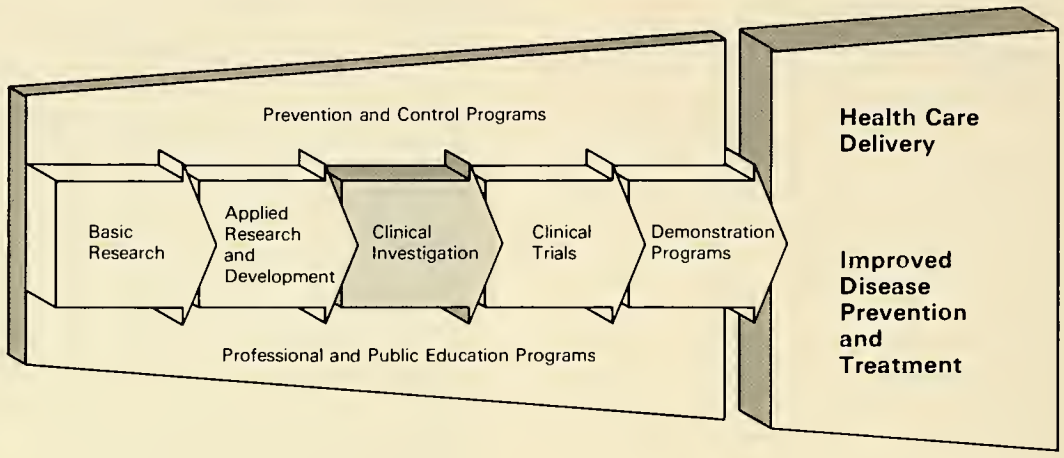
Recent studies have shown that, while the hydroxamate ligands such as deferoxamine (Desferal) are kinetically unable by themselves to remove iron from transferrin, these new ligands readily remove the iron from this iron-transport protein of human serum. While toxicity studies with mice for related compounds support the expectation of low toxicity for these compounds, their biological properties are being further determined by *in vivo* tests.

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 to designing preventive measures. Further, clinical research translates clinical observations into research focused on determining disease etiology.

Hypertension Program
. . . *Patient Compliance With Antihypertension Medication Regimens*

A working group formed to develop a state-of-the-art document on hypertensive patient compliance recently



reported to the NHLBI. The report contains selective, in-depth reviews of highly pertinent areas of compliance research. The reviews address the theory of compliance behavior; the measurement of compliance; strategies for improving compliance; in-depth analyses of two important and rapidly developing areas, namely, the role of the patient-clinician interaction and of social support; the state of implementation of compliance management strategies in public and private practices and ethical concerns raised by the monitoring and management of patient compliance.

In addition to a thorough assessment of the current state of the art for its topic, each chapter of the report, where appropriate, also provides the author's expert opinion on further research that is required or desirable, and recommendations for practical implementation of existing knowledge. The report appears to have been well received by both the research and clinical communities.

Hypertension

. . . *Beta-adrenergic Blockade and Blood Pressure*

Two important recent studies addressed the complexities of evaluating the role of sympathetic activation in blood pressure regulation. With the use of beta-adrenergic blockage on "high cardiovascular reactors" versus "low cardiovascular reactors" (to behavioral challenge), it was noted that there were significant differences in systolic decrease and diastolic increases. These findings suggested that the twofold increase in diastolic blood pressure in the "high reactor" group is related to alpha-receptor activation, which is usually masked by beta-receptor dominance, and they also reinforced the need to evaluate blood pressure reactivity to environmental "naturalistic" challenge as well as the traditional "resting" measurements, which would not identify the hemodynamic phenomena noted in this study.

A complementary finding using beta-blockade on stress-induced hypertensive mice indicated that while blood pressures were reduced, progressive renal damage continued. This finding suggests that while the pharmacologic blockade may have reduced one marker of blood pressure regulation, obvious pathologic consequences were continuing unabated. Further investigation may elucidate the mechanisms of these results.

Coronary Heart Disease

. . . *Framingham Heart Study*

Additional analyses of the lipid and lipoprotein data from the Framingham Heart Study have resulted in a number of important findings. First, there appear to be strong relationships between levels of plasma lipoprotein cholesterol and the risk of coronary heart disease (CHD) at all ages in both men and women. The findings for males under age 55 are based on prevalence data published in November 1980. More realistic interpretation of logistic regression results has been developed when there are strong relationships between independent variables. The conclusion from a forthcoming report will be that, while caution on firm conclusions is necessary, very low density lipoproteins (VLDL) appear to be an important indicator of CHD risk, especially in women. Also, the relationships between personal factors (such as cigarette smoking, obesity, and alcohol consumption) and plasma lipoprotein cholesterol levels are very strong in some cases.

A report published in November 1980 highlighted the striking relationship between obesity and low density lipoprotein (LDL) cholesterol in young men. This significant finding suggests that obesity as a risk factor for CHD

may be underestimated. The new data collection continues, and although based on incomplete and preliminary data, some surprising results have emerged. The results from over 3,000 1-hour ambulatory ECG's reveal a substantial number of individuals at all ages with high-grade ventricular arrhythmias, even in those without clinically recognized CHD. In addition, early indications from the results of echocardiography suggest very high percentages of participants having various cardiac structure abnormalities. For example, about 14 percent of women under 50 years of age appear to have detectable mitral valve prolapse. All of these findings suggest that it is feasible to use cardiological methods in an epidemiologic setting, and that considerable heterogeneity for cardiac function and structure exists in this population.

Innovative Therapy for Coronary Heart Disease

. . . *Percutaneous Transluminal Coronary Angioplasty*

Percutaneous transluminal coronary angioplasty is a new, potentially revolutionary therapy for chronic coronary atherosclerosis. A thin catheter with a deflated balloon at the tip is inserted into a blocked blood vessel. When in position, the balloon is inflated to open up the blockage. After deflation, the balloon catheter is removed. Angioplasty by means of balloon catheter has been used in peripheral atherosclerosis since 1964. Gruntzig and his colleagues first applied the procedure to the coronary arterial system in September 1977.

A voluntary registry was created by the NHLBI in 1979 to collect data on PTCA success and failure rates including not just mortality but other long-term outcomes such as angina and the quality of life. PTCA may be used in the future to defer indefinitely coronary bypass surgery in patients with severe angina. The ultimate place for PTCA in the treatment of coronary artery disease will be determined over the next several years.

Coronary Heart Disease

. . . *Coronary Prone Behavior and Coronary Heart Disease*

The Review Panel on Coronary Prone Behavior and Coronary Heart Disease comprises biomedical and behavioral scientists and is charged with the task of critically evaluating all available research and theory linking behavior to coronary heart disease. This panel affirmed the relationship of the type A behavior pattern to coronary heart disease but challenged researchers to identify which specific behavioral components of the global constellation of the type A pattern contribute to the development of coronary heart disease. Review groups examined the association of the coronary prone behavior pattern (CPBP) with coronary heart disease, the assessment of the CPBP, the physiologic mechanisms related to the CPBP, developmental aspects of CPBP, and intervention strategies. The review groups assessed the theories and data for their respective sections and recommended to the Institute future research directions.

Several lines of investigation have attempted to develop a model of cardiovascular response to a combination of situational and idiosyncratic variables. For example, one investigator demonstrated a significant correlation between "hostility" scores (MMPI subscale) and coronary blood flow, *independent* of type A/B classification. Another investigator demonstrated significant differences in cardiovascular reactivity between type A subjects classified as "high" and "low" on hostility.

Another series of studies found that nerve hormone measurements appear consistent with the observations described above. Preliminary data from a current study involving post-myocardial infarction patients suggest that efforts to modify type A behavior through a combination of medical counseling, behavior modification, and cognitive restructuring may reduce morbidity and mortality as compared with a control ("usual care") population.

Population Studies: Local Analysis

. . . *Lipid and Lipoprotein Distributions in Black Adults*

Age- and sex-specific distributions have been determined for plasma cholesterol, triglyceride, and high and low density lipoproteins in 627 black adults (206 males and 421 females), 20 to 59 years of age. Comparisons have been made with white males and females who were sampled from the same population by identical methods.

Black men were found to have cholesterol levels comparable to those of white men, whereas black women had cholesterol levels higher than those of white women. Black men, however, had lower levels of triglycerides and lower density lipoprotein but higher high density lipoprotein (HDL) levels than did white men. Black women not taking exogenous sex hormones had higher cholesterol and HDL levels, but lower triglyceride and LDL levels, than did white women not taking sex hormones. In contrast, black women taking exogenous sex hormones had lower cholesterol, triglyceride, and LDL levels, and higher HDL levels than did white women also taking sex hormones.

Although it is not known to what extent these data are generalizable to other American black populations, the finding provides valuable information to physicians and researchers on CHD risk factors in an area where very few data are available.

"Warning: The Surgeon General Has Determined That Cigarette Smoking Is Dangerous to Your Health."

Cardiovascular Disease

. . . Clustering of Five Risk Factors

In a prevalence survey, associations among five risk factors—cholesterol, triglycerides, blood pressure, obesity, and cigarette smoking—were examined for 4,389 men and women, ages 30 to 89 years. All age-adjusted correlations between any two risk factors, except smoking, were positive and significant. The strongest associations between pairs were observed for cholesterol and triglyceride, triglyceride and obesity, and obesity and blood pressure. Again, smoking was the exception.

Clustering of risk factors was strongest for those subjects at the higher (≥90th percentile) level of these risk factors. This clustering of risk factors at the ≥90th percentile has not been previously reported.

Since risk factors tend to cluster and are considered to operate synergistically, this information may be of use in the clinical evaluation of patients at risk for CHD.

Population Studies: International

. . . Cultural Differences in Dietary Intake Among 17-Year-Old Jewish Residents of Jerusalem

Dietary intake of 17-year-old Jewish residents of Jerusalem was assessed in 634 males and 522 females by 24-hour dietary recall. There were marked differences in nutrient intake of subjects whose fathers immigrated from different countries. Food intake of those whose fathers were born in Israel, Europe, or North America revealed significantly higher intakes of fat (only among boys), saturated fatty acid, and cholesterol, and lower intakes of carbohydrate and starch than those whose fathers were born in Asia or North Africa. Data obtained by Lipid Research Clinics in the United States for 17- to 19-year-old white residents show similar dietary intake.

Population Studies: Nutrition

. . . The NHLBI Nutrition Data System

A description of the NHLBI's standardized system for the collection and processing of dietary information in large-scale studies has recently been published. Components of the system include training interviewers and coders, continuing education and certification, automated procedures for identifying and quantifying fat, guides for classifying and quantifying foods, procedures for system maintenance and quality control, and a food table containing about 800 food items and 450 recipe items. The system has the flexibility for responding to changes in the market. Unique automated features make it particularly useful in identifying and quantifying different dietary fats.

The system was developed through active Federal interagency collaboration and with the assistance of industry. Although it is focused on fat to meet the needs of the Lipid Research Clinics Program and Multiple Risk Factor Intervention Trial, it can be modified for the nutrient focus of other studies.

As the country's food supply becomes more complex, there will be greater demands for nutritionists to measure the impact of such changes on public health. The NHLBI Nutrition Data System was developed in response to the needs of the cardiovascular research community. Other investigators may wish to build on this experience in designing their own systems.

Congenital Heart Disease

. . . HDL in Cerebrotendinous Xanthomatosis

Researchers studying the plasma lipoprotein profiles and high density lipoproteins in patients with the genetic disease cerebrotendinous xanthomatosis (CTX) reported

that the mean HDL-cholesterol concentration in CTX plasma was about one-third the normal value. Also the ratio of apoprotein to total cholesterol in the HDL of CTX was two to three times greater than normal. The proportion of apoproteins was also abnormal in the HDL of CTX. It has been suggested that abnormalities in lipoprotein distribution profile in CTX may significantly perturb the normal physiological functions of the HDL, possibly including modulation of LDL-cholesterol uptake and the removal of excess cholesterol from peripheral tissues.

Chronic Obstructive Pulmonary Disease

. . . An Index of Risk May Be Available Soon

Chronic obstructive pulmonary disease is generally characterized by a progressive obstruction of the airways and can be measured as a percent reduction in respiratory flow or volume when compared to that in normal individuals of the same age and body build. In order to predict an individual's risk of developing COPD, quantitative "index of risk" models for men and women have been constructed with information from several community health studies. The major risk factors for COPD presently determined in this project are age, initial lung function, and smoking history. Smoking is significant in this context because it is the only modifiable variable among these factors. With reliable information on the individual's likelihood of developing COPD, greater success in modifying smoking behavior may be possible. The index of risk is being validated with data from additional populations, including groups of workers in high risk occupations. When the index is ready for widespread use, it will be incorporated into the smoking cessation program.

Smoking and Chronic Obstructive Pulmonary Disease

. . . A Lower Incidence in Pipe Smokers

Identifying and modifying risk factors are important aspects of COPD prevention. NHLBI has supported research concerning findings that indicate that cigarette smokers have a faster decline in pulmonary function, a higher incidence of COPD, and a higher incidence of lung cancer than pipe smokers. The reason for this appears to be that more toxic material deposits in the lungs of cigarette smokers than in those of pipe smokers. The deposition of toxic solids, carried in the smoke, depends on smoking technique and on the physical properties of the smoke, primarily the concentration of particles in the smoke and their aerodynamic size. With the use of a device employed in aerosol studies to measure concentration and size of particles, it was discovered that smoke from cigarettes was 10 to 20 times more concentrated than smoke from pipes. Even when tobacco from cigarettes was smoked by pipe, the concentration of solid particles was reduced tenfold. Particle size was the same in all cases.

The concentration of cigarette smoke of standard research cigarettes and several popular brands of filtered cigarettes was also measured. It was found that filters reduced particle concentration, but none of the filters caused a sizable reduction in the number of smoke particles available for delivery to the respiratory tract. The substantially lower concentration of smoke particles inhaled from pipes may explain why pipe smokers have a lower risk of developing lung disease than cigarette smokers.

Evaluating Infants With Respiratory Distress Syndrome

. . . Recording Brainstem Electrical Potentials

A new, noninvasive technique developed for recording the conduction of electrical potentials within the central nervous system (CNS) shows promise of providing a sensitive index of the extent of maturation and function of the CNS as well as providing important diagnostic information on the presence of lesions in the brainstem that may have developed as a result of trauma or inadequate oxygenation of the brain following failure of the respiratory system.

Until recently, this technique had been used primarily in adults for detecting hearing deficits. It is recognized, however, that certain brainstem structures along the auditory pathway are preferentially vulnerable to many of the conditions that compromise a prematurely born infant with respiratory problems. Subtle impairments to these regions may go unnoticed until obvious and severe behavioral defects become apparent later in life. Brainstem auditory evoked potential has recently been introduced as a new tool for evaluating infants with respiratory distress.

New Immunosuppressive Regimen

. . . Combined Heart-Lung Transplantation

Cardiac transplantation is a therapeutic alternative for small numbers of patients with severe left ventricular dysfunction. The initial costs and the required long-term immunosuppression with attendant risks of severe infection remain major barriers to more widespread application of this therapeutic option. In addition, the requirement for normal pulmonary vascular resistance has further restricted such application.

Cyclosporin-A has recently been developed, and it is a very effective immunosuppressive agent. This advance led to exploratory animal experiments that culminated in a successful heart-lung transplant in a human in March 1981.

Improvements in postoperative care exemplified by Cyclosporin-A may eventually reduce the overall cost of cardiac transplantation and make it more commonly applicable. It appears that development of this drug may be a substantial advance.

Compatible Linings for Implantable Blood Pumps

. . . Successful Chronic Implantation Studies in Calves

Scientists have fabricated blood pump bladders of polyurethane with textured inner linings that are integral with the bladder. When implanted as left ventricular assist devices, these blood pumps have operated for periods up to 1 year, and a thin, fibrin-like coating that inhibits subsequent clotting of the blood develops on the textured lining.

If the bladders are seeded with fetal fibroblasts prior to implantation, the fibrin is gradually replaced by a strongly adherent collagenous layer whose amino acid composition resembles that of the natural aorta of the animal. The results to date are based on two dozen implants in calves over the past few years. Current studies seek to optimize the thickness of the textured lining.

Asthma in Childhood

. . . A Possible Risk Factor for Adult Obstructive Airway Diseases

In a study designed to identify childhood risk factors for the development of adult obstructive airway diseases, respiratory histories and spirometric measurements were obtained on 650 children, 5 to 9 years of age. Persistent wheezing was the most frequently reported chronic symptom, occurring in 9.2 percent of these children. Parental cigarette smoking was directly related to the occurrence of persistent wheezing in these children. Children who wheezed had histories of more respiratory illness (asthma, acute lower respiratory illness) than those who did not. When followed prospectively, the children who wheezed were seen to have higher incidences of acute illness of the lower respiratory tract.

Related to these findings, data from an Australian study in which 277 children who had reported wheezing before the age of 7 were followed until 21 years of age suggest that it should not be presumed that children with wheezing will "outgrow" their asthma. About 60 percent of the subjects who had stopped wheezing continued to have increased bronchial reactivity to inhaled histamine. Furthermore, many of the children who reported wheezing in their late teens had abnormal pulmonary function tests at 21 years of age. These studies indicate that wheezing in childhood may be a risk factor for the development of obstructive airway disease in adulthood.

Bronchiolitis

. . . New Grounds for Optimism for Immunoprophylaxis

Bronchiolitis occurs and recurs in infants even when the infants possess passively or actively acquired antibodies. This observation led to the hypothesis that preexisting antibodies may actually exert an "immunopathologic" effect of initiating the disease, rather than confer protection. Vaccination, therefore, was ruled out as a possible preventive measure for bronchiolitis. Recently completed prospective clinical and animal studies, however, appear to indicate that acquired immunity may provide some protection from infections. Moreover, these studies of immunity versus infection and reinfection with respiratory syncytial virus in infants discount an immunopathologic origin for bronchiolitis and provide hope that immunoprophylaxis may be a realistic tool for amelioration of the illness, if not for its prevention.

Occupational Lung Disease

. . . Trimellitic Anhydride Stimulates Complex Antibodies

Trimellitic anhydride, which is a highly reactive molecule, is used in the manufacture of plastics to chemically join individual hydrocarbon chains into large polymers. Because the agent is supplied as a light powder, considerable likelihood exists for its becoming airborne and ultimately inhaled. It can result in a spectrum of pulmonary signs and symptoms ranging from an initial irritant effect to a hypersensitivity pneumonitis-like syndrome. Such findings remove doubts concerning the immunologic nature of the disease and are expected to lead to more effective therapy of acute attacks.

Silicosis

. . . Underlying Pulmonary Health May Be an Important Factor in Disease Development

The inhalation of silica dust and subsequent development of silicosis in certain individuals continues to be a hazard to sandblasters and others working in a sandblasting environment. Investigations of animals have provided insight into the disease process that may prove important in the management of sandblasters prior to the emergence of clinical disease.

These studies suggest that careful monitoring of the pulmonary health of individuals known to have been exposed to silica dust along with timely diagnosis and early treatment of incipient pulmonary infections may delay or even prevent the development of this disease.

Pneumonia and Adult Respiratory Distress Syndrome

. . . New Role for Fibronectin

Bronchopulmonary infection, particularly by gram-negative bacilli, is a frequent and serious complication of the human adult respiratory distress syndrome (ARDS). These pneumonias reduce the chances of survival, prolong hospitalization, and possibly impair healing and recovery of the injured lung. The physical attachment and colonization by bacteria on the upper respiratory epithelium has long been recognized, but until now, the factors that actually mediate the bacterial adherence have been poorly understood. Recently, evidence was found that the cells that line the respiratory tract are normally coated by the protein fibronectin, which shields the attachment sites for gram-negative bacteria on the host cells. During the development of ARDS, proteolytic enzymes in the patient's respiratory secretions degrade the fibronectin. Such degradation renders the cell surfaces highly susceptible to bacterial infection. Once the identity of the proteolytic enzymes is established, it should open new avenues for the prevention of the fibronectin-depleting sequence that leads to bacterial colonization and pneumonia, and thereby to improved chances of successful recovery of the ARDS patient.

Total Parenteral Nutrition

. . . Increased Metabolic Rate Could Lead to Respiratory Failure

Total parenteral nutrition (TPN), which supplies all of the body's metabolic needs through solutions administered intravenously, is advocated for acutely ill as well as nutritionally depleted patients. Following the development of respiratory distress in a patient given this regimen, a study was made of the effects of TPN on patient metabolism. Research findings confirmed that these hypercaloric solutions should be given with caution to patients who might be susceptible to respiratory distress.

Diagnosis of Pulmonary Embolism

. . . Ventilation-Perfusion Scans and Pulmonary Angiography Have Major Shortcomings

It is estimated that 500,000 instances of pulmonary embolism occur annually in hospitalized patients in the United States and that 50,000 hospital deaths are due to pulmonary embolism each year. Although pulmonary embolism is prevalent and often occurs as a complication of chronic cardiac or pulmonary disease, there is no reliable method currently available for diagnosing the condition. The most commonly used methods are ventilation-perfusion scans, a technique that employs radioactive tracers to visualize the airways and circulatory pathways of the lung, and angiography, another radiologic technique that allows examination of the pulmonary circulation. Ventilation-perfusion scans are minimally invasive but lack the desired specificity. Angiography is more specific, but it presents a risk to the patient. In addition, angiography is invasive, expensive, and requires specialized equipment and personnel. In a study of 55 patients suspected of having pulmonary embolism, ventilation-perfusion scans failed to give a definitive diagnosis at least 38 percent of the time. Many patients in whom a definitive diagnosis cannot be made receive anticoagulant drugs, which are associated with a 30 percent incidence of damaging hemorrhage. Because many of these patients do not actually have pulmonary emboli, they are subjected unnecessarily to high-risk anticoagulant therapy. The accuracy of angiography in excluding pulmonary embolism has not been tested adequately; however, it might be a relatively low-risk method for defining the need for high-risk anticoagulant therapy. The development of new, accurate, and specific tests for pulmonary embolism retains a high priority.

Cooley's Anemia

. . . Improved Transfusion Therapy

Advances in the treatment of patients with thalassemia major have resulted from the removal of iron from patients with iron overload caused by repeated transfusions. New therapeutic maneuvers have been designed to decrease the rate of iron accumulation. It has been demonstrated that the persistent maintenance of hematocrits above 35 percent (supertransfusion) is not associated with an increased transfusion requirement because such blood replacement decreases whole blood volume. Methods have been developed for obtaining units of blood from normal donors that contain primarily young red cells (''neocytes''). These cells have a prolonged *in vivo* survival as measured by the interval between transfusions.

With the use of the IBM cell washer, which is routinely employed to deglycerolize frozen red cells, other steps have been added to the process to achieve a centrifugal density separation. This method is quick and, according to preliminary experiments, can be used to separate young cells from standard blood bank units at a great saving as compared to continuous-flow cell separators. Clinical trials using the cell washer with a limited number of patients will begin shortly.

Cooley's Anemia

. . . Switch From Fetal to Adult Hemoglobin Synthesis

Human globin gene expression is abnormal in thalassemia and hereditary persistence of fetal hemoglobin

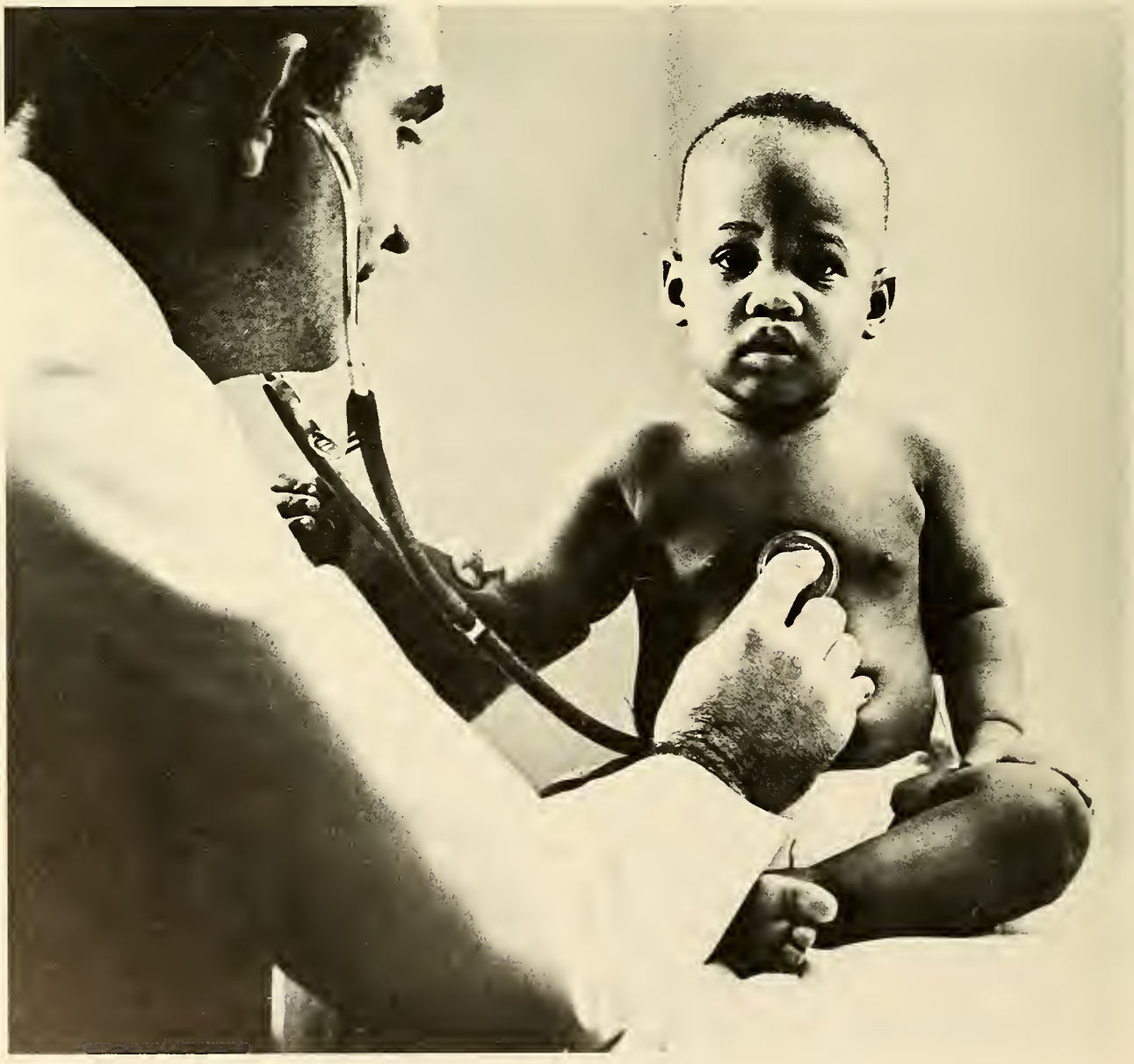
(HPFH). Research in this area has led to the identification of specific gene sequences involved in controlling certain developmentally regulated genes.

These findings represent an initial step toward localizing sequences that are involved in controlling the switch from fetal to adult beta-like globin gene expression in man. Similar analysis of additional cases of HPFH and delta-beta-thalassemia may ultimately lead to the identification of sequences that are involved in controlling these developmentally regulated genes.

Alpha-Globin Genotypes in Patients With Sickle Cell Disease

. . . Effect on Clinical Severity

Using the technique of restriction endonuclease gene mapping, alpha-globin genotypes have been characterized in a large group of patients with sickle cell disease. Although the measurement of the clinical severity in each patient was made difficult by inaccurate and complex scoring systems, it has been determined that those patients



Physician examines young patient with sickle cell anemia.

with a more severe form of alpha-thalassemia tended to have higher levels of hemoglobin F. It appears that two factors that ameliorate the severity of sickle cell disease, the presence of alpha-thalassemia and high levels of hemoglobin F, may be causally related. A larger patient population will be investigated to confirm this relationship statistically and to establish a means for clinical classification.

Prenatal Diagnosis of Sickle Cell Anemia
. . . *Gene Mapping*

Fetuses at risk for sickle cell anemia have a 25 percent chance of having the disease when each of the parents carries one gene for the sickle cell hemoglobin (HbS). Currently, a diagnosis of sickle cell anemia *in utero* can be made by one of two methods, neither of which is widely available. One technique, called fetoscopy, involves the removal and analysis of a small sample of blood from the fetus *in utero* and determining the kinds of hemoglobin produced. This technique is accompanied by a 3 to 5 percent spontaneous abortion rate. The second method involves sampling the amniotic fluid around the fetus and looking for a series of nucleic acid fragments that are linked to the HbS gene. While amniocentesis is much safer than fetoscopy, the use of the analytic procedure is limited by the degree of association of the polymorphism with HbS, which is currently estimated to be only about 60 percent. Preliminary studies, however, indicate that it may now be possible to use amniotic fluid cells to *directly* analyze the sickle cell gene mutation. If successful, this kind of test would provide an accurate, rapid, inexpensive, and safe means of diagnosing sickle cell anemia prenatally.

Complications of Sickle Cell Disease
. . . *Low Incidence of Hypertension*

Arterial blood pressures casually recorded during hospitalization or clinic visits of 187 adult patients with sickle cell disease were compared to blood pressures from age- and sex-matched black Americans. Blood pressures in the patients with sickle cell disease were significantly lower than those in the control subjects in all ages from 18 to 54 and did not demonstrate the expected rise with advancing age. There was no difference between blood pressures in the sickle cell disease patients when compared as to sex, degree of anemia, or hemoglobin genotype. Four patients had diastolic hypertension and two had systolic hypertension. The prevalence of hypertension was significantly less than that in the black population as a whole. These findings in sickle cell disease patients may be the result of a renal tubular defect responsible for increased sodium and water excretion. The latter phenomenon may blunt the plasma volume expansion necessary for sustained hypertension, and thus contribute to lower arterial pressures similar to those observed in patients with salt-losing nephritis.

Thrombocytopenia and Altered Platelet Kinetics
. . . *Consequences of Pulmonary Artery Catheterization*

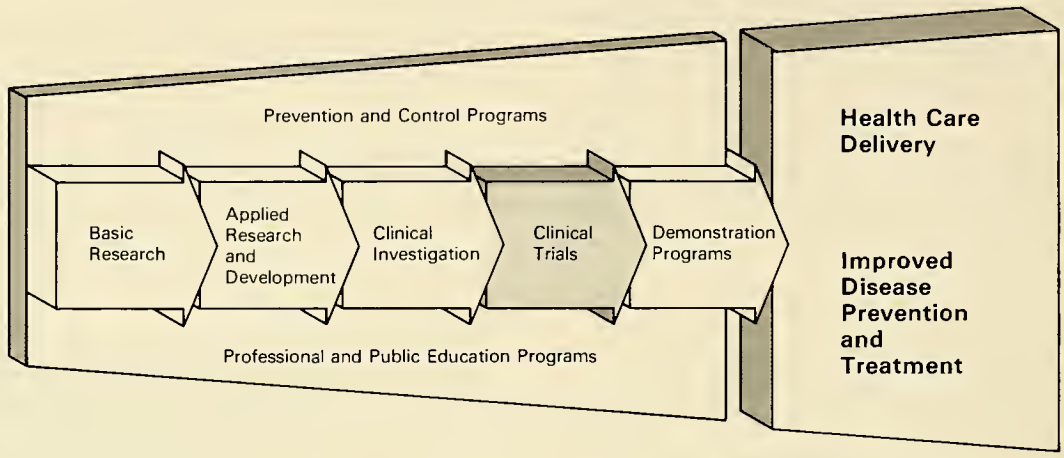
Thrombocytopenia, a condition in which blood platelets decrease in number, develops frequently in patients who are critically ill, and it often contributes to morbidity and mortality. Flow-directed, balloon-tipped catheters placed in the pulmonary artery are commonly used in critically ill patients and are known to be thrombogenic (clot producing) in man. The rate of platelet consumption associated with indwelling catheters and the extent to which platelet consumption contributes to thrombocytopenia have been studied in animal models. Calculated platelet survival time decreased nearly 30 percent in animals with the catheters as compared to controls. Similar results were found in a group of patients. Also, thrombus formation along the catheter was found in both animals and man. The results indicate that the introduction of a catheter into a blood vessel may itself contribute to diminution in platelet lifetimes and to overall pathology associated with underlying disease.

Aplastic Anemia: Bone Marrow Transplantation
. . . *Identification of Patients at Risk for Graft Rejection*

Peripheral blood mononuclear cells from 35 patients with aplastic anemia were studied *in vitro* to determine whether the patients had possible immune-mediated aplastic anemia and whether they had been sensitized against the donor's marrow by having received transfusions prior to bone marrow transplantation. Pre- and posttransplantation data were compared. Six of the 35 patients had marrow graft failure or graft rejection. *In vitro* tests showed five of these six were positive for either immune-mediated aplastic anemia or 100 percent inhibition of donor burst-forming units-erythrocyte (BFU-E). Further studies will determine whether these *in vitro* tests will be useful in identifying aplastic anemia patients at risk for graft rejection. Observations from these studies will also help explain why rejections of HLA-identical marrow grafts occurred in some otherwise untransfused patients with aplastic anemia who were given blood products within 24 hours of the procedure.

Blood Component Therapy
. . . *Development of a Fractionation Procedure for the Isolation of Cytomegalovirus Immune Globulin for Therapeutic Purposes*

Recipients of renal, bone marrow, or cardiac allografts frequently develop infection with cytomegalovirus



(CMV). These infections can cause a variety of clinical syndromes, some of which may be severe or fatal. In an ongoing study, it was shown that CMV-immune globulin can be prepared from selected aliquots of normal human plasma in sufficient quantities to permit clinical trials of its efficacy in preventing or modifying CMV infections that complicate organ transplantation.

Clinical Trials

In a carefully controlled setting, clinical trials test the efficacy and safety of preventive and therapeutic regimens with the potential to save lives and dollars. The clinical trial is a key step in the long, difficult, and complex process that converts research findings into the prevention and treatment of disease.

The objective of the large-scale clinical trial is to gain information regarding the effect of a given form of medical or surgical intervention. Clinical trials are used to test new drugs, to compare alternative patient management modes, to determine the effectiveness of different treatments, and to measure the efficacy of intervention programs for high-risk populations. Trial results validate successful clinical intervention and provide for 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 complete a trial successfully can range anywhere from 2 to over 10 years, depending on its size and complexity. Successful completion of a trial involves the concerted effort of countless scientists, clinicians, analysts, and support personnel; the cost can reach tens of millions of dollars by the time it is completed and its results are disseminated. Therefore, the decision to undertake a clinical trial is not made without very careful 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, impartial experts. Results of the trial, however, are not revealed until some significant finding is made or until the trial has run its full, allotted course.

Coronary Artery Disease
. . . The Multiple Risk Factor Intervention Trial

The primary prevention of coronary artery disease continues to be a major goal of cardiovascular research. An important clinical trial in this area is designed to learn whether and to what extent a decrease in several coronary risk factors will prevent coronary events such as heart attacks. The Multiple Risk Factor Intervention Trial (MRFIT) is a long-term study to determine whether lowering three major factors simultaneously—elevated levels of plasma cholesterol, high blood pressure, and smoking—has a significant effect on cardiovascular morbidity and mortality. Now in its fourth year, the NHLBI investigation is continuing to gather and analyze data on the 12,800 high-risk men (age group 35 to 37) involved in the study. Results to date show that the design goals for smoking cessation are being reached, or even exceeded, and that the goals for the reduction of diastolic blood pressure and of plasma cholesterol are being approached. Further opportunities in MRFIT include more detailed analysis of the information collected prospectively over at least 6

years regarding men at above-average risk of death from coronary heart disease.

Limitation of Infarct Size

. . . Thrombolytic Therapy in Acute Myocardial Infarction

Long-term survival after myocardial infarction is directly related to infarct size, that is, the amount of residual damage to the heart muscle. Infarct size is not established at the onset of chest pain and may be modified over the next 12 to 24 hours. The potential for limiting infarct size has been investigated actively for the past decade both with animal models and in a number of clinical trials.

It appears that a substantial number of patients with chest pain and ECG changes indicative of acute myocardial infarction have a coronary arterial blood clot. It is possible that these thrombi are superimposed upon an atherosclerotic plaque and, further, that a majority may be dissolved by means of thrombolytic agents delivered into the coronary artery or the peripheral veins. Thrombolytic therapy appears most promising for limitation of infarct size and may in some cases actually prevent infarction.

Myocardial Infarction

. . . Beta-Blocker Heart Attack Trial

The Beta-blocker Heart Attack Trial is designed to determine whether or not the regular administration of propranolol (a beta-blocking agent) to people who have had at least one documented heart attack will result in a significant reduction in mortality over a 3-year period. Figure 14 illustrates the locations of 36 medical centers in the United States and Canada where this trial is being conducted. Data that have been collected on approximately 4,000 men at baseline and subsequent visits will provide a unique base for addressing issues related to the natural history of heart disease, compliance, and efficacy of intervention. Approximately two-thirds of the patients are currently on full protocol dose of the study medication; most of the remaining third are on a reduced dose. The Policy Data Monitoring Board, an independent

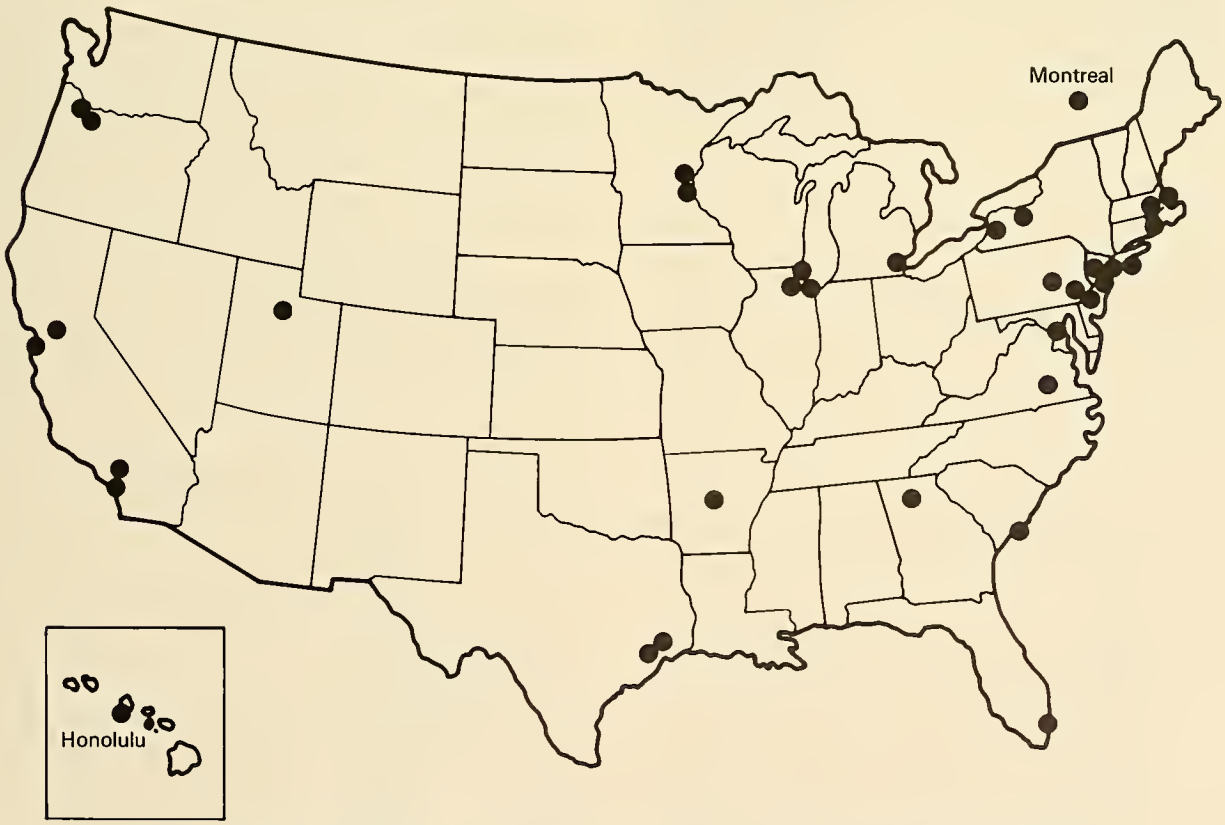


Figure 14. The Beta-blocker Heart Attack Trial was conducted in 36 medical centers in the United States and Canada.

advisory group, meets semiannually to review such results as adherence and toxicity data and has recommended continuing patient followup to its scheduled termination in 1982.

Hepatitis

. . . Clinical Trial With Hepatitis B Vaccine

Under the sponsorship of the NHLBI, the first major clinical trial of a new vaccine to prevent hepatitis has been completed. This vaccine provides nearly complete protection against developing type B. Several populations in the United States with a high risk of hepatitis type B virus (HBV) infection were considered for the trial. For this study, a population of healthy, young HBV-susceptible homosexual men appeared to be the most suitable.

The development of the hepatitis B vaccine and the demonstration that such a vaccine prevents HBV infection are major advances in the control of this extremely widespread and debilitating disease.

Mass immunization programs against HBV infection may ultimately affect not only the incidence of acute hepatitis B and the pool of chronic carriers but may also reduce the morbidity and mortality from chronic active hepatitis, cirrhosis, and hepatocellular carcinoma.

Granulocyte Transfusion

. . . Beneficial and Harmful Effects of Granulocyte Transfusion

Data were collected during a 4-year study to evaluate the usefulness of prophylactic and therapeutic transfusion of granulocytes for episodes of bacterial sepsis. The results of the prophylactic trial indicate that incidence of sepsis was significantly decreased by the use of prophylactic granulocyte transfusions; however, the incidence of other infections was not affected. Furthermore, pulmonary infiltrates were increased in patients receiving granulocyte transfusions, and overall survival was not improved by the transfusion of granulocytes prophylactically. It is therefore concluded that granulocytes given prophylactically cannot be recommended as standard therapy during leukopenic states. The results of the therapeutic trial are currently undergoing analysis.

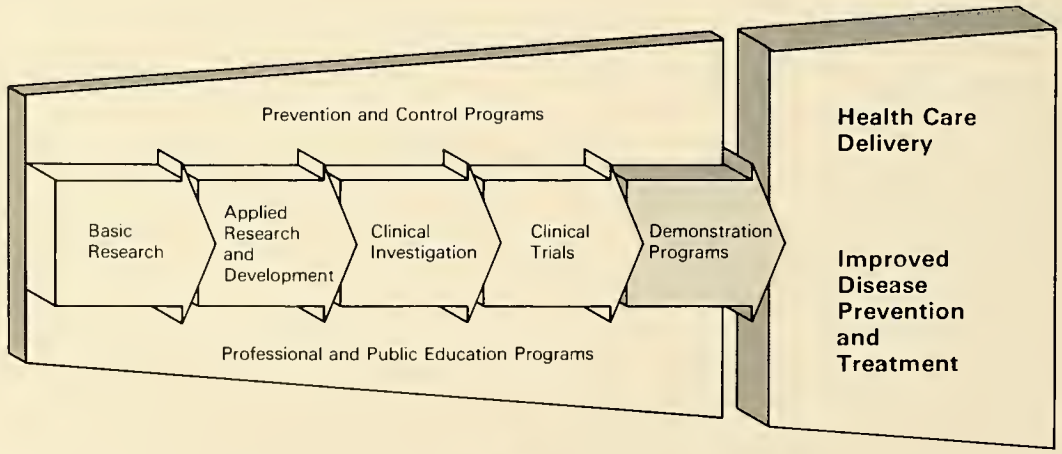
Demonstration Programs

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

Arteriosclerosis

. . . Biobehavioral and Psychosocial Issues in Arteriosclerosis

Extensive consultation with Specialized Centers of Research (SCOR) on arteriosclerosis has resulted in increased efforts toward biobehavioral research objectives in several programs. Following the visits of "mini" teams of consultants to four SCOR programs, a Workshop on Biobehavioral Approaches to the Development of Arteriosclerosis was held in New Orleans for the staffs of five SCOR programs. Feedback from participants suggests that the workshop accomplished its primary objective of acquainting the multidisciplinary staffs with the interrelationships of behavior to biochemical, nutritional,



physiologic, and genetic variables in the development of arteriosclerosis.

Hypertension

. . . Biobehavioral Treatments for Hypertension

The NHLBI has encouraged the development and evaluation of biobehavioral therapies for the treatment of hypertension. It is evident that there are benefits to be derived from the treatment of mild hypertension. The results of the Hypertension Development and Followup Program and other clinical trials have definitively identified the cohort of mild and borderline hypertensives as beneficiaries of reduced blood pressure. To date, the only clinically tested therapy involves the use of pharmacologic agents with their own inherent risks. Recognizing the potential complications of placing 25 million Americans on lifelong pharmacologic therapy, the NHLBI has encouraged the development of alternative biobehavioral therapies by the scientific community.

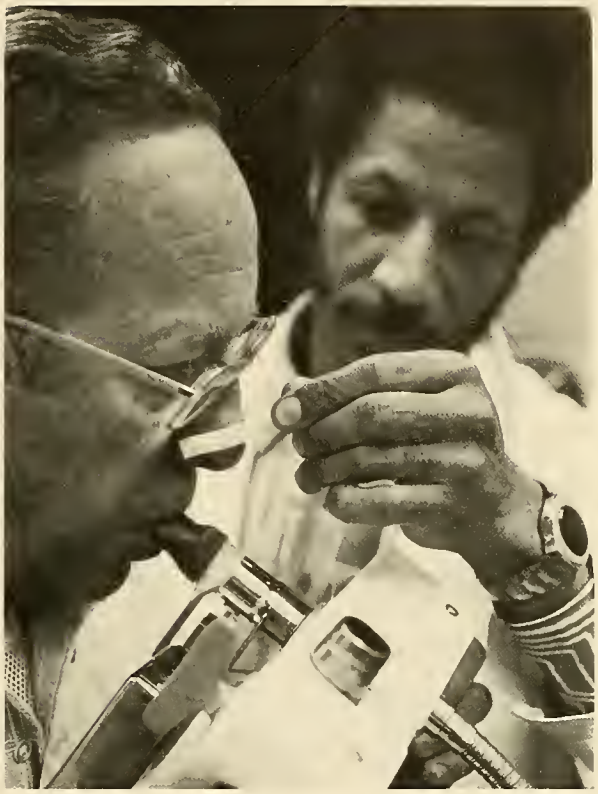
Additional work in this area is being encouraged by facilitating communications among investigators interested in this problem, as in a recent U.S.S.R.-U.S. exchange in hypertension. Soviet scientists reported on the use of biobehavioral therapies in the treatment of hypertension. Autogenic training, acupuncture, psychotherapy, and social psychological approaches in use in the Soviet Union were described and discussed by participants from both countries. All participants were concerned about the development of nonpharmacological therapies and prevention strategies.

Chronic Obstructive Pulmonary Disease

. . . Evaluation of a Self-help Program

Patients with chronic obstructive pulmonary disease are often so severely impaired that they are unable to perform day-to-day activities. This impairment may result in patient depression and emotional strain on the family. There are activities, however, that can help the patient cope with the psychological and medical problems associated with the chronic illness. An educational program, recently developed and evaluated, has shown that these activities can be taught to the patient and that patients can be motivated through such an approach to help themselves.

A "Breathing Workshop" which consists of six 2-hour sessions attended by COPD patients and their families assists individuals in developing preventive and restorative health care behavior and provides an opportunity for psychological support for COPD patients and their families. Topics covered in the workshop include medication, complications, nutrition, effective coughing, breathing retraining, relaxation and mobility exercises, physical endurance building, and basic respiratory anatomy and physiology. The sessions, which are conducted by local health care providers, also feature small group discussions to aid participants in identifying and coping with problems that arise in living with a chronic respiratory illness.



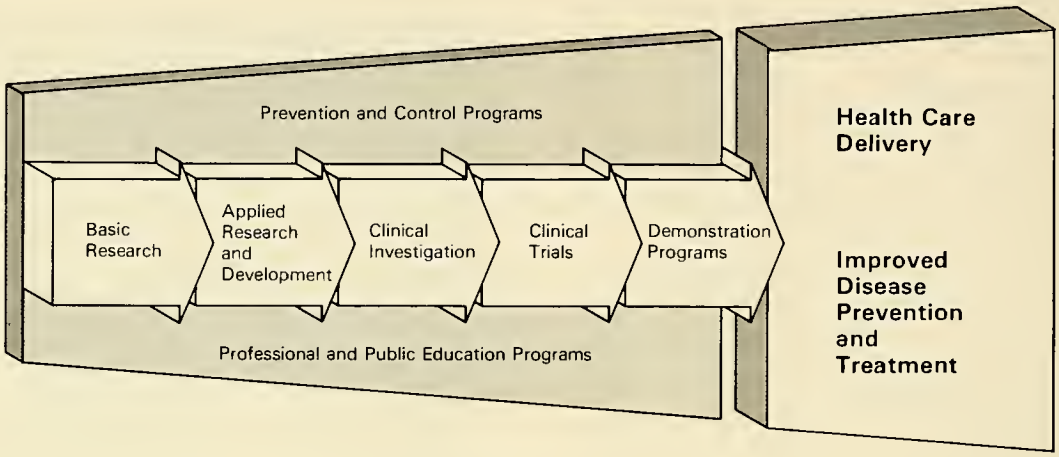
The spirometer, used to measure forced exhaled air, is a useful tool in the diagnosis of impaired lung function.

Following the workshop, patients report that they are much more willing to take actions to help themselves than before. Additional workshops are being conducted in diverse locations, and the information obtained from these will enable a more detailed evaluation of the impact of workshops on the ability of COPD patients to take actions to manage their condition.

Recognition and Management of Neonatal Respiratory Insufficiency

. . . National Impact of New Education Program Is Significant

Respiratory failure is the most common cause of newborn infant death. A national education program that seeks to raise the level of perinatal care practiced in community hospitals to the existing state of knowledge and technology has been successful as measured by decreased mortality rates. The level of knowledge, skills, and procedures



commonly found among professionals in community hospitals was improved considerably in hospitals where educational programs were instituted, and neonatal mortality decreased in areas where the programs were in operation. The American Academy of Pediatrics has begun a national program based on the success of these programs. One project was given the Outstanding Instructional Development Award in 1980, and its programs adopted by the California Department of Maternal and Child Health for use throughout the State. Other States are inquiring as to the availability of the training modules for use in their hospitals.

Newborn Screening for Sickle Cell Disease
. . . A Preventive Approach

Sickle cell disease is a major cause of illness and death in children primarily because of overwhelming infections and wholesale loss of sickled red cells. Early detection of sickle cell disease in the infant permits parental education about the course of the disease, the need for early entry into the health care delivery system, and often the early diagnosis and treatment of potentially fatal infections. Of the 29,910 newborns screened since 1978 at sickle cell centers, 40 were shown to have clinically significant red cell problems. These infants have been provided comprehensive medical care and have been closely monitored by the center staff. To date, there have been no deaths under the age of 2 in this group of children.

Prevention, Education, and Control

The ultimate focus of biomedical research, 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 is responsible.

Through the efforts of investigators at all levels of research, advances have been realized that offer great potential for the treatment and prevention of diseases.

Cardiovascular Health and the Worksetting
. . . Health Education Programs for Industry

Cardiovascular disease (CVD) is the leading cause of death in the United States. It touches lives at home, at work, and at play. The effects of CVD are particularly evident in the workplace. Economic losses in the United States in 1980 from CVD are estimated to be in excess of $75 billion, affecting both employer and employee in lost workdays and wages, lost productivity, increased health care costs, and lower morale.

In recent years, many major corporations have become aware of their losses—in dollars and employees—due to cardiovascular disease and have started their own health promotion and disease intervention programs. The decision to implement these programs has not been easy, since the evidence and information available to industry are often inconsistent and conflicting.

In recognition of the problem and in the hope of increasing and improving CVD health education programs, the NHLBI has produced a document entitled *Cardiovascular Primer for the Workplace*. The primer provides information in three major areas related to the development of educational programs: (1) what is known about cardiovascular disease risk factor reduction and health promotion, (2) factors to be considered in the adoption of health promotion programs, and (3) how to identify available resources to implement a program.

Hypertension in Minority Populations

. . . Detection, Treatment, and Control of High Blood Pressure in Black and Hispanic Populations

High blood pressure (HBP) is a condition that affects approximately 60 million Americans annually. It is almost twice as prevalent in black populations as in the general population and affects more than one out of every four black adults. Untreated HBP is more likely to exist in all minority populations and also among those that cannot afford health care.

Even though a high level of public and professional awareness exists about the consequences and control of HBP, many people are not receiving adequate care. The NHLBI and the Health Services Administration (HSA) have recently developed an educational program to improve HBP control in primary care settings at five demonstration sites. These sites will address the large Hispanic and black (urban and rural) populations. The program will include a training curriculum for both the center and the community, and educational activity directed toward health providers, patients, and the public.

Self-management of Children's Asthma

. . . Reducing Families' Medical Costs and Children's School Absenteeism

Asthma affects millions of children each year and is the leading chronic disease causing school absenteeism. Asthma attacks disrupt family routines and prohibit many children from participating in daily activities. Asthma attacks are often preventable, however, if the patient takes responsibility for self-management of the asthmatic condition. A recently developed educational program shows

Of those occupational groups under regular stress, only air traffic controllers have blood pressure that is consistently higher than normal.

that children and their parents can often self-manage the condition without undue reliance on the medical system.

The principal behaviors targeted in the educational program were those that contribute to the onset or to an exacerbation of the asthma attack. These behaviors include a lack of medication compliance and failure to avoid known irritants such as animals, dust, organic substances, and cigarette smoke. Other behaviors that exacerbate the attacks or interfere with treatment are failure to discriminate the onset of an attack or the inability to relax and take preventive measures during an attack. Results of an evaluation of the educational program indicate that parents made significant gains in knowledge of asthma.

Children who were enrolled in the education program were subsequently able to attend school more days per year. The youngsters were absent an average of 17.3 days in the year prior to their involvement in the project. During the year that they acquired self-management skills, the average number of days missed from school decreased to 11, and the year after the program, the children were absent an average of only 6.4 days. Parents of the asthmatic children experienced a 66 percent decrease in health care expenditures after participation in the program.

The results of this project should be encouraging for community organizations, asthma clinics, and school systems that are attempting to meet the educational needs of asthmatic children and their parents. The project has added significantly to knowledge about children's self-management of asthma. Future work in the area will implement and evaluate this program in other settings.

Tutorial Program

. . . Social Services for Sickle Cell Patients

An academic tutorial program for children with sickle cell disease or trait and for their siblings began in 1974 as a means to meet the academic deficiencies that have been observed in many school-age sickle cell anemia patients. This program was begun without funds and with volunteer tutorial aid for children with sickle cell anemia whose school records indicated repeated absenteeism from class and low levels of performance over several years. As the program developed, it was submitted as a research model that became part of an overall comprehensive program to meet the needs of patients.

The overall goals of the program are based on the general concept that children with sickle cell anemia, like all other children, need an education that will enable them to help plan and manage their own lives in order to reach their highest potentials. It has become evident that ordinary educational opportunities provided by the regular classroom teachers are often not enough to reach some of the special needs of these children. Such needs may be for individual academic aid or may involve encouragement of the child to remain in school, to develop normal friendships and family relationships, and to grow in self-esteem while dealing with an ongoing illness. The tutorial program is committed to developing additional approaches to assist these children in their special needs by working jointly with schools, tutors, parents, and agencies that are involved.

5. Selected Issues with Implications for the Future

A wall of tissue only two cells thick, where capillaries cling to alveoli in the lung, is the vital site of exchange between oxygen and carbon dioxide.

5. Selected Issues With Implications for the Future

The process of scientific investigation continues today the examination of new ideas and modes of treatment for yet uncurable diseases. This chapter examines a number of ideas about which the biomedical and behavioral research community is currently trying to draw conclusions. All of these issues have major implications for the future prevention and treatment of certain diseases.

Cholesterol and Noncardiovascular Disease

Evidence has accumulated over the past decades that identifies high serum cholesterol levels as a risk factor in the development of cardiovascular disease. Recent evidence has suggested an increased rate of cancer in men with low serum cholesterol levels. Since the public has been encouraged to lower cholesterol intake, this new evidence is extremely important.

In 1980, the NHLBI and the National Cancer Institute sponsored a workshop to review eight epidemiological studies for the possible relationship between low serum cholesterol levels and increased risk of cancer. At that time, the data from three of the studies (Framingham, Puerto Rico, and Honolulu) suggested that such a relationship exists for men. It was recommended that another workshop be convened when additional data from these and other studies are available.

Recently, data from 17 international studies were reviewed in a second workshop. The studies reported inconsistent relationships only for men between cholesterol concentrations and mortality from noncardiovascular disease. In four studies (Framingham, Hawaii, Stockholm, and Hiroshima-Nagasaki), a significant association was found between low blood cholesterol and colon cancer in men. No other specific sites of cancer showed a significant association in more than one study. In the studies that suggested it, the excess cancer risk tended to be most pronounced at the lowest end of the cholesterol distribution for that population (usually below 180 mg/dl). If the increase in risk of colon cancer is real, the question arises as to what is responsible for the increase.

Among the factors considered in both reviews is that the observed correlations may reflect traits, possibly genetic, present in only small numbers of individuals. There are a number of avenues of research of potential usefulness in clarifying any association between serum cholesterol level and cancer risk. Among the research topics that have been suggested are: studies of bile acids and dietary lipids in relation to the absorption of dietary vitamin A (a substance that appears to confer some degree of protection against tumors); studies of whether depletion of cell membrane cholesterol when serum cholesterol levels are unusually low might be a factor in precancerous cell changes or tumor induction; and continued research on genetic determinants of cholesterol metabolism, plasma cholesterol levels, and bile acid turnover, especially in persons with very low cholesterol levels.

No basis has been found to recommend changing the widely held position that elevated blood cholesterol poses a risk from premature arteriosclerosis and its complications. Reducing elevated cholesterol by diet is still considered to be beneficial.

Coronary Artery Bypass Surgery

Coronary heart disease is recognized by the physician as the clinical syndromes of angina pectoris, acute myocardial infarction, sudden cardiac arrest, or ischemic cardiomyopathy. Confirmation of the diagnosis can be made with various levels of certainty by one or more special diagnostic tests. Once the diagnosis is confirmed, a decision must be made as to treatment.

Presently, two major treatment modes are available: the use of long-term administration of medications such as nitroglycerin, beta-adrenergic blocking drugs, long-acting nitrates, antiarrhythmic agents, and digitalis; or coronary artery bypass surgery (CABS). Bypass surgery is a technique that improves blood supply through the heart by constructing detours whereby blood bypasses the narrowed portion of the coronary arteries to keep the heart muscle supplied. These detour routes are constructed by grafting veins and arteries from other parts of the body, where they are not essential, onto the heart. Those involved in the management of coronary heart disease have expressed concern as to the efficacy of this treatment modality.

The NHLBI has undertaken a Coronary Artery Bypass

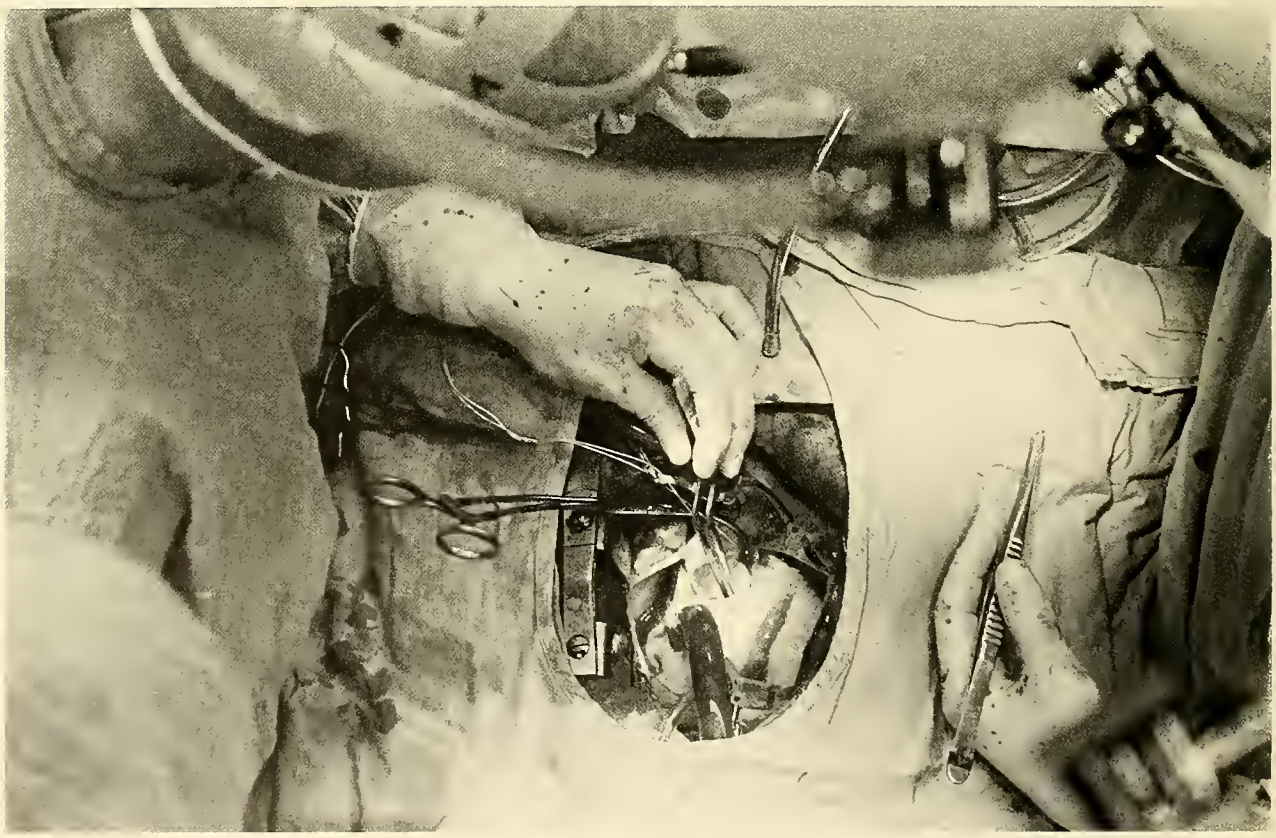
Surgery Study, which will be completed in 1983. Its purpose is to compare results of medical and surgical treatments in a well-defined group of patients with angiographically proven coronary artery disease. Specific end points for followup of the patients enrolled include mortality, rate of myocardial infarction, and "quality of life." The results of this project should provide answers about the ability of CABS to prolong life.

In addition, the NHLBI recently held a consensus development conference to consider the status of CABS. Biomedical investigators, practicing physicians, consumers, and others gathered to provide a scientific evaluation of CABS and to attempt to reach an agreement concerning its safety and effectiveness. The committee addressed the technique in relation to five specific questions:

- What is the overall management of coronary artery disease—that is, in what context should coronary artery bypass surgery be considered?
- What constitutes a reasonable diagnostic workup before recommending medical or surgical therapy?
- What is known about long-term survival after coronary artery bypass surgery in specific patient groups?
- What is known about long-term quality of life after coronary artery bypass surgery?
- What is the rate of success for the procedure in various settings, and what factors may be important in influencing this outcome?

After examining the available data, the committee members concluded that CABS represents a major advance in the treatment of patients with coronary artery disease. An improvement in the quality of life, a decrease in myocardial ischemia, and an increase in survival have been demonstrated after CABS in a selected subset of patients.

A technology assessment forum was also convened to discuss the economic, ethical, and social issues surrounding CABS. The forum participants concluded that there was not sufficient time to consider in depth the many issues surrounding CABS. It is hoped, however, that publications resulting from the conference will increase awareness and understanding and lead to further reflection and research regarding the use of CABS.



A surgeon implants an artificial heart valve in the course of open chest surgery.

Detection and Treatment of Emphysema

Most scientists believe that emphysema is caused by an imbalance between certain enzymes that break down the lung wall (proteases) and their antagonists (antiproteases). This belief was based initially on research that showed that when extra protease is placed in the lungs of experimental animals, they develop a "disease" which closely resembles emphysema. Recent work has demonstrated that people with emphysema have more degenerative enzymes in their lungs than healthy people have. Cigarette smoking exaggerates the condition by increasing the number of cells in the lung that release proteases and by decreasing the effectiveness of antiproteases through the altering effects of oxidants. Currently, the NHLBI is studying ways to detect and treat this disabling disease.

Recent advances have suggested the possibility of a new, simple, fast, and inexpensive method to detect early lung damage by measuring fragments of the lung protein, elastin, in the urine or blood. This technique would replace the lung function test, which is expensive, time-consuming, and not very sensitive.

A number of research studies have centered on the development of better methods of treatment for those in advanced stages of the disease. Patients with emphysema often cannot get enough oxygen into their blood by breathing air. There has been some controversy over the use of continuous oxygen therapy as opposed to oxygen given for 12 hours at night. A recent study provided data showing that continuous oxygen therapy is more beneficial in extending life.

Aerosol drugs are the major route of delivery of medication to the respiratory system. A number of investigators supported by the Institute are studying the properties of aerosols. It is hoped that this research will lead to more effective methods of drug delivery.

One clinical study compares a machine that administers medication to the lungs by intermittent positive pressure breathing (IPPB) with one that also delivers the medicine but relies on the patients' own breathing. Although home use of IPPB machines is widespread, studies to date have not conclusively shown whether they are effective. This study should produce evidence to help answer the question.

Methods to treat emphysema before it becomes disabling remain important. Scientists have been using experimental animal models to see whether natural or synthetic antiproteases can be used to prevent the development of emphysema-like lesions in these animals. Preliminary results appear promising. Further animal research is necessary, however, before the safety and effectiveness of these agents can be tested in humans.

Alanine Aminotransferase Testing

During recent years, the question of the use of alanine aminotransferase (ALT) testing as a method to reduce the risk of transmitting non-A,non-B hepatitis during transfusion has been a key concern to the blood community. Unlike hepatitis B, there is no serologic test to determine whether a blood donor is at risk of transmitting NANB hepatitis.

ALT testing, an assay that measures damage to liver function, has been indicated as a possible indirect test for detecting NANB-contaminated blood samples. Questions about this test lie in the determination of what level of ALT is abnormal and of the way in which such elevations relate to the transmission of NANB hepatitis.

Survey studies have suggested that many factors unrelated to NANB hepatitis may cause ALT levels to be elevated. Alcohol use, exercise, and Tylenol® are a few of the agents that are suspected. A tendency for females to have lower levels than males has also been shown. Moreover, ranges of ALT levels differ significantly from one region of the country to another. Despite these findings, a recent study conducted by the NHLBI-supported Transfusion-Transmitted Virus Study Group followed over 8,000 blood recipients, donors, and controls in five different centers. It was shown that the incidence of NANB hepatitis is directly related to the ALT level of the donor.

An ad hoc Advisory Committee on ALT Testing coordinated by the NHLBI recently met to discuss the issue. The committee included individuals with expertise in liver diseases, viral hepatitis, and blood services. Available data were reviewed, and subgroups of the committee examined medical, scientific, and societal aspects of the problem.

The committee concluded that the available data are insufficient for a decision to introduce routine ALT testing of blood donors at this time. The committee also identified areas where additional information is needed as follows:

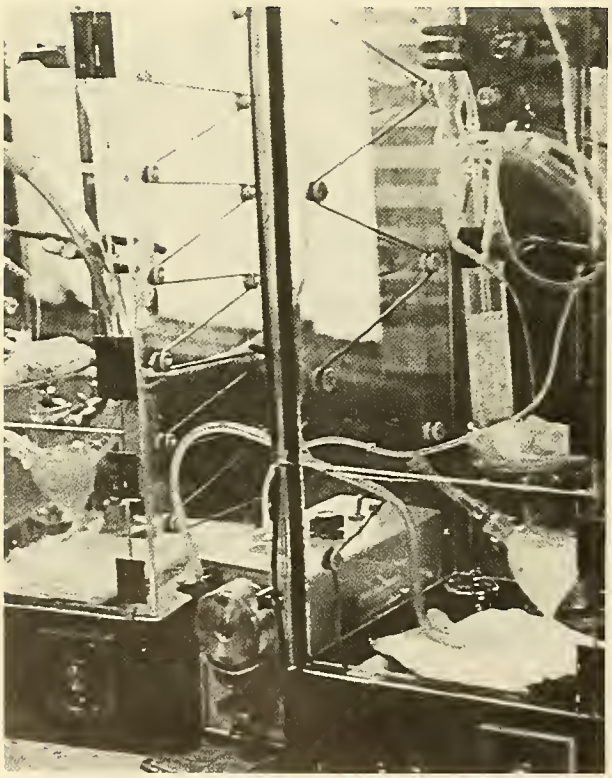
- Consistency of serial ALT levels in individual blood donors
- Further analysis of causes of ALT elevations in donors
- Further epidemiologic analysis of the data that appear to implicate donors with abnormal ALT levels in transmission of NANB hepatitis
- Problems related to technical aspects of assay of enzyme activity
- Effect of ALT testing on blood supply
- Information and referral practices for donors with ALT elevations
- Legal ramifications of ALT testing
- Cost/benefit analysis of ALT testing.

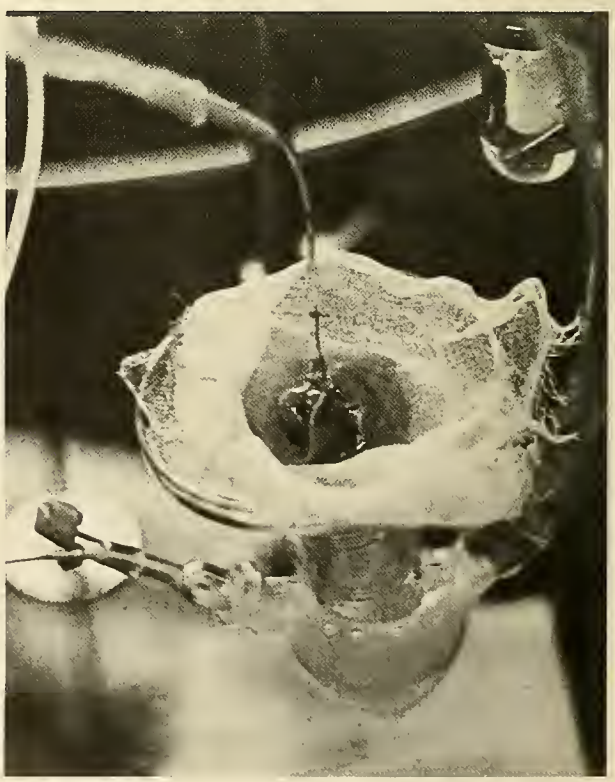
Synthetic Blood Substitutes

Perfluorochemicals have the ability to dissolve appreciable quantities of oxygen and carbon dioxide. This property makes them likely candidates for blood substitutes. The NHLBI has supported research to study this possibility, which holds major implications for the treatment of accident and disease victims. At present, four new perfluorochemicals are being synthesized and screened for their suitability as blood substitutes. Progress in this area is promising.

Studies are also being conducted on the biological effects of perfluorochemicals. One of the studies has shown a positive effect on the reduction of myocardial ischemic damage. Anesthetized dogs with experimental occlusions of the coronary artery breathed 100 percent oxygen while they were bled to a red blood cell level 25 percent that of normal levels and were infused with either perfluorochemical or nutrient solution. Dogs breathing room air and receiving no treatment served as controls. After undergoing 6 hours of coronary occlusion, animals bled and treated with perfluorochemicals developed smaller infarctions than those that received nutrient solution or no treatment. In the nutrient-treated group, 103 percent of the myocardium at risk became infarcted, and in the perfluorochemically treated group, only 70.2 percent of the myocardium at risk became infarcted. In the untreated controls, 97 percent of the myocardium at risk became infarcted.

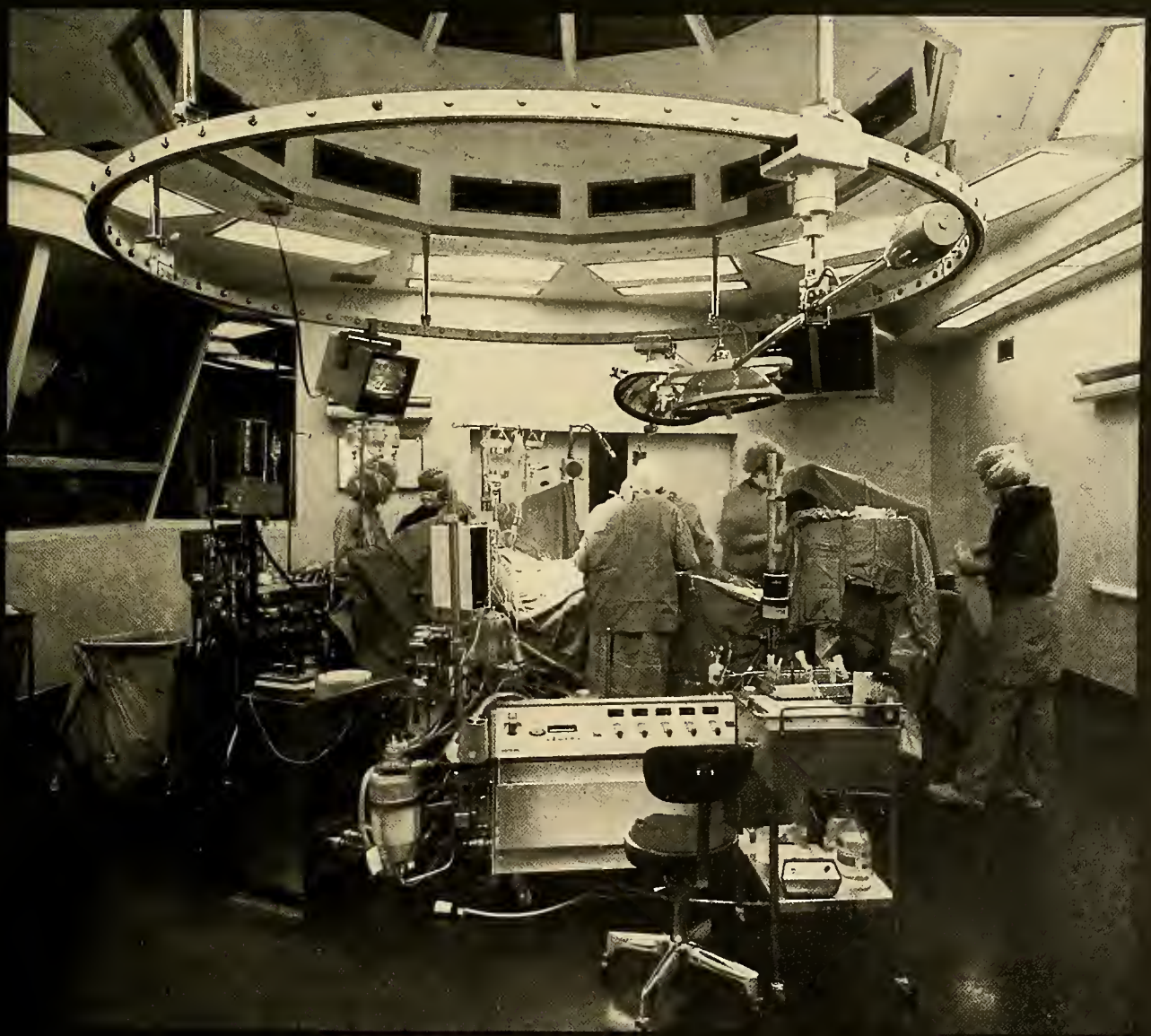
Although the mechanism by which perfluorochemicals limit infarct size is not clear, perfluorochemicals may increase oxygen delivery because their oxygen-carrying capacity at high oxygen tension is actually better than that of blood. Also, because the viscosity of perfluorochemicals is less than that of blood, collateral blood flow to the myocardium may be increased, since most of the deaths in patients hospitalized with acute myocardial infarction result from destruction of extensive amounts of myocardial tissue. Thus, it is conceivable that perfluorochemicals might have a beneficial effect on acutely ischemic myocardium.





A perfluorochemical solution—a potential blood substitute—is perfused through an experimental organ preparation in the laboratory.

6. Resource Allocation and Manpower Development



The modern research hospital requires not only sophisticated electronic equipment but, more important, well-trained and highly skilled clinical investigators.

6. Resource Allocation and Manpower Development

As a result of the National Heart, Blood Vessel, Lung, and Blood Act of 1972, Congress enlarged the National Heart, Lung, and Blood Institute mandate to include responsibilities in:

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

The Institute has kept abreast of the latest scientific knowledge. In response to these mandates, moreover, the NHLBI annually receives a growing number of relevant, program-oriented research proposals.

Fiscal Resources

In 1972, the year in which the National Heart, Blood Vessel, Lung, and Blood Act was passed, the Institute's appropriation was $232.6 million. By 1982, appropriations for the NHLBI will rise to more than $550 million. Funding levels reflect NHLBI expansion and the inclusion of resources to keep up with inflation (table 8). Estimates of future needs are based on NHLBI professional estimates and do not reflect competing priorities within the Department or the administration.

The major issues that this year's projects address are summarized below.

Investigator-Initiated Research. The NHLBI must emphasize its strong commitment to investigator-initiated research.

National Research and Demonstration Centers. National Research and Demonstration Centers allow the Institute to achieve a majority of the goals of the National Program. These centers are engaged in the application of new research findings to health care and disease prevention.

Prevention, Education, and Control Programs. In response to new mandates, this program's major function provides health professionals and the public with the most recent information on cardiovascular disease risk factors and the effect of their modification.

Construction. The National Heart, Lung, and Blood Advisory Council stresses the importance of the construction of research facilities for the National Program. Construction of appropriate and adequate facilities and extensive renovation of old and outmoded facilities is important for the planned increase in program activity; however, it is not the highest priority.

Research Manpower Development. 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 over the past 9 years. In FY 1980, the clinical investigator award was implemented in an effort to reverse this downward trend and to create a basis for increases in the number of new trainees.

Intramural Research. The intramural research budget projections reflect an increase to sustain present program activities.

NHLBI Staff Allocation Plan

The growth of the Institute's mandates and of the programs designed to fulfill them has placed increased responsibilities on the NHLBI staff. As each new program is initiated, a high ratio of staff manpower to dollars is required, especially for clinical trials and targeted activities. To operate the National Progam effectively, the NHLBI may need to expand staff at the middle and upper professional levels as well as in support positions. Programs such as disease prevention, control, and education and comprehensive centers, as well as review and evaluation, require additional personnel with knowledge and skills different from those previously available within the Institute.

To initiate these extensive new programs within the available manpower resources, the Institute has conserved manpower in several ways, including reorganization and centralization of special activities, adoption of dual organizational functions by a number of top-level personnel, and transfer of staff from established ongoing programs to new program needs.

Table 8. Projected Resource Allocation* for the National Heart, Blood Vessel, Lung, and Blood Program, Fiscal Years 1983 to 1987

	1983	1984	1985	1986	1987
			($ in millions)		
Extramural Research Programs					
Heart and vascular diseases	$298.1	$310.4	$331.4	$354.5	$379.3
Lung diseases	82.1	89.9	92.7	99.0	105.9
Blood diseases and resources	84.6	96.2	99.8	106.7	114.2
National Research and Demonstration Centers	7.0	12.0	14.0	16.0	17.0
Prevention, education, and control programs	40.3	42.8	45.7	48.1	50.9
Research manpower development	35.5	37.6	39.8	42.2	44.7
Subtotal, Extramural Research Programs	$547.6	$588.9	$623.4	$666.5	$712.0
Intramural Research Programs	51.8	52.9	53.9	57.6	61.6
Direct Operations and Program Management	41.4	43.9	46.5	49.2	52.1
Total	$640.8	$685.7	$723.8	$773.3	$825.7

* These tabulations give the primary thrust of activities, even though the activities generally involve more than one subprogram.

Training and Manpower Development

The success of the NHLBI programs is dependent upon the availability of well-trained research scientists and clinicians in a wide range of fundamental and clinical research areas. Research training programs are the most effective means of assuring a sufficient number of dedicated professionals knowledgeable in the most up-to-date methods of investigation and clinical applications. This need has become even more evident as the fields related to heart, lung, and blood diseases become increasingly more sophisticated. To accomplish the Institute's goals, research training and manpower development are essential.

The NHLBI has gradually increased the number of trainees it is able to support. In 1981, a total of 1,620 trainees participated in both fellowship and graduate training programs (table 9). This increase reflects the need for new researchers to keep pace with the growth of NHLBI mandates covering expanded areas of investigation.

Programs and Awards

The Institute's manpower programs can be considered in four distinct but interrelated categories:

Training of individuals. These programs are grouped in the national research service awards (NRSA) and include

training grants, fellowships, and certain minority training programs. In addition to supporting postdoctoral fellows in specified areas of cardiovascular biomedical and behavioral research where a documented need for trained manpower exists, the NRSA mechanism also supports institutions in developing or enhancing research training opportunities.

Transition between training and research for new investigators. The new investigator research award and the newly established clinical investigator award programs, for example, are designed to encourage new investigators (including those who have interrupted early promising research careers) and recently trained physicians to develop their basic and clinical research interests and capabilities in heart, lung, and blood diseases, and the blood transfusion sciences.

Research career development for both clinicians and academic investigators. Research career development awards are available to those with doctorates in either the clinical or nonclinical sciences whose research potential is apparent but who need further experience in the development of independent research careers.

Special needs such as curriculum development or specialty manpower shortages. The preventive cardiology

Table 9. Number of Trainees by Activity (Full-Time Equivalents), Fiscal Years 1972 to 1981

	FY 1972	FY 1973	FY 1974	FY 1975	FY 1976	FY 1977	FY 1978	FY 1979	FY 1980	Est. FY 1981
Fellowship programs										
Postdoctoral and special fellowships (F02, F03)	144	72	36	10	1	—	—	—	—	—
Individual research training fellowships (F22)	—	—	167	56	43	2	—	—	—	—
Individual NRSA (F32)	—	—	—	138	193	188	215	168	238	219
Senior fellowships NRSA (F33)	—	—	—	—	—	—	—	—	7	9
Minority access to research career fellowships NRSA (F34)	—	—	—	—	—	—	2	4	4	6
Subtotal, fellowships	144	72	203	204	237	190	217	172	249	234
Graduate training programs										
Graduate training grants (T01)	1,225	1,100	1,065	609	449	233	37	—	—	—
Institutional NRSA (T32)	—	—	—	279	491	702	1,107	1,214	1,168	1,222
Minority summer hypertension NRSA (T32)	—	—	—	—	—	10	17	28	29	30
Pulmonary faculty training NRSA (T17)	—	—	—	24	24	24	24	24	24	24
Off-quarter professional student training NRSA (T35)	—	—	—	—	—	—	—	—	79	110
Subtotal, training grants	1,225	1,100	1,065	912	964	969	1,185	1,266	1,300	1,386
Total training programs	1,369	1,172	1,268	1,116	1,201	1,159	1,402	1,438	1,549	1,620

academic award, for example, was initiated in 1979 to provide a stimulus for the development of a preventive cardiology curriculum in those schools of medicine and osteopathy that do not have one and to strengthen and improve the preventive cardiology curriculum in those schools that do.

Each of the three NHLBI divisions of heart, lung, and blood diseases has made significant accomplishments in research training during the past year.

Division of Heart and Vascular Diseases

The Division of Heart and Vascular Diseases (DHVD) currently supports 690 postdoctoral and 225 predoctoral training positions. This total of 915 trainees, however, is about 80 percent of the number supported in 1972 and 28 percent of the number estimated as necessary to meet the needs projected by the Heart, Blood Vessel, Lung, and Blood Act. All program areas need specially trained independent investigators. There is a particular need for academic physicians, clinical investigators, epidemiologists, nutritionists, behavioral scientists, and geneticists in cardiovascular areas. Despite the fact that the level of support remains close to that of 1972, even in the previous year, it was noted that there were 223 unfilled faculty vacancies in cardiovascular medicine, cardiovascular pediatrics, and cardiovascular surgery in 96 major medical schools.

The National Research Council's *1978 Report on Personnel Needs and Training for Biomedical and Behavioral Research* stated that budgeted faculty vacancies for clinical departments in medical schools had decreased 11 percent per year since 1972 and that basic science departments reported an average increase in vacancies of 4 percent per year. In addition, a number of special shortage areas have been identified. These include:

- Behavioral science
- Basic investigation of tissue metabolism and regional blood control under conditions of ischemia
- Cardiovascular biomedical engineering
- Population genetics
- Study of lipoprotein metabolism
- Endocrinology as it relates to the cardiovascular complications of diabetes
- Specialized study of coagulation in heart disease and stroke
- Nutrition
- Epidemiology
- Biostatistics
- Hypertension control
- Adult and pediatric cardiology.

In a continuing effort to meet these issues, the Division of Heart and Vascular Diseases made expansions in new areas during FY 1981.

National Research Service Awards. NRSA training awards have supported 225 predoctoral and 690 postdoctoral trainees in addition to the 5 senior fellows from FY 1981 funds.

Short-term Training for Students in Health Professional Schools. Continued support from the Division for this new program resulted in the funding of five new awards enabling the support of 344 students on 17 grants in FY 1981.

Clinical Investigator Award Program. Twelve new awards were approved for funding in addition to the 17 commitments based on FY 1981 actions. The strong interest expressed suggests that this program will succeed in increasing the pool of physician investigators.

Preventive Cardiology Academic Award Program. Ten new awards were approved for funding in FY 1981.

Minority Hypertension Research Development Summer Program. Seventeen awards in FY 1981 enabled the support of 41 graduate students and 105 faculty members of 70 minority institutions.

Continuing Education Program in Cardiovascular Epidemiology. This program has sponsored a sixth annual workshop, bringing the total number of graduates to 124.

Research Career Development Award Program. The RCDA program funds 21 new competing awards each year and provides continued support for 80 previously approved applications.

Special Emphasis Research Career Award in Diabetes Mellitus. The DHVD has provided funds for seven FY 1980 awards, two of which were new awards. Two additional awards will be supported for FY 1981.

Minority Biomedical Support Program. Participation in this program is intended to attract students at minority institutions into careers in cardiovascular research. Twenty awards supporting 108 students were funded in FY 1981.

Minority Access to Research Careers Program. The DHVD participates in this National Institute of General Medical Sciences program to encourage minority students by supporting three fellowships for cardiovascular research training.

Division of Lung Diseases

Over an 8-year period, the number of postdoctoral trainees supported by the Division of Lung Diseases has increased substantially; the number of M.D.'s receiving training has doubled, and the number of Ph.D.'s has tripled. Despite these successes, the proportion of physician investigators is declining and creating a serious need. In addition, the Division recognizes a need to enlarge the pool of investigators in special areas such as:

- Epidemiology
- Behavioral medicine
- Mucus biology
- Lung cell biology
- Membrane transport
- Pediatric pulmonary disease.

In an effort to meet these needs, the Division of Lung Diseases has developed programs in new areas:

Research Career Development Awards Program. The RCDA program currently includes 36 awards. Interest in this program seems firmly established after having reached a very low point in 1978.

Research Career Award Program. The Division continues to support seven senior investigators, all of whom are nearing their 20th year of funding.

Pulmonary Academic Award Program. As a result of the competition held during FY 1980, four new pulmonary academic awards were initiated and a total of 65 medical schools have held PAA's at some time during the past 10 years. A special program evaluation is being conducted to assess program impact.

Clinical Investigator Award Program. The second competition for this new program resulted in 18 applications that are assigned to the Lung Division. Of these, 17 were recommended for approval; 10 awards will be made in July 1981.

Medical School Pulmonary Faculty Training Award Program. The last group of awardees began their training in July 1980. Altogether, the program has sustained 33 junior faculty trainees from 25 institutions. The Division is now developing a plan to evaluate the program through a series of site visits to schools whose junior faculty awardees have completed the training period.

Division of Blood Diseases and Blood Resources

A top priority of the Division of Blood Diseases and Blood Resources is the support of research training and research career development to ensure that well-prepared investigators can conduct research in all its mandated areas including: blood transfusion sciences, thrombosis, hemostasis, red cell studies, sickle cell disease, and thalassemia.

It is estimated that 180 fellows per year are needed in research training as replacements for investigators to conduct research in all the high-priority areas cited above. Particular emphasis is placed on providing training in the blood transfusion sciences, since this is a rapidly expanding and increasingly complex area. In FY 1981, the Division supported 257 fellows (includes 56 short-term trainees) in research training and 38 awardees in research career development programs.

Six major program mechanisms have been used to continue research training and research career development efforts:

National Research Service Award Program (Individual). Twenty-four new awards were issued in FY 1981 for a total of 53 postdoctoral fellows. Thirty-three fellows are conducting research in thrombosis and hemostasis problems, 12 in red blood cell diseases, 4 in sickle cell disease, and 4 in blood transfusion sciences.

NHLBI Research Service Award Program (Institutional). Four new institutional awards were added in FY 1981, for a total of 36 grants to support 145 trainees. Training programs in blood transfusion sciences have been particularly encouraged because large numbers of trained professionals are needed to fill vacancies in research in regional blood banking centers.

Ten awards now support 46 trainees for research in the blood transfusion sciences. Seventeen awards support 61 trainees in thrombosis and hemostasis, 7 awards support 29 trainees in red cell disorders, and 2 awards support 9 trainees in sickle cell disease research.

National Research Service Award Program (Senior Fellow). The Senior Fellow Award reenacted the "special fellow" program that was terminated in 1973. One new award was funded in FY 1981 for a total of three senior fellows; two are in thrombosis and hemostasis research and one is in blood resources research.

National Research Service Award for Short-term Training: Students in Health Professional Schools. The Division continues to support two programs in FY 1981

that provide 56 positions for the exposure of talented students to structured research training experience for up to 3 months.

Research Career Development Award Program. Two new research career development awards were made in FY 1981 for a total of 26 awards. Sixteen of these awards are in thrombosis and hemostasis, five in red blood cell disorders, two in sickle cell disease, and three in blood transfusion sciences.

Clinical Investigator Award Program. Seven new awards were funded in FY 1981, making a total of nine clinical investigators. Five are in the area of thrombosis and hematosis, two are in blood resources, and two are in the red blood cell disorders.

Acknowledgments

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