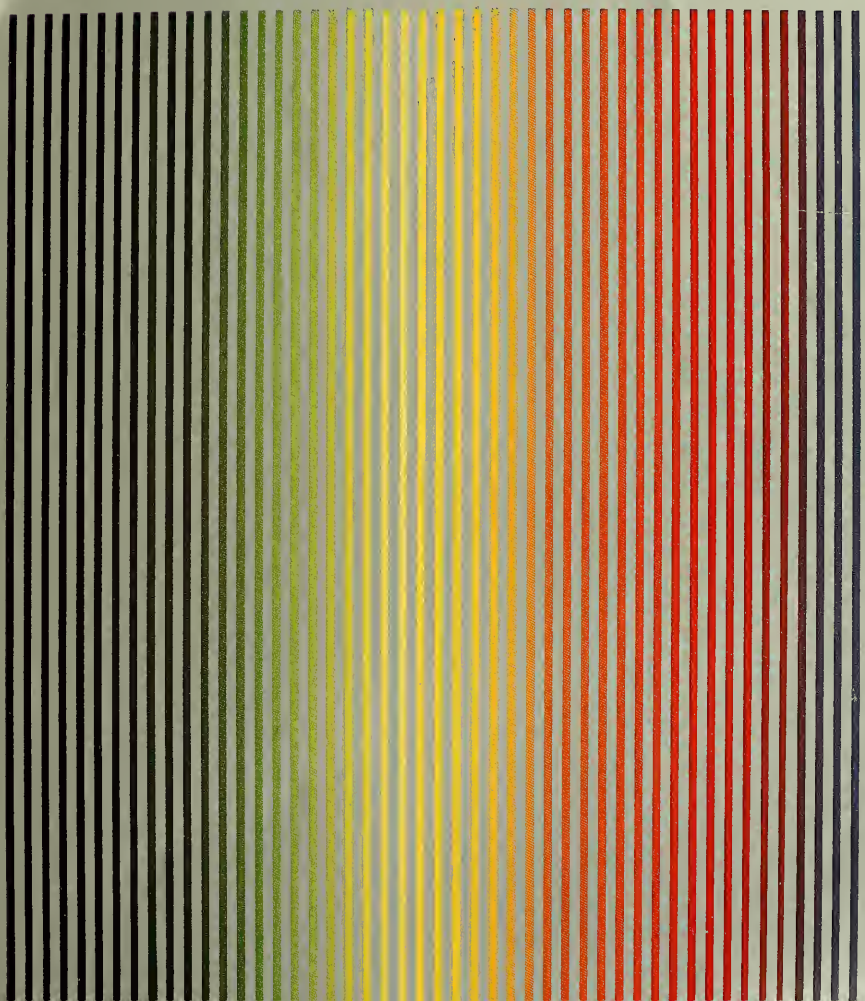
National Heart, Lung, and Blood Institute
Eleventh Report of the Director

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



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November 1983

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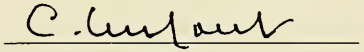
Director's Introduction

The *Eleventh Report of the Director of the National Heart, Lung, and Blood Institute* (NHLBI) presents the Institute's research accomplishments and program highlights during fiscal year 1983 and describes its plans for future research. The accomplishments and the plans are both based on a multifactorial approach to health and disease. Basic research, clinical application, validation, and education are necessary and interrelated steps in biomedical progress. Each category in the research continuum adds to and advances the work of the others, often by raising new questions to investigate. As discussed in chapter 2, basic researchers, using new approaches to study the basic functions of cells, are gaining fresh insights into the causes and treatments of heart, blood vessel, lung, and blood disorders. New laboratory techniques are providing scientists with an understanding of the mechanisms of cell biology and with insights into the events that occur when these mechanisms go awry. Magnetic resonance imaging provides a method of visualizing the metabolic reactions that occur within the cell. Monoclonal antibodies show promise for diagnosis and treatment of disease. The techniques of cloning and DNA sequencing are leading to the development of new therapeutic agents.

In cardiovascular disease, dramatic reductions in morbidity and mortality have resulted from the development of new surgical procedures, sophisticated diagnostic tools, and effective disease prevention strategies. Scientists are increasing their understanding of the functions of the heart and the manifestations of its disorders, which will allow even better therapeutic and preventive interventions. Lung disease is entering an age of intervention. The past focus on providing symptomatic relief has been augmented by research on lung physiology. Progress has also been remarkable in the area of blood diseases, where techniques for diagnosis and treatment are some of the most advanced in medicine. Techniques of molecular biology are now used extensively, and genetic therapy is becoming a realistic concept. During the past 11 years, the concept of disease prevention has been expanded. As epidemiologists have identified new risk factors for disease, research continues on the best approaches and techniques for facilitating healthy behavior.

Building on the foundation of basic research, clinical research scientists are developing and refining medical care practices, which are tested in clinical trials. Dissemination of new and existing knowledge to health professionals and the American public is positively affecting community public health efforts as well as individual health.

In fulfilling its congressional mandate to "develop a plan for a National Heart, Blood Vessel, Lung, and Blood Diseases and Blood Resources Program to expand, intensify, and coordinate the activities of the Institute respecting heart, blood vessel, lung, and blood diseases and blood resources (P.L. 92-423, Section 413)," the NHLBI will continue to encourage and support a balanced program of research and prevention activities. This balanced program will, we believe, continue to make important and effective contributions to improving the health of this Nation.



Claude Lenfant, M.D.

Chapter 1
Magnitude of the Problem

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At the beginning of the 20th century, the three leading causes of death for persons living in the United States were infectious and parasitic diseases. Over the past 80 years, improved sanitation and the discovery and use of antibiotics have brought about dramatic changes in these statistics, as illustrated in figure 1. In 1900, heart disease was the fourth leading cause of death; by 1940, heart disease and stroke became the leading and the third causes of death, respectively. Despite significant improvement in diagnosis and treatment and despite the decreasing death rate, the heart and vascular (cardiovascular) diseases continue to be the Nation's number one threat to life and health.

In response to its congressional mandates, the National Heart, Lung, and Blood Institute coordinates and manages the Nation's research programs for diseases of the heart, blood vessel, lung, and blood and for blood resources, which are organized in 20 areas as outlined in table 1. In addition, the Division of Intramural Research is responsible for the Institute's active intramural program, and the Division of Extramural Affairs supports NHLBI grant and contract activities. The total number of deaths from cardiovascular, lung, and blood diseases for 1968, 1978, and 1980 are shown in table 2. The 10 leading causes of death in the United States for 1982 are listed in table 3 by totals, by mortality rate per 100,000 population, and by percentage. The NHLBI is responsible for research into four of these diseases: heart disease (first); cerebrovascular diseases (third); chronic obstructive lung disease (fifth); and atherosclerosis (tenth). These four diseases accounted for over 1 million deaths in the United States in 1982. Every 30 seconds, someone in the United States dies from a cardiovascular, pulmonary, or blood disease. Every day, countless others endure suffering, disability, and financial loss from the same illnesses. The enormity of the social and economic losses from these diseases indicates the magnitude of the problem that is the responsibility of the NHLBI.

The number of deaths from cardiovascular diseases peaked in 1962, when deaths from these diseases amounted to 55.1 percent of the Nation's total mortality. Despite significant declines in the mortality rate since the 1960's, cardiovascular diseases caused almost 1 million deaths in 1982, with atherosclerosis causing the majority of these deaths and with 20 percent of the mortality occurring in persons under 65 years of age. Today, 1 in every 3 males and 1 in every 10 females can be expected to develop some major cardiovascular disease before reaching age 60 (1). At least 60 million persons, or 25 percent of the Nation's population, have cardiovascular diseases (2). In 1978, they accounted for an estimated 600 million days of restricted activity, 170 million bed days, and 45 million work-loss days (3).

Table 1—National Program Areas

Heart and Vascular Diseases	Lung Diseases	Blood Diseases and Resources
Arteriosclerosis	Structure and function of the lung	Bleeding and clotting disorders
Hypertension	Chronic obstructive pulmonary disease	Red blood cell disorders
Cerebrovascular disease	Pediatric pulmonary diseases	Sickle cell disease
Coronary heart disease	Occupational and immunologic lung diseases	Blood resources
Peripheral vascular disease	Respiratory failure	
Arrhythmias	Pulmonary vascular diseases	
Heart failure and shock		
Congenital and rheumatic heart disease		
Cardiomyopathies and infectious of the heart		
Circulatory assistance		

Figure 1—Ten Leading Causes of Death:* Death Rates per 100,000 Population, U.S., 1900, 1940, 1960, 1970, 1980

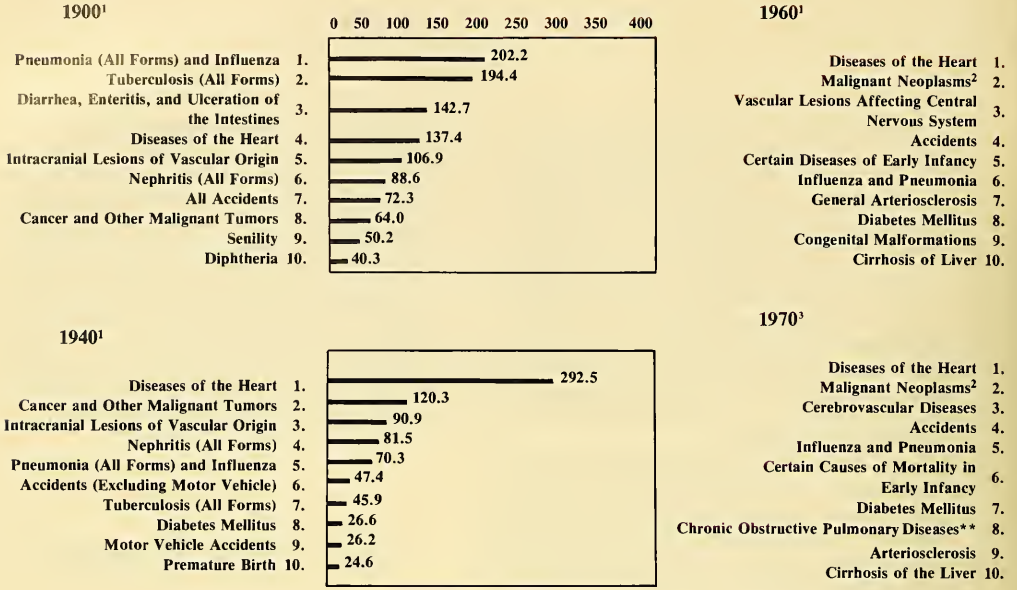


Table 2—Number of Deaths From Cardiovascular, Lung, and Blood Diseases, United States, 1968, 1978, 1980

Cause of Death	1968 Number	1968 Percent	1978 Number	1978 Percent	1980 Number	1980 Percent
Cardiovascular Diseases*	1,038,627	87.0	988,569	87.8	999,976	87.4
(involving blood clotting)**	(412,329)	(34.5)	(345,433)	(30.7)	(328,943)	(28.8)
(pulmonary embolism)***	(9,686)	(0.8)	(10,941)	(1.0)	(10,598)	(0.9)
Lung Diseases†	149,550	12.5	131,298	11.7	136,727	12.0
Blood Diseases††	5,799	0.5	5,889	0.5	7,091	0.6
TOTAL	1,193,976	100.0	1,125,756	100.0	1,143,794	100.0

* ICD/9 codes 390-459, 745-747.

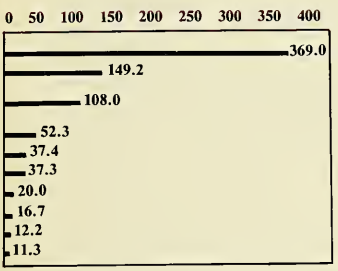
** ICD/9 codes 410 (68%), 433 (80%), 434, 435-438 (80%), 444, 451-453.

*** Subcategory of cardiovascular diseases involving bloodclotting; ICD/9 code 415.

† Does not include cancers, leukemias, and other neoplasms, or pulmonary embolism; ICD/9 codes 011, 135, 277.0, 464.3, 464.4, 466, 480-486, 487, 490-496, 500-508, 515, 517, 518.4, 518.8, 765, 768-770.

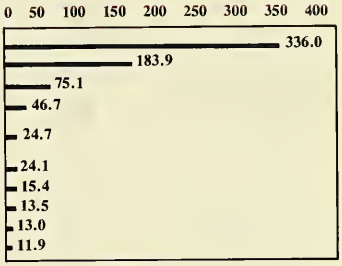
†† Does not include cancers, leukemias, and other neoplasms or pulmonary embolisms; ICD/9 codes 070, 275.0, 277.1, 280, 282-287, 289, 325, 362.3, 634-639, 671, 673, 713.2, 773, 776.

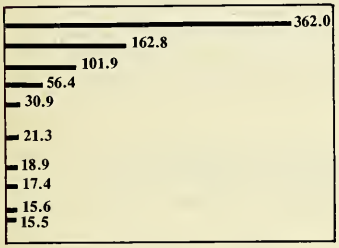
Source: Prepared by the NHLBI; data from the NCHS.



1980[4]

Diseases of the Heart	1.
Malignant Neoplasms[2]	2.
Cerebrovascular Disease	3.
Accidents	4.
Chronic Obstructive Pulmonary Diseases and Allied Conditions	5.
Influenza and Pneumonia	6.
Diabetes Mellitus	7.
Chronic Liver Disease and Cirrhosis	8.
Atherosclerosis	9.
Suicide	10.





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

[1]Source: *Vital Statistics Rates in the United States 1940-1960,* National Center for Health Statistics, PHS Pub. No. 1677.

[2]Including neoplasms of lymphatic and hematopoietic tissues.

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

[4]Source: *Monthly Vital Statistics Reports,* Vol. 32, No. 4, Supplement (Aug. 11, 1983), NCHS.

**Although this category was not identified by the NCHS as a leading cause of death in 1970, it is included here for two reasons: it would have ranked 8th in 1970 if it were not for an artifact in the classification of deaths to the 8th Revision of the ICD; and it is a comparable category to that which is ranked 5th in 1980 under the 9th Revision of the ICD.

Respiratory diseases (acute and chronic) rank first as a cause of bed disability days (4). In addition, more people seek the attention of a physician for respiratory illnesses than for any other reason (4). The age-adjusted death rate for emphysema and chronic bronchitis (chronic obstructive pulmonary disease) doubled between 1950 and 1960, and doubled again between 1960 and 1970 (5,6). Between 1970 and 1980, however, the COPD death rate increased only by 27 percent.

The impact of blood disorders is far greater than the mortality attributed to them. Blood-related disorders either cause or significantly contribute to the development of a wide range of life-threatening conditions such as stroke, myocardial infarction, diabetes, autoimmune diseases, cancer, hypertension, liver diseases, and nephritis. Many blood diseases are chronic disorders that require management with blood products to extend the life of the patient.

Because hundreds of thousands of patients require transfusions of blood or blood products for a variety of diseases, activities at the NHLBI related to blood resources are of major importance to the health of the American people. More than 11 million units of whole blood are collected in the United States each year. Given the importance of blood resources to the Nation's medical care system, it is essential that the risks of transmitting such diseases as hepatitis and the recently observed acquired immune deficiency syndrome (AIDS) be minimized.

Recent trends in mortality and morbidity caused by or related to cardiovascular, lung, and blood diseases indicate both the significant progress made in the Nation's fight against these diseases and the challenges that remain for the future. Life expectancy has never been greater in the United States than it is now, as shown in figure 2. During the 10 years, 1972-1982, the death rate (age-adjusted) declined more than 2 percent per year, indicating that today's leading causes of death are amenable to preventive and therapeutic management. The following material represents the latest available disease statistics and economic costs of diseases related to the Institute's mission.

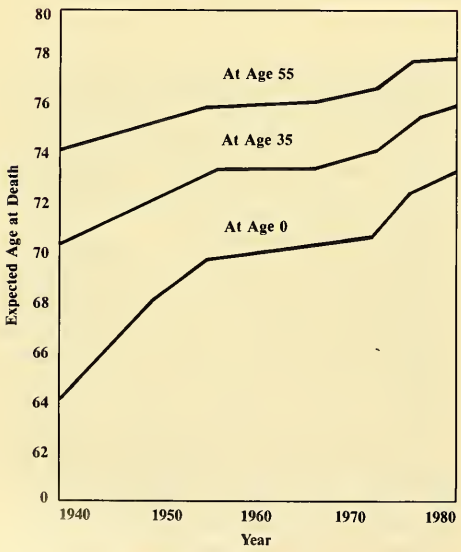
Table 3—Ten Leading Causes of Death, United States, 1982*

Cause of Death	Number	Mortality Rate per 100,000 Population	Percent
All Causes	1,986,000	857.6	100.0
1. Diseases of heart	759,050	327.8	38.2
2. Malignant neoplasms†	435.550	188.1	21.9
3. Cerebrovascular diseases	159,630	68.9	8.0
4. Accidents	95,680	41.3	4.8
5. Chronic obstructive pulmonary disease and allied conditions	59,480	25.9	3.0
6. Pneumonia and influenza	50,460	21.8	2.5
7. Diabetes mellitus	33,220	14.3	1.7
8. Suicide	27,860	12.0	1.4
9. Chronic liver disease and cirrhosis	27,250	11.8	1.4
10. Atherosclerosis	26,550	11.5	1.3
All other causes	310,770	134.2	15.7

*Provisional statistics.
†Includes neoplasms of lymphatic and hematopoietic tissues.

Source: *Monthly Vital Statistics Reports*, Vol. 31, No. 13 (Oct. 5, 1983), NCHS.

Figure 2—Expected Age at Death for Persons at Age 0, at Age 35, and at Age 55, 1940 to 1980, for Total Population, U.S.

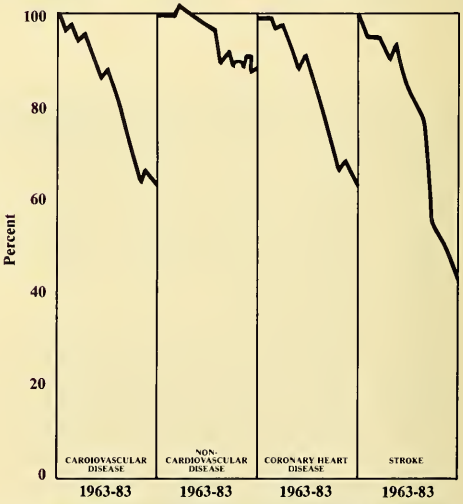


Source: Prepared by the NHLBI; data from the NCHS.

HEART AND VASCULAR DISEASES

Mortality rates from the major forms of cardiovascular disease have been declining dramatically for two decades or more. Figure 3 traces the 20-year trend in cardiovascular and noncardiovascular death rates as a percent of the 1963 rates. Between 1963 and 1983, the age-adjusted death rate for all cardiovascular diseases declined by 37 percent, with the death rate for coronary heart disease declining by 38 percent and stroke by 54 percent. During the same period, noncardiovascular mortality rates declined 13 percent. Thus, the reduction in cardiovascular mortality rates accounted for 72 percent of the overall national mortality reduction and the major portion of the increase in life expectancy during the same period. Preliminary data for 1982 and 1983 indicate a continuation of this favorable trend. Despite this progress, cardiovascular diseases accounted for approximately 985,000 deaths in 1982, which represented 49.6 percent of the Nation's total mortality (table 4). Approximately 77 percent of these deaths were caused by heart disease and 16 percent by stroke. Tables 5 and 6 list the data for the prevalence

Figure 3—20-Year Trend in Cardiovascular and Noncardiovascular Death Rates* as a Percent of Rates in 1963, U.S.



*Age-adjusted to U.S. population, 1940. Because of serious breaks in comparability in 1968 and 1979 caused by revisions in the ICD, crude comparability ratios were applied to death rates for years 1968-1978 for coronary heart disease and stroke to improve comparability over time.

Source: Prepared by NHLBI; data from NCHS.

and underlying cause of death of selected heart and vascular diseases. The leading cause of death and the most prevalent cardiovascular disease is atherosclerosis, causing clinical manifestations in an estimated 11 million persons and 762,000 deaths in 1982.

Coronary heart disease is the major cause of death after age 40 in men and after age 50 in women. Each year the incidence of coronary attacks is estimated to be 1,250,000 of which 800,000 are first attacks. In 1982, 555,000 people died from coronary attacks. The data in table 7 show that prevalence rates for most cardiovascular diseases increase markedly with age, and that coronary heart disease is more than twice as prevalent in the 65 and over age group than in the 45 to 64 age group.

The decline in coronary heart disease mortality, however, reverses the earlier epidemic rise persisting into the 1960's, and it coincides with improvements in the management of the major cardiovascular risk factors, more vigorous and effective treatment of the acute episode, and greater efforts at prevention of complications. The decline in coronary heart disease mortality in the United States exceeds that observed elsewhere in the world. If coronary heart disease could be eliminated, it is estimated that a 30-year-old American male would survive to age 79 rather than 73.

Hypertension is the most prevalent cardiovascular disease (table 7) in the age groups 45 to 64, and 65 and over. The total prevalence of hypertensive persons is estimated at 60 million extrapolated to all ages and including persons on antihypertensive medication (table 5). Hypertensive disease is the most important contributing factor to the approximately 500,000 cases of stroke that occur each year (NHLBI estimate); it is the main contributor to all 160,000 deaths from stroke and to the 27,000 deaths from cardiac failure in 1982. The 3 percent of cardiovascular deaths in 1982 attributed to hypertensive disease therefore fails to reflect its real impact on total cardiovascular mortality.

The annual costs of cardiovascular diseases were estimated at $88 billion in 1981 (table 8), by far the largest for any diagnostic group of diseases. For patients with cardiovascular disease in that year, the Nation spent $37.9 billion in direct costs (hospital care, physician and other professional services, drugs, and nursing home care), or 1 percent of the GNP. The economy lost $50 billion in indirect costs (lost productivity from illness and premature deaths attributed to these diseases). Coronary heart disease

Table 4—Deaths by Cause and Percentage of Total Deaths, 1968, 1982

Cause	Number of Deaths			
	1968*	Percent of Total Deaths	1982†	Percent of Total Deaths
Cardiovascular diseases				
Coronary heart disease	674,747	35.0	554,900	27.9
Cerebrovascular disease	211,390	11.0	159,630	8.0
Other	162,176	8.4	270,511	13.6
Cardiovascular subtotal	1,048,313	54.3	985,041	49.6
Cancer	318,547	16.5	435,550	21.9
Accidents and adverse effects	114,864	6.0	95,680	4.8
Pneumonia and influenza	73,492	3.8	50,460	2.5
Chronic obstructive pulmonary diseases and allied conditions‡	30,390	1.6	56,980	3.0
Other causes	344,476	17.8	362,349	18.2
TOTAL all causes	1,930,082	100.0	1,986,060	100.0

*Based on the Eighth Revision of the International Classification of Diseases.
†Provisional data. Based on the 9th Revision of the International Classification of Diseases, which assigns almost 80,000 fewer deaths to coronary heart disease and results in other less serious discontinuities of trends.
‡Coded in 1968 as bronchitis, asthma, and emphysema.

Note: Percentages may not add to 100 due to rounding.

Source: Prepared by the NHLBI; data from the NCHS.

Table 5—Estimated Prevalence of the Heart and Vascular Diseases, U.S.

Heart and Vascular Diseases	Number of Persons	Year
Total	*	
Atherosclerotic-related diseases:	11,000,000**	1982
Coronary heart disease	5,700,000	1982
Cerebrovascular diseases	1,900,000	1982
Peripheral vascular diseases	3,400,000	1982
Hypertension	60,000,000†	1979
Rheumatic heart disease	1,500,000	1982
Congenital heart and vascular diseases	560,000	1982
Cardiac failure	2,300,000‡	1984
Phlebitis and thrombophlebitis	900,000	1982
Varicose veins	6,100,000	1982
Hemorrhoids	8,000,000	1982

*An estimate of the total prevaleoce of these diseases cannot be made. ft must be in excess of the 60 million persons with hypertension.
**This estimate is overstated to the extent that some persons are in more than one of three disease groups defined as atherosclerotic-related.
†Hypertension is defined as a systolic blood pressure of 160 mm Hg or greater or diastolic of 90 mm Hg or greater, or taking antihypertensive medication. This estimate was made by the NHLBI based primarily on data from the 1971-74 Health and Nutrition Examination Survey of the NCHS.
‡This estimate was made by the NHLBI based on prevalence rates observed in two small community studies reported by Gibson in J. Chron. Dis. 19:2: 141-152. 1966.

Source: Except as noted, these estimates are from the National Health Interview Survey, 1982, NCHS (unpublished).

Table 6—Number of Deaths From Heart and Vascular Diseases, U.S., 1980 or 1982

Heart and Vascular Diseases	ICD/9 Code	Number of Deaths	Year
Total	390-459 745-747	985,000*	1980/82
Atherosclerotic-related diseases:		762,000	1982
Coronary heart disease	410-414	554,900	1982
Cerebrovascular diseases	430-438	159,600	1982
Peripheral vascular diseases	440-448	47,100	1982
Hypertensive disease	401-405	31,500	1982
Rheumatic fever and rheumatic heart disease	390-398	6,700	1982
Congenital heart and vascular disease	745-747	6,600	1980
Cardiac failure†	428	27,400	1980
Cardiomyopathy†	425	7,900	1980
Cardiac dysrhythmias†	427	30,700	1980
Pulmonary embolism†	415.1	10,600	1980
Subacute bacterial endocarditis†	421.0	700	1980
Phlebitis and thrombophlebitis†	451	2,000	1980
Other heart and vascular diseases‡	Residual	98,900	1980/82

*This figure is obtained from the addition of 973,600 deaths in 1982 classified to "major cardiovascular diseases" (390-448) plus 11,400 deaths in 1980 classified to "diseases of veins" (451-459) and to the congenital heart and vascular diseases (745-747).
†Because of imprecisioo in diagnosing, certifying, and classifying deaths to this diagnostic category, the number of deaths assigned to this category as the underlyiog cause of deatb is oot necessarily accurate.
‡Some of these deaths would have been classified to a specific rather than generalized cause of death if appropriate information had been available at the time of deatb certificatioo.

Source: National Center for Health Statistics public use tape for deaths in 1980 and the *Monthly Vital Statistics Report*, Vol. 31, No. 13, Oct. 5, 1983. Data for 1982 are provisioonal.

Table 7—Prevalence Rates per 1,000 Persons for Cardiovascular Conditions for Selected Age Groups, United States, 1981

Cardiovascular Diseases	Ages 45-64	Ages 65 and Over
Heart conditions	122.7	277.0
Active rheumatic fever and chronic rheumatic heart disease	11.2	12.0
Coronary heart disease	54.5	117.7
Other specified heart disease	8.5	20.5
Unspecified disorders of heart rhythm	29.8	60.2
Heart trouble*, NOS	17.1	63.5
Hypertensive disease*, NEC	243.7	378.6
Cerebrovascular diseases	13.0	45.4
Arteriosclerosis, NEC	21.3	97.0
Phlebitis and thrombophlebitis, NEC	7.5	13.3
Poor circulation, NOS	4.2†	18.1
Congenital anomalies of the circulatory system	3.2†	1.9†

*This estimate understates prevalence because it does not include persons unaware of their condition.
†This estimate does not meet standards of reliability or precision.
NOS: not otherwise specified.
NEC: not elsewhere classified.

Source: National Health Interview Survey; NCHS (unpublished).

Table 8—Direct and Indirect Economic Costs of Illness From Cardiovascular, Lung, and Blood Diseases, United States, 1981

	Amount ($ Billions)				Percent Distribution*			
		Direct	Indirect Costs			Direct	Indirect Costs	
	Total	Costs†	Morbidity	Mortality‡	Total	Costs†	Morbidity	Mortality†
Cardiovascular diseases	87.6	37.9	11.1	38.6	18.4	15.4	15.8	24.1
(involving blood clotting)	(28.5)	(7.7)	(2.5)	(18.2)	(6.0)	(3.1)	(3.6)	(11.4)
(pulmonary embolism)**	(1.1)	(0.5)	(0.5)	(0.1)	(0.2)	(0.2)	(0.7)	(0.1)
Lung diseases††	24.7	7.0	11.8	6.0	5.2	2.8	16.8	3.7
Blood diseases††	2.1	1.4	0.3	0.4	0.4	0.6	0.4	0.2
TOTAL, cardiovascular, lung, and blood diseases	$114.4	$46.3	$23.2	$45.0	24.0%	18.8%	33.1%	28.1%
TOTAL, all diseases	$475.9	$245.7	$70.1	$160.1	100.0%	100.0%	100.0%	100.0%

*Numbers may not add to 100 percent due to rounding.
†Includes only personal health care expenditures allocated to diagnoses (86 percent of total direct health care expenditures).
‡Based on a 6 percent discount rate of loss of future earning because of premature death.
**Subcategory of cardiovascular diseases involving blood clotting.
††Does not include cancers, leukemias, and other neoplasms, or pulmonary embolism.

Source: Prepared by the NHLBI; data from the NCHS.

Table 9—Number of Deaths From Selected Lung Diseases, United States, 1980

Cause of Death (ICD/9 code)	Number of Deaths	Subtotals
Diseases of the Airways		57,245
Chronic obstructive pulmonary disease		
Chronic obstructive pulmonary diseases, NEC (496)	34,753	
Emphysema (492)	13,877	
Chronic bronchitis (490, 491)	3,728	
Other chronic airways obstruction (495)	10	
Asthma (493)	2,891	
Cystic fibrosis (277.0)	543	
Bronchiectasis (494)	801	
Acute bronchitis and bronchiolitis (496)	642	
Pneumonias		54,853
Pneumonias with organisms unspecified or manifestations of other infectious diseases (484-486)	45,234	
Bacterial pneumonia (481-482)	5,622	
Mycoplasma pneumonia (483)	91	
Myocotic pneumonia (039, 114, 115, 117.3)	234	
Viral pneumonia (includes influenza pneumonia) (480, 487)	3,672	
Neonatal Pulmonary Disorders		19,430
Sudden infant death syndrome (798.0)	5,510	
Respiratory distress syndrome (including hyaline membrane disease) (769)	4,997	
Immaturity, unqualified (765)	3,663	
Asphyxia of the newborn (768)	1,518	
Other respiratory conditions of fetus and newborn (770)	3,742	
Disorders of the Pulmonary Circulation		12,421
Pulmonary embolism (415.1)	10,576	
Pulmonary heart disease (416)	1,457	
Pulmonary edema* (518.4)	331	
Cor pulmonale (415.0)	22	
Other diseases of pulmonary circulation (417)	35	
Interstitial Lung Disorders (by etiology)		6,666
Chronic interstitial pneumonia (515)	3,006	
Granulomatous diseases including sarcoidosis (135, 446.4)	387	
Occupational lung diseases† (495, 500-506)	1,635	
Tuberculosis (011, 012)	1,638	
Lung Cancer		103,680
Bronchus and lung (162.2-162.9)	103,680	
TOTAL		254,295

kills and disables people in their most productive years, and it accounted for $8.6 billion of the $37.9 billion spent in 1981 for cardiovascular disease patient care. It is the leading cause of premature permanent disability in the American labor force, accounting for 19 percent of disability allowances by the Social Security Administration. Intangible costs such as suffering from pain, mental anguish, and disruption of family life cannot be measured.

LUNG DISEASES

About one in every five persons in the United States has some chronic respiratory problem (7). More than one-half of these persons, however, have chronic sinusitis or hay fever, two conditions not under NHLBI purview. In 1979, the lung diseases listed in table 9 accounted for approximately 25 million visits to physicians (8), 21 million days of hospital care, and 2.5 million hospital discharges (9). Chronic obstructive pulmonary disease and asthma are especially prevalent, afflicting nearly 10 million and 7.2 million persons, respectively (10). In 1982, an estimated 56,900 deaths occurred from COPD, including emphysema, chronic bronchitis, and otherwise unspecified chronic obstructive pulmonary disease; 49,700 deaths from pneumonia; and 3,600 from asthma. Lung diseases are the underlying cause of approximately 254,000 deaths each year and are a contributing cause in approximately 240,000 additional deaths. Table 9 lists the number of deaths from selected lung diseases for 1980.

Except for COPD and lung cancer, downward trends in mortality for most lung diseases have been observed over the past 10 years. For example, the death rate for influenza and pneumonia declined by 43 percent; for asthma, mortality declined by 42 percent. In 1968, infant mortality due to lung diseases accounted for 50 percent of all infant mortality, but by 1980, infant lung disease mortality declined to 36 percent. Overall infant mortality declined to 42 percent between 1968 and 1980; 75 percent of that decline was due to the decline in infant lung disease deaths (figure 4). However, medical scientists are concerned about the contrasting increase of 28 percent in deaths from chronic obstructive pulmonary disease, which was the fifth leading cause of death in 1982.

NEC: Not elsewhere classified.

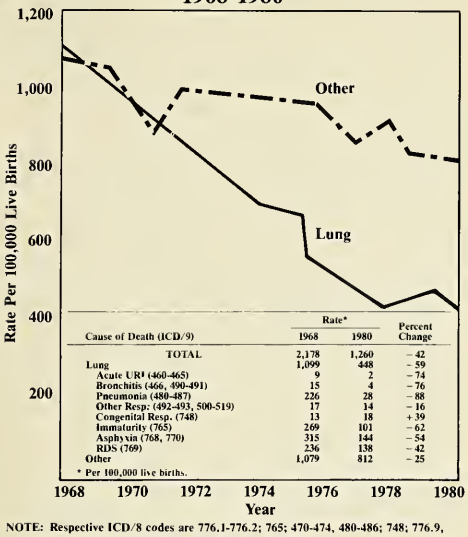
*Excludes pulmonary edema related to heart failure.

†Includes occupational bronchitis and occupational asthma as well as interstitial disorders.

Note: Data on diseases outside the NHLBI lung disease program, such as lung cancer, tuberculosis, pneumonia, and influenza, are included for perspective.

Source: Prepared by the NHLBI; data from the NCHS.

Figure 4—Infant Mortality Rate for Lung Diseases and Other Causes of Death, U.S., 1968-1980



Cause of Death (ICD/9)	Rate* 1968	Rate* 1980	Percent Change
TOTAL	2,178	1,260	– 42
Lung	1,099	448	– 59
Acute URI (460-465)	9	2	– 74
Bronchitis (466, 490-491)	15	4	– 76
Pneumonia (480-487)	226	28	– 88
Other Resp. (492-493, 500-519)	17	14	– 16
Congenital Resp. (748)	13	18	+ 39
Immaturity (765)	269	101	– 62
Asphyxia (768, 770)	315	144	– 54
RDS (769)	236	138	– 42
Other	1,079	812	– 25

* Per 100,000 live births.

NOTE: Respective ICD/8 codes are 776.1-776.2; 765; 470-474, 480-486; 748; 776.9, 776.0, 776.3-776.4; 466, 490-491; 460-465; 492-519.

Source: Prepared by the NHLBI; data from the NCHS.

The prevalence of emphysema has increased from an estimated 1.3 million persons in 1970 to an estimated 2.1 million persons in 1981; in 1983, emphysema was the underlying cause of death for 12,700 Americans (11).

The economic costs of lung diseases were estimated at $24.8 billion in 1981 (table 8). The direct costs of care were $7 billion, and the estimated costs of lost productivity from illness and premature death were $17.8 billion. These indirect losses to the Nation's economy from lung diseases are in excess of morbidity losses from any other medical diagnosis.

*BLOOD DISEASES AND RESOURCES**

The health effects of blood-related diseases range from mild to life-threatening and from transitory to continuous. Blood diseases were a contributing factor in about 580,000 deaths and an underlying cause of death for 351,000 persons in 1978. These figures represent a 13 percent decline from 1970 levels. The major effects of blood diseases on mortality and health care are reflected in table 10.

The actual impact of blood-related disorders is far greater than the mortality attributed to blood diseases. Recent research findings have revealed the widespread involvement of thrombosis (clotting) in numerous disorders. Aggressive chemotherapy for cancer often increases the susceptibility of patients to bleeding disorders, such as clotting disorders associated with the depletion of platelets. Many blood disorders either cause, accompany, or result from various types of diseases and injury. Approximately 33 percent of cardiovascular disease deaths result from abnormalities in blood clotting. Pulmonary embolisms were reported as the cause of about 11,000 deaths in 1981. The prevalence of thrombosis (clotting) is difficult to estimate, but thrombosis is known to be involved in numerous disorders. An estimated 900,000 persons suffer annually from phlebitis and thrombophlebitis.

Many chronic blood disorders require management with blood products for the lifetime of the patient. Nearly 50,000 black Americans suffer from the debilitating condition of sickle cell anemia. Over 25,000 Americans are afflicted with hemophilia, three-quarters of whom require lifetime treatment with costly derivatives of human blood plasma. Approximately 1,000 Americans suffer from the genetically transmitted Cooley's anemia.

In 1981, personal health care expenditures for blood diseases were $1.4 billion. The indirect cost of blood diseases was estimated at $700 million (see table 8).

The quantities and costs of blood collected, processed, and transfused are not routinely reported. The NHLBI has sponsored studies to determine quantities and costs for 1979 and 1980. Those studies have provided data that make it possible to estimate these figures accurately as well as to describe the numbers and types of patients receiving transfusions of whole blood and red blood cells.

Table 10—Impact of Blood Diseases, 1978

Contributing cause of death	579,846
Underlying cause of death	351,322
Hospitalizations for which blood diseases were primary causes	1,378,000
Days of hospital care due to blood diseases	16,130,000
Visits to physicians' offices for treatment of blood diseases	6,695,000

Source: Prepared by the NHLBI from published and unpublished data, NCHS, NHLBI. See *Tenth Report of the Director, NHLBI, Volume 4*, NIH Publication No. 84-2359, pp. 45-104.

*Tabulation, explanation, and sources of many of these statistics are in the *Tenth Report of the Director, National Heart, Lung, and Blood Institute, Volume 4*, NIH Publication No. 84-2359, pp. 45-104.

Nearly two dozen blood products, ranging from whole blood to individual proteins separated from blood plasma, are transfused to patients. In 1980, almost 7 million Americans donated whole blood or blood components, with more than 6.5 million giving whole blood, more than 250,000 giving plasma, and an estimated 50,000 donating white cells or platelets.

From 10,880,000 units of blood collected in 1980 by hospitals and blood centers, the following were prepared:

- 2,720,000 units of whole blood for transfusion.
- 8,160,000 units of red cells for transfusion.
- 3,440,000 units of platelets for transfusion.
- 2,210,000 units of plasma for transfusion.
- 590,000 units of cryoprecipitated antihemophilic factor for transfusion.

More than 14,800,000 units of these blood fractions were transfused to patients. Also in 1980, 3,270,000 patients received whole blood or red cells, or both, as a part of their therapy. Table 11 shows the groups of diseases for which these patients received transfusion therapy and the number of patients in each group.

The principal adverse effect of transfusion of every blood product (except for albumin) is transfusion-transmitted hepatitis. In 1980, about 280,000 recipients of blood products were infected in this way by a hepatitis virus. Most of these cases (85 to 90 percent) were non-A,non-B hepatitis. Although most cases of non-A,non-B hepatitis produce no immediate debilitating symptoms, hepatitis transmitted by transfusion is still a major public health problem.

Table 11—Diseases for Which Patients Received Transfusions, 1980

Disease	Number of Patients (approximate)
Cancer	600,000
Cardiovascular and cerebrovascular disease	450,000
Gastrointestinal disorders	450,000
Trauma	400,000
Blood disorders, obstetrical problems, bone and joint disorders, and gynecologic and breast diseases	125,000-250,000 each
Respiratory, liver, kidney, and bladder disorders	50,000-125,000 each
Benign tumors, gallbladder, genital, metabolic, skin and soft tissue disorders, and complications of other disorders	25,000-50,000 each
Infections, hernias, diabetic complications, pancreatic disorders, and nervous system disorders	10,000-25,000 each

Source: Published and unpublished data, NHLBI. See *Tenth Report of the Director, NHLBI, Volume 4*, NIH Publication No. 84-2359, pp. 48-104, for sources and ICD codes.

References

1. National Heart, Lung, and Blood Institute, the Framingham Heart Study.
2. An estimate of the total prevalence of these diseases has not been made. Based on the 1971-1974 Health and Nutrition Examination Survey, NCHS, the Institute estimated that by 1979 there were 60 million persons in the United States with hypertension.
3. Special tabulation for the NHLBI from the National Health Interview Survey, NCHS. All diseases of the circulatory system are included except varicose veins and hemorrhoids.
4. Rice, D.P., Feldman, J.J., and White, K.L. The Current Burden of Illness in the United States. Presented at the annual meeting of the Institute of Medicine, October 27, 1976, Washington, D.C.
5. National Center for Health Statistics, "Mortality from Diseases Associated with Smoking, United States, 1950-64," *Vital and Health Statistics,* PHS Publication No. 1000, Series 20, No. 4, October 1966.
6. National Center for Health Statistics, "Mortality from Diseases Associated with Smoking, United States, 1960-77," *Vital and Health Statistics,* DHHS Publication No. (PHS) 82-1854, January 1982.
7. National Center for Health Statistics, Prevalence of Selected Chronic Respiratory Conditions, United States—1970, DHEW Publication No. (HRA) 74-1511, September 1973.
8. Unpublished estimate from the Ambulatory Medical Care Survey, NCHS, 1979.
9. Unpublished estimates from the National Hospital Discharge Survey, NCHS, 1982.
10. Unpublished estimates from the National Health Interview Survey, NCHS, 1982.
11. An unknown portion of this increase in the prevalence of emphysema could have been due to the revision of the International Classification of Diseases in 1979.

Chapter 2
Cell Biology: A Closer Look

Chapter 2
Cell Biology: A Closer Look

Medical practice constantly improves, and the pace is quickening. As scientists provide new knowledge and new instruments for acquiring it, new prospects for better health care become realized. Foremost among the several reasons for improvements in medicine is basic research in the natural and social sciences. In the biological sciences in particular, a veritable revolution is presently under way, and it promises an impact at least as significant as that of the industrial revolution that preceded it. Cell biology provides the focus for much of this intense activity. Although the cell is the smallest and simplest living entity, it is an inordinately complex and highly integrated functional unit. It is comprised of large and small chemical molecules arranged into hierarchical levels of structure and activity, together capable of growth, reproduction, repair of injury, and response to stimuli. It has all the characteristic features of life. Most human cells exist in interdependent and specialized groups of tissues and organs, although some, such as the cells of the blood, lead a more independent existence. In all cases, however, the activities of cells determine the well-being of the whole organism, and it is here that the very nature of life itself resides.

Ever since the first successful pioneering attempts at the turn of the present century to grow animal cells in the laboratory, there has been a steady increase in the extent and variety of studies in cell biology. Cells grown and handled in this way—in "cell culture"—provide well defined and homogeneous populations under the precise control of the experimenter, whose investigations are consequently unfettered by the inherent complexities of the whole, intact organism. The technique of cell culture has thus made dramatic advances possible in almost every area of the life sciences. It has provided the means to acquire knowledge of normal and disease states of blood and brain, of tumor and virus, and of an endless variety of living systems.

Despite this progress and despite the fact that animal cells in culture have been used in the laboratory for the greater part of the present century, some of the most interesting and crucially important human cell types have unfortunately remained refractory to culture until very recently. Such is the case with the human endothelial cell. The endothelium is the layer of cells that lines the body cavities, particularly those inside the heart and the blood and lymph vessels. Within the heart and blood vessels, it provides an interface between living solid tissue and the flowing blood. Formerly considered a simple, inert barrier, the endothelium is now understood to be a dynamic, physiologically active system with a wide spectrum of biological activities, not all of which are yet fully elucidated. Put very simply, as the flowing blood provides the tissues with nutrients, oxygen, and components of the immune defense mechanisms, and removes waste products, the endothelium interacts with it to maintain the fluidity of blood and influence its composition. At the same time, the endothelium is the site of important pathological processes in the development of various diseases of the heart, lungs, and blood.

Recently developed techniques to cultivate large numbers of endothelial cells in the laboratory and to analyze their biochemical and biophysical properties

Descendents of cells from chick embryo, established in culture by Alexis Carrel at the Rockefeller Institute in 1912, and shown here under the microscope in 1938, having been growing and multiplying continuously in the laboratory for 26 years.

are making it possible for scientists to work out the details of the complex mechanisms that underlie the role of the endothelium in human health and disease. Today, endothelial cells from a variety of animal sources are routinely used for experimentation in cell culture, and the first reports of the successful cultivation of human endothelial cells are beginning to appear, their fastidious growth requirements notwithstanding. Research in this burgeoning area is developing a body of scientific knowledge that makes the endothelium a versatile model for a virtual microcosm of modern cell biology.

The Cell Biology of the Endothelium

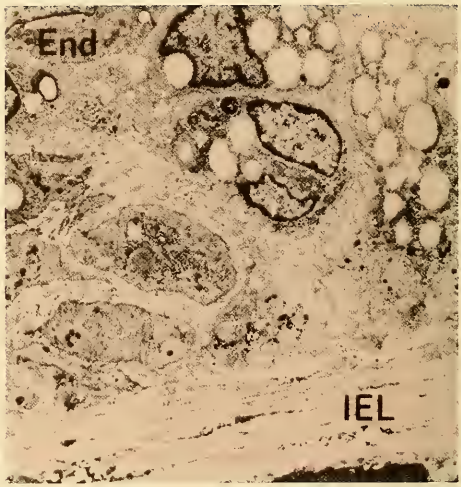
Prevention of blood clotting, control of the passage of solutes and gases, protection of underlying tissues, modulation of water exchange, synthesis and secretion of chemical messengers and enzymes—these are a few of the multitude of vital functions performed by the endothelium. It is perhaps not surprising, therefore, to find that endothelial cells show considerable diversity in size, shape, and activity, depending on their location. The micrograph below reveals the specialized structural modifications in the endothelium of the visceral capillaries, where unique surface structures, the fenestrae, can be found. These appear to be specific sites for the control of transport of substances involved in the local biochemical relationships between the blood and the underlying tissues. In view of these regional specializations, the cell biology of the endothelium is best approached by a discussion of fairly discrete sites, functions, or processes rather than by an attempt at a unified account of the total system.

Capillary endothelial cells from the adrenal gland of the hamster, seen in the electron microscope, showing fenestrae (f) in the cell surface.

Role of the Endothelium in Atherogenesis and Coronary Heart Disease

The endothelium of the large arteries, such as the aorta and the coronary and cerebral arteries, and others involved in atherogenesis and coronary heart disease is somewhat unusual in several ways. Compared to the small vessel endothelium with its vast area and enormous number of cells, the endothelium of the large arteries is on a relatively small scale and more localized in its effects. Unlike the endothelium of the lung, it cannot act as a general regulator, influencing whole body metabolism. Nor does its behavior as a selectively permeable membrane involve major fluxes; its influence is limited to exchanges with adjacent tissues. These local phenomena are of critical importance, however, in the pathological events that express themselves as atherogenesis, arterial spasm, or thrombosis.

The first discernible lesions produced in the course of atherogenesis appear as yellow swellings on the endothelial surface of affected arteries. These plaques result from the deposition of fats and cholesterol just beneath the endothelium in the intima, or innermost layer, of the artery, as shown below. Their progressive growth, associated with the abnormal proliferation



Electron micrograph of an early fatty streak in the aorta shows the accumulation of lipid droplets in smooth muscle cells, which have begun to proliferate and separate the endothelium (End) from the internal elastic lamina (IEL) on which it normally lies.

of muscle cells from the artery wall as well as continued fatty infiltration and later deposition of mineral salts, can eventually result in severe narrowing of the artery. In the case of the coronary arteries, this condition predisposes the subject to heart attack.

To begin the process of atherogenesis, the fats and other molecules that come to reside in atherosclerotic plaques must pass from the blood through the endothelium. Passage is partly dependent on the concentration of the lipoproteins and other carrier molecules in the blood, but partly also on regional differences in the surface membranes of the endothelial cells. For example, where the membrane has been perturbed, larger amounts of fat molecules may pass through. When endothelial cells are lost or badly damaged, again allowing access to the intima, they are almost immediately replaced by cell movement or proliferation, but such healing takes place at different rates in different regions and seems to be dependent on local conditions. Clearly, the endothelium is the gatekeeper to the intima, and as such, it is crucial in the progression of atherosclerosis.

The formation of a blood clot, or thrombus, in a coronary artery can lead to a myocardial infarction by stopping the blood supply to an area of the heart muscle. Endothelial cells are also involved here, since they can influence clotting reactions in the blood and affect subsequent clot dissolution. This influence is felt principally on the circulating platelets, which promote thrombus formation, and on the plasma proteins involved in the regulation of blood coagulation. Essentially, when the endothelium is damaged, the underlying structures that become exposed to the blood provide a surface to which platelets can adhere and form aggregates. This is an early step in thrombus formation. The endothelial cells, however, also respond to signals provided by such substances as thrombin and initiate reactions that eventually inhibit coagulation. Here again, the arterial endothelium is a critical element in events that can lead to or modify the consequences of heart attack.

Recent evidence points to a role for the endothelium in changes in the muscular activity of blood vessel walls, such as those that accompany arterial spasm. The muscles causing the blood vessels to constrict or dilate are stimulated to do so by a number of chemical substances found in the blood. For example, acetylcholine, which dilates blood vessels, seems to require the presence of a "relaxing factor" derived from the endothelium in order for its full effects to be felt. Serotonin, which constricts blood vessels, is derived from aggregating platelets and is continuously released at sites of injury to the endothelium, where platelet adhesion and subsequent aggregation is facilitated. Relaxation occurs only if the endothelium is intact. After atherosclerosis develops, vasoconstriction in response to serotonin becomes exaggerated. Arterial spasm can thus compound the problem of vessels already narowed by plaque. Although relatively small in area, the arterial endothelium is a highly appropriate focus for studies at the cellular level designed to elucidate the complex physiological interactions that underlie atherogenesis and coronary heart disease.

The Pulmonary Endothelium

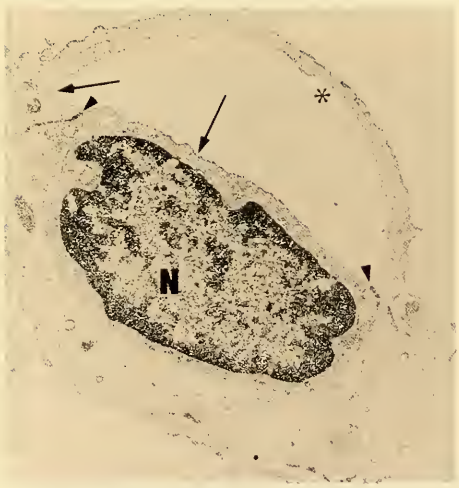
In the human lung, the endothelium covers a large surface area (about 70 square meters) and lines the single largest vascular bed in the body. It is unique not only in the extent of its coverage but also in its location between the arterial and venous circulations, where it forms a major area of transition between the two. In this position, the pulmonary endothelium comes into contact with the entire output of the heart. This provides it with the potential to act as a mediator of events at some distance from the lungs themselves.

Newly developed methods to prepare materials for the electron microscope, including fast freezing and labeling with immunological probes, as well as improvements in the isolation and culture of pulmonary endothelial cells have helped in understanding the mechanisms by which these cells selectively process circulating substances in the lung. Studies of cultured endothelium, for example, have provided direct evidence that these cells perform a wide range of metabolic activities, including the uptake or clearance from the bloodstream of drugs, hormones, and other chemical messengers, and the synthesis and release or uptake of substances involved in the control of blood pressure. In the last-mentioned activity, an important component is angiotensin-converting enzyme (ACE), which is produced at the free surface of endothelial cells and has direct access to circulating substances in the plasma, including angiotensin I and bradykinin, both of which are involved in the control of blood pressure. The action of ACE is to break down the blood-pressure-lowering hormone bradykinin and to convert angiotensin I to angiotensin II, which is a blood-pressure-raising hormone.

Clearly, the extent to which ACE is made accessible to the bloodstream by the pulmonary endothelium plays a significant role in the modulation of the systemic blood pressure. The inactivation of ACE appears to have no unwanted side effects, and this finding has led to the utilization of drugs that inhibit ACE in the clinical treatment of high blood pressure and severe congestive heart failure. Here is an instance in which basic findings at the cellular level can be directly translated into useful medical practice.

There are numerous other instances in which the endothelium exercises a profound influence on the physical state of the blood. Certain prostaglandins, for example, are produced in the pulmonary endothelium, and one of these—prostacyclin—is particularly important in view of its pronounced ability to dilate blood vessels, and also because it is the most potent inhibitor of platelet aggregation produced in the body. Prostacyclin is believed to play a major role in the prevention or limitation of clot formation, and, therefore, in the maintenance of the fluidity of the circulating blood.

The cells of the pulmonary endothelium that reside in the terminal portions of the small airways—the alveoli—are particularly flattened and attenuated as a consequence of their role in the control of gas exchange between the airways and the blood, and this means that they are readily susceptible to mechanical injury. It is becoming increasingly apparent that pulmonary endothelial cells are also highly susceptible to chemical injury, which can occur, for example, during exposure to high concentrations of oxygen. Recent studies have shown over 40 percent loss of endothelial cells in the lungs of laboratory animals allowed to breathe 100 percent oxygen for prolonged periods. The molecular mechanisms of this oxygen toxicity are thought to involve the formation of short-lived "free radicals," which are highly reactive chemicals derived from oxygen and capable of various toxic activities, including the breakdown of enzymes and the perturbation of membranes. One possible pathway involves the production of the strong oxidizing agent hydrogen peroxide. Another may be through the generation of intense destructive heat within very localized sites. A problem that continues to perplex investigators is why the cells of the pulmonary endothelium lining the blood vessels (micrograph below, asterisk) are so much more easily damaged by oxygen than are the epithelial cells that line the airways (micrograph below, arrows), which are in direct contact with the incoming high concentrations of the gas. It now seems that interaction of the endothelium with passing blood cells may multiply the toxic effect of free radicals. In other words, pulmonary endothelium is subjected to a two-pronged attack by free radicals, first from the endothelial cells such as platelets, in close apposition to the blood vessel lining.



Cross section of an area of the small airways, seen in the electron microscope, shows the ultrathin nature of the pulmonary endothelium (asterisk), which, nevertheless, serves as an efficient gatekeeper between the air and the blood in the lungs.

Thus the pulmonary endothelial cells not only serve as a molecular filter in the lung and as an agent of control of general metabolic processes, but also form a vulnerable site for injury from certain inhaled environmental toxins. These cells are therefore a tissue of vital importance to general health and well-being.

The Endothelial Cell in Hemostasis

Many surfaces, including those of naturally occurring tissues, are thrombogenic; that is, they cause clots to form on coming into contact with liquid blood. Such is not the case, however, with endothelial cells, and this is to be expected of the cells that form the inner lining of the blood vessels. This very property has stimulated intense interest in the nature of the interactions of endothelial cells with plasma proteins and platelets that may regulate or contribute to coagulation and hemostasis. In the earlier discussion of atherogenesis, brief mention was made of the way in which injury to the endothelium can expose underlying thrombogenic surfaces to the blood. This injury is often sufficient to trigger a complex series of events that result in clotting and involve conversion of the plasma protein fibrinogen to a network of fibrin strands, which separate out from the blood to form the essential matrix of a blood clot. This sequence can be life-threatening if it occurs in coronary arteries narrowed by atherosclerotic plaque, but it is essential to life when invoked to prevent unrestricted bleeding, as in the circumstances of normal wound healing.

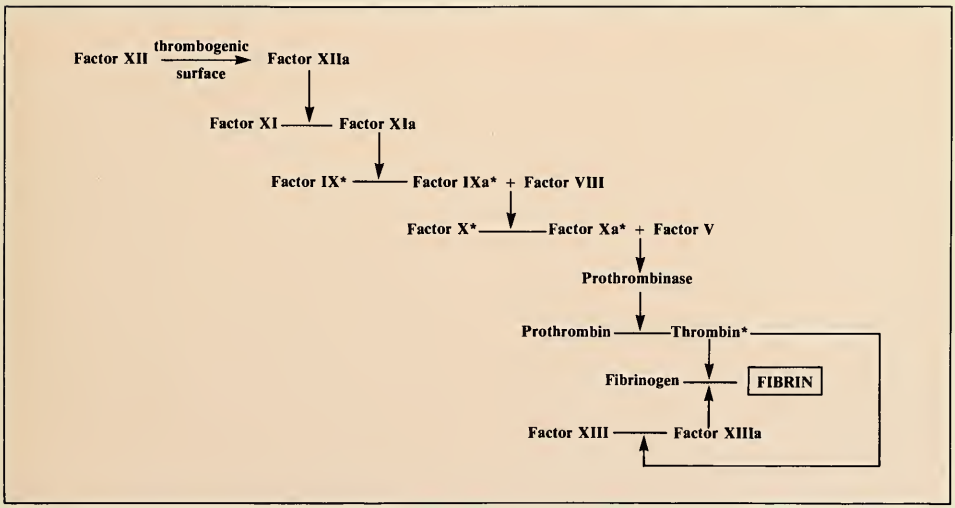
The sequence of chemical reactions in the blood that results in coagulation is an intricate chain of events involving many different factors, most of which are found in an inactive form in normal liquid plasma. Activation of these factors is necessary before they can play an effective role in the coagulation sequence. Such starting points for blood clotting

as exposure of blood to thrombogenic surfaces have precisely this effect of coagulation factor activation. It has become very important, therefore, to determine what part the endothelium may play in these events. Although, as has been said, the vascular endothelium is nonthrombogenic, it is possible that alterations in the surface of endothelial cells may change this condition. Recent investigations have shown that when endothelial cells from blood vessels are grown in culture, certain coagulation factors from plasma may be induced to bind to the cells and there become activated. Under these conditions the bound and activated factors retain their ability to function actively in the coagulation sequence. Furthermore it has been possible in similar experiments to show binding of thrombin to endothelial cells in culture. (Thrombin is the enzyme responsible for the conversion of fibrinogen to the strands of fibrin that form the blood clot matrix.) These observations, although recent and in some regards preliminary, clearly indicate the possibility that subtle changes in the physical state of the endothelial cell surface may promote and localize blood clotting within intact blood vessels. Information like this, resulting from laboratory studies by cell biologists, can give new directions to research on such human diseases as thrombophlebitis, disseminated intravascular coagulation, and coronary thrombosis.

Concluding Remarks

In 1954, Rudolph Altschul suggested, with remarkable perspicacity, that "blood vessels...are primarily endothelial tubes, with secondary, accessorial walls, and, therefore, it may be postulated that the endothelium has a great importance in our life and that its failure will cause the death of many of us." Thirty years later, Altschul's insights have become entirely justified, but not after finding the answers to questions about the endothelium itself, so much as to those about broader physiological issues, such as: What are the cellular sources of certain blood clotting factors? Is there a source of enzymes in the blood vessel wall that can inactivate biologically active substances? Why do some injected drugs disappear so rapidly from the circulation?

The endothelial cell itself has eventually become the focal point of attention, and questions today include: What is the full range of metabolic activities of the endothelium? How do these activities influence the functions of the heart, lungs, and blood? How does injury to endothelial cells affect the nature and quantity of substances circulating in the blood? What are the physiological and clinical consequences of these changes? Although these questions will remain only partially answered in the decade of the 1980's, it has now become realistic to pose them, and the techniques and ideas of modern cell biology have made this advance possible. It will surely take far less than 30 more years to fully substantiate Altschul's predictions.



Simplified version of the intrinsic blood coagulation sequence (cofactors and feedback pathways not shown). Asterisks indicate factors known to bind to endothelial cells.

Chapter 3
Program Highlights and Research Accomplishments

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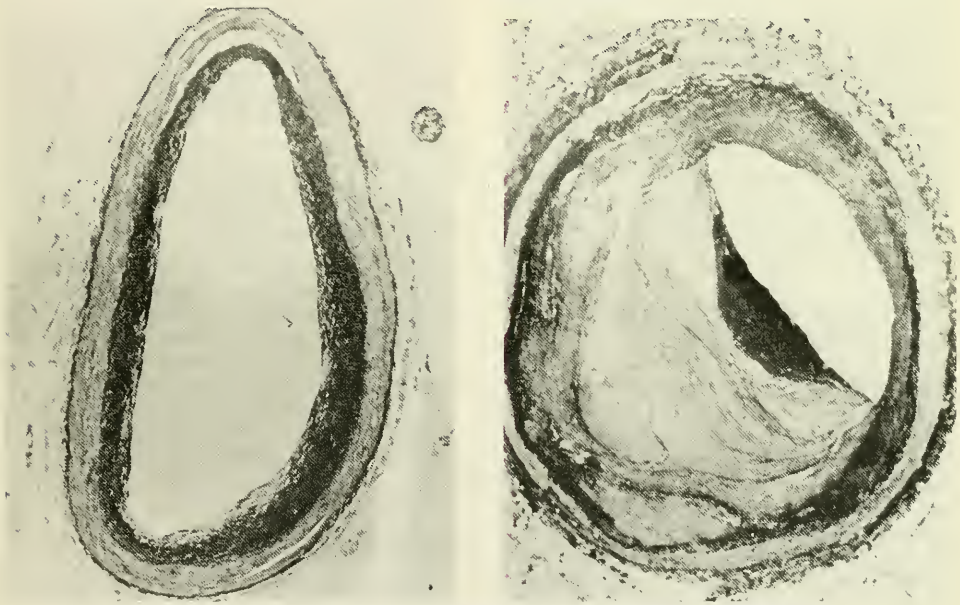
Program Highlights and Research Accomplishments

HEART AND VASCULAR DISEASES

Emphasis in the heart and blood vessel disease program is focused on increasing the knowledge of causes, diagnosis, treatment, and prevention of these diseases. Research support is divided among 10 progam areas: arteriosclerosis, hypertension, cerebrovascular disease, coronary heart disease, peripheral vascular disease, arrhythmias, heart failure and shock, congenital and rheumatic heart disease, cardiomyopathies and infections of the heart, and circulatory assistance. Advances in knowledge about the basic biological processes and mechanisms of normal and abnormal heart and blood vessel phenomena are applied to the prevention and treatment of disease. Highlights of recent research accomplishments within the 10 National Program areas are presented below.

ARTERIOSCLEROSIS

Arteriosclerosis, or hardening of the arteries, is a group of diseases characterized by chronic pathological changes in the blood vessels that result in thickening and loss of elasticity of the arterial walls. Its most common form is atherosclerosis, in which the inner lining of the arteries becomes thickened, rough, and covered with deposits (atheromas) of yellowish plaque that contains cholesterol and other lipoid material. Eventually the atheroma encroaches on and obstructs the lumina, or channels, of the blood vessels. As a result, blood flow in the diseased arteries slows or even stops. This atherosclerotic obstruction is a major cause of heart attacks, strokes, and occlusive disease of the peripheral vessels. Thus an understanding of the basic biological processes that result in hardening of the arteries will ultimately be used to improve the treatment of a number of circulatory diseases.



Normal artery, left, permits unrestricted flow of blood; atherosclerotic deposits in the blood vessels, right, progressively impede blood flow.

Unique Properties of Very Low Density Lipoproteins Found in Patients With High Triglycerides

The two principal fats in the blood are cholesterol and triglycerides. Because they are insoluble in blood, they combine with proteins and are carried in the blood as lipoproteins. Three fractions of lipoproteins are commonly discussed: high density lipoproteins (HDL), low density lipoproteins (LDL), and very low density lipoproteins (VLDL). Each fraction contains varying amounts of apoprotein, cholesterol, and triglycerides. The VLDL fraction is composed primarily of triglycerides. Elevated VLDL is often accompanied by conditions such as hypertension, obesity, and glucose intolerance. The association between elevated VLDL and premature atherosclerosis, however, is uncertain.

The properties of the VLDL isolated from subjects with elevated serum triglycerides (HTG-VLDL) are markedly different from the properties of VLDL isolated from normal subjects. When mouse macrophages are exposed to VLDL, LDL, and HDL isolated from normal subjects, no lipid accumulation occurs in the macrophages. In contrast, HTG-VLDL produces massive accumulation of triglycerides in these cells. The accumulation has been shown to be the direct consequence of the uptake, internalization, and degradation of the HTG-VLDL by a specific receptor that is distinct from the macrophage receptor for low density lipoprotein.

The distinct properties of HTG-VLDL are also manifested in the mechanism for its uptake by fibroblasts. In fibroblast systems (cells from connective tissue), HTG-VLDL is metabolized by a unique receptor, whereas VLDL from normal subjects is metabolized along a nonspecific pathway that is independent of receptors. The distinct properties of VLDL from hypertriglyceridemic subjects may be important in the exacerbation of arteriosclerosis in hypertriglyceridemia.

New Information Gained About Lipoprotein Metabolism

Degradation of low density lipoproteins occurs through two cellular pathways: a receptor-dependent one and a receptor-independent one. A new method has been developed that permits differentiation and quantification of the two. Recent studies have established that 75 to 80 percent of LDL clearance from plasma occurs through the receptor-dependent pathway and 20 percent through the receptor-independent pathway.

Understanding such mechanisms of synthesis and degradation of lipoproteins in the blood should lead to a new understanding of the arteriosclerotic disease process. In particular, the need for receptors to clear lipids from the plasma appears crucial.

Factor in Prostacyclin Synthesis Recently Found

Aspirin, which is a potent antiplatelet drug, has been tested in clinical trials for its ability to inhibit atherogenesis. In recent in vitro experiments that utilized vascular smooth muscle cells, aspirin was shown to inhibit synthesis of prostacyclin, a naturally occurring vasodilator that acts in blood vessels as an inhibitor of platelet aggregation.

When the aspirin is withdrawn from the cell culture, smooth mucle cells recover their ability to synthesize prostacyclin within 2 hours. This recovery is dependent on the synthesis of an as-yet undefined factor present in the serum of all species thus far studied, including humans. The factor is thermolabile and is of high molecular weight, and the amount varies from individual to individual and from day to day. In addition to permitting recovery of prostacyclin synthesis in aspirin-treated cells, the factor also increases prostacyclin synthesis by two- to threefold in normal vascular cells. This observation may lead to a means of regulating the protective compound prostacyclin in vivo.

Surgical Treatment

The portacaval shunt is an innovative surgical treatment for glycogen storage disease, and it has been used to reduce circulating cholesterol in a small number of patients with familial hypercholesterolemia. This rare genetic defect causes afflicted persons to have up to eight times the normal level of cholesterol in their blood. Such persons develop heart disease early in life and generally die of the disease in their early twenties.

A recent study in which patients were followed 1.5 years after surgery showed that the portacaval shunt was effective in reducing plasma cholesterol, body cholesterol synthesis, bile acid synthesis, and total body cholesterol pool. No liver damage or other complications, which were previously experienced in other groups of patients who underwent the surgical procedure, were detected in the study patients. These findings suggest a possible strategy that might be utilized in selected patients to control the atherosclerotic process, and a nationwide clinical trial is under way to test this hypothesis.

HYPERTENSION

Hypertension, or high blood pressure, is considered a serious risk factor for the most commonly encountered forms of heart and blood vessel disease. It

is the most important factor contributing to the development of stroke, and it accelerates atherosclerosis in the coronary and peripheral blood vessels. In addition to basic research, the Institute has expanded its program to increase public information about hypertension and to stimulate compliance with control measures. Some groups in the population are at significantly increased risk due to prevalence of uncontrolled high blood pressure. Black people, and perhaps other minorities, have a greater incidence of high blood pressure than others in the U.S. population. Also, working populations, rural populations, and elderly populations need special efforts to increase access to care, and motivation to seek care and adhere to treatment.

Patient education improves knowledge and awareness for controlling high blood pressure.

Adaptation of the Microvasculature in Different Organs Described

To study the long-term effects of chronic hypertension on the microvascular circulation, scientists have investigated the microvasculatures of the intestine, skeletal muscle, and brain of the spontaneously hypertensive rat. They found that the number and branching of the intestinal arterioles are normal early in life but that as hypertension develops, certain arterioles are lost to the circulation and the branching pattern of the microvascular system is completely restructured. Furthermore, the vessel walls of second and third order arterioles undergo significant hypertrophy. In addition, the investigators found that the reaction of the skeletal muscle vasculature to hypertension is different from the reaction of the intestinal vasculature. Loss or closure of the smallest rather than the larger arterioles occurs, along with minimal vessel wall hypertrophy. Brain microvasculature adaptation to hypertension, however, is similar to that which occurs in the intestine.

These different responses suggest that the vascular system of each organ has a unique means of adapting to hypertension or that the process of hypertension is expressed differently in various types of vascular beds.

Inherited Predisposition to Blood Pressure Responses During Stress

Although psychological stress may contribute to high blood pressure, not everyone who experiences stress develops the problem. Animal research has shown that stress causes salt retention in young rats with a genetic tendency to develop high blood pressure. Normally, a temporary rise in blood pressure is corrected by an increase in the output of salt and water in the urine. Retention of salt would tend to prolong the rise in blood pressure. Salt retention may also affect blood vessel walls by increasing their reactivity to stimuli that result in an increase in blood pressure. Thus, retention of salt and water may be a mechanism by which stress leads to high blood pressure in persons with an inherited predisposition for the condition.

Studies have been made of the interaction of stress and hypertension in young men who did not have high blood pressure but who, being born of hypertensive parents, were at increased risk of developing the disease. During stressful mental tasks for which the incentive was money, those with hypertensive parents showed changes in kidney function that led to changes in retention of salt and water. Salt retention was greatest in the men who showed the largest increases in heart rate and blood pressure.

If these experimental findings are confirmed and expanded, they could lend further support to emerging preventive and therapeutic concepts that address stress reduction and sodium avoidance.

Systolic Hypertension in the Elderly Responds to Diuretic Therapy

The Systolic Hypertension in the Elderly Program (SHEP) was a pilot study to assess the feasibility of a definitive clinical trial of the effect of drug therapy in elderly patients with systolic hypertension. Preliminary data from this program showed that isolated systolic hypertension in men and women over the age of 60 can be successfully treated with low doses of the diuretic drug chlorthalidone, that treatment does not cause severe adverse effects, and that elderly people will willingly participate in a placebo-controlled trial

and comply with drug intervention. A full-scale clinical trial is being planned.

Dietary Management Prevents Elevated Blood Lipids Induced by Antihypertensive Medicines

Preliminary results of the Multiple Risk Factor Intervention Trial (MRFIT) showed that certain commonly used antihypertensive medications may have undesirable effects on blood lipid levels and could offset efforts to reduce blood lipid levels in certain subgroups of individuals. Results of the MRFIT and other research also suggest that appropriate nutritional therapy may help to prevent or alleviate blood lipid elevations in some patients. Investigators from these various studies and clinical trials relating to nutrition and hypertension participated in an NHLBI Workshop on the Role of Dietary Management in the Prevention or Reversal of Blood Lipid Elevations Induced by Antihypertensive Medications. Participants pooled existing knowledge of the effects of antihypertensive agents on blood lipids in humans, evaluated the role of dietary management in the prevention or reversal of such effects, and identified areas where further research is needed.

Behavioral Approaches for Hypertension Treatment Described

As an adjunct to the pharmacological treatment of hypertension, researchers have investigated the use of relaxation therapy to lower blood pressure. Subjects' blood pressures obtained in a variety of settings were correlated and used to determine reliability, validity, and predictability of the relaxation effect. Within a given 24-hour period, blood pressures during waking and sleeping states were highly correlated. Pressures during sleep averaged 12 mm Hg lower than pressures while awake. Such 24-hour records of blood pressure may be helpful in identifying persons whose blood pressure declined during sleep and who may be more likely to respond to relaxation therapy.

Worksite Hypertension Control Programs Developed

Four methods for improving hypertension control among employees were tested at selected Ford manufacturing plants in Detroit: (1) screening and physician referral with no other intervention; (2) physician referral with semiannual followups at the worksite; (3) physician referral and frequent followups at the worksite; and (4) worksite treatment and followup.

Analysis of the results revealed that all methods significantly increased the proportion of employees under treatment and that methods 2, 3, and 4 significantly improved hypertension control. After 2 years, 56 to 62 percent of persons in methods 2, 3, and 4 had blood pressures below 140/90 mm Hg. Of those with no followup, 21 percent had blood pressures below 140/90 and 47 percent below 160/95 after 2 years.

It was concluded that worksite hypertension programs can produce substantial improvements in blood pressure control if they include systematic, routine followups that provide employees with information about their condition and offer support for maintenance of therapy.

Hypertension control programs at the worksite facilitate control of high blood pressure among employees.

Screening for Hypertension Studied in the Inner City

In the Detroit Community High Blood Pressure Control Project program that in 1978 surveyed a predominantly black population of 800 adults, 38 percent either had elevated blood pressure (140/90 mm Hg) or were on medication for high blood pressure. Of those aware of their hypertension, 86 percent were under treatment. Of these, 26 percent were considered to have their hypertension under control.

Younger respondents, especially males, were less likely to be aware of their hypertension, to be under treatment, or to have their hypertension controlled. These data indicate that future blood pressure screening and referral efforts should be targeted to younger adults, especially men aged 18 to 44.

CEREBROVASCULAR DISEASE

Cerebrovascular disease, or stroke, is the result of interrupted blood flow to brain tissue. It occurs when an artery supplying blood to the brain is blocked, ruptured, or injured. The resulting deficit of oxygen causes damage to or destruction of brain tissue. Stroke symptoms depend on the area of the brain where the damage occurs. More than one-half of stroke victims are completely or partially disabled. The majority of strokes are caused by arteriosclerosis, particularly that associated with hypertension. NHLBI-supported research emphasizes the importance of public education about risk factors, such as high blood pressure treatment, control of clotting disorders, and management of disorders of the blood vessel walls.

New Knowledge About the Cerebral Vasculature

Most isolated arteries relax in the presence of thrombin. When injected into the circulation, thrombin causes a drop in blood pressure. This action is attributable to an effect of thrombin on the endothelium of the vessel. It has recently been reported, however, that certain arteries, especially those of the brain, constrict markedly in the presence of this clotting factor. Thrombin initially produces a brief relaxant effect in the cerebral artery that is due to an increase in potassium conductance caused by an unknown factor released from the endothelium. Destruction of the endothelium abolishes this relaxant effect and enhances the vasoconstrictor effect of thrombin. These observations illustrate the importance of studying cerebral arteries specifically to elucidate the pathophysiological mechanisms of cerebrovascular disease.

Psychosocial Factors in Stroke Identified

The relationship of psychosocial characteristics to the 10-year incidence of stroke was examined among men and women, ages 45 to 77 years, in the Framingham Heart Study. Between 1965 and 1967, an extensive psychosocial questionnaire was administered to 1,654 individuals who had no clinical evidence of coronary or cerebrovascular disease. The occurrence of stroke during the subsequent 10 years was correlated with psychosocial factors.

Analysis of the data revealed that stroke in women was significantly associated with increased emotional lability, inability to express anger, and symptoms of tension. Women categorized as having type A personalities had significantly higher rates of stroke than those categorized as having type B. Those with blue-collar occupations had higher rates of stroke than clerical and white-collar workers. Working women who felt they were overworked developed more stroke. In addition, those who had subordinates they could not rely on or who interfered with their work had higher rates of stroke than women whose subordinates were reliable and noninterfering. Housewives who reported that they were unable to relax during the day were at higher risk than those who reported that they could relax.

Staff members of the community-based Framingham Heart Study, which was designed to examine long-term associations of various genetic, psychological, and behavioral factors with cardiovascular disease.

Men identified as type A on the job-related component of the Framingham type A scale were at higher risk than those identified as type B if they experienced work-overload. In addition, those who

reported they had a poor chance of achieving the income they would like within the next 5 years had significantly higher rates of stroke than men who did not report these characteristics.

CORONARY HEART DISEASE

Coronary heart disease, the predominant form of heart disease in adult Americans, results from atherosclerosis in the arteries that supply the heart muscle. When blockage of a coronary artery prevents oxygen-rich blood from reaching the heart muscle, a heart attack occurs. The lack of oxygen supply, or ischemia, causes death of portions of the heart muscle, technically called myocardial infarction. Coronary heart disease may also result in angina pectoris (chest pain brought on by exercise or stress), heart failure (impaired performance of the heart that leads to accumulation of fluid in the body and congestion in the lungs), arrhythmias (disturbances of heart rhythm), and sudden death. Research on coronary heart disease is leading to a better understanding of the mechanisms of myocardial infarction and more effective methods of treatment. To increase the possibility of prevention of coronary heart disease, information about risk factors is being made widely available to the American people.

Better Treatment of Coronary Thrombosis Suggested

Many cases of acute myocardial infarction are now believed to result from a blood clot occluding a coronary artery that supplies a segment of heart muscle. Invetigators have been looking for methods of reperfusing the myocardium by dissolving (thrombolysis) or removing the clot. Some thrombolytic agents, however, also cause an impairment of the clotting mechanism throughout the circulatory system (systemic fibrinolysis) that can lead to a bleeding problem. An ideal agent would confine its clot-dissolution activity to the site of thrombosis without causing systemic adverse effects.

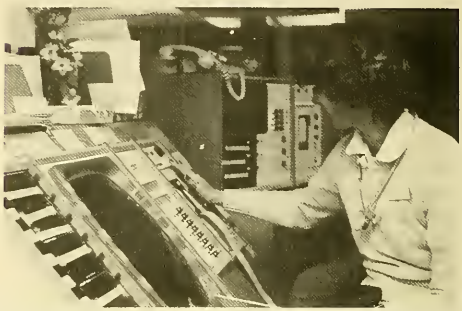
Human tissue plasminogen activator (tPa) is a thrombolytic agent that has been purified from human melanoma cells grown in tissue culture. In contrast to other thrombolytic agents, tPa is fibrin-specific and seems to dissolve the thrombus without causing systemic fibrinolysis.

Thrombosis was induced in a group of experimental animals. Either tPa or streptokinase (another thrombolytic agent) was administered 1 to 2 hours later, either by intravenous or by intracoronary route. With the use of intracoronary streptokinase, thrombolysis was achieved after 85 minutes. Both intracoronary and intravenous human tPa achieved thrombolysis within 10 minutes.

In the near future, investigators plan to administer human tPa to patients with coronary thrombosis in the early hours of acute myocardial infarction. If the results are similar to those observed in animals, the tPa may effectively limit the size of infarcts in humans. Careful clinical trials of the use of this substance will then follow.

New Approach to Treatment of Heart Attack Victims

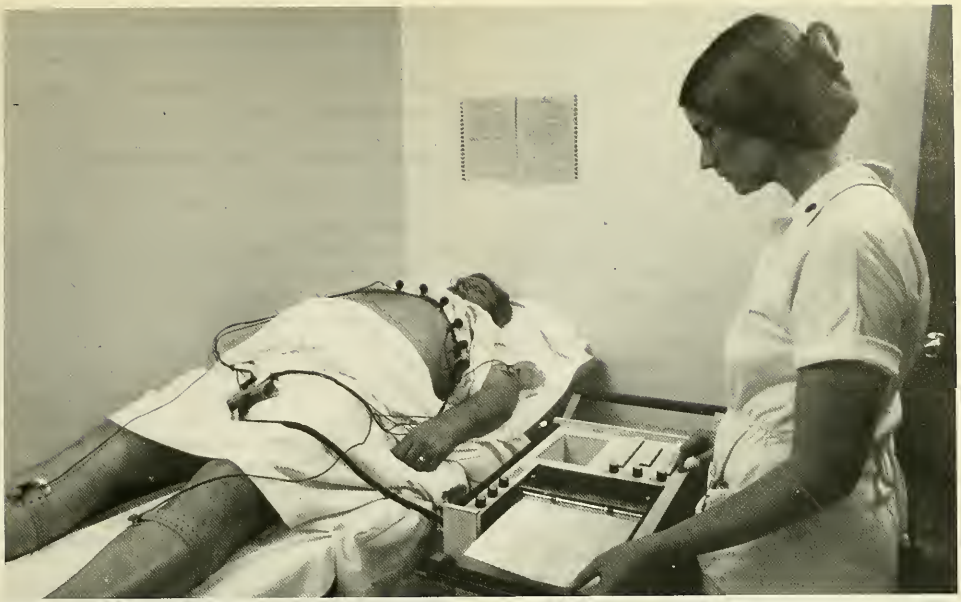
In patients who have suffered a myocardial infarction (heart attack), there is a relatively high number of sudden deaths during the healing period. It is believed that these sudden deaths are due to lethal arrhythmias. During a heart attack, there is an increase in the chemical compound thromboxane (TX) in the venous blood. This TX production could result from the aggregation of blood platelets in the area of the heart muscle injured by the infarct. Increases in the concentration of TX have been shown to correlate with the frequency of the arrhythmias.



Medical personnel use sophisticated equipment to monitor the condition of heart attack patients in hospital coronary care units (CCU's).

Recent studies have shown that two types of white blood cells (polymorphonuclear leukocytes and macrophages) that invade the injured heart muscle synthesize TX. Early in the healing process, platelets and leukocytes are trapped in the heart muscle. After they disappear, the macrophages appear, and it is believed that the macrophages are the source of TX in the healing muscle. The vasoconstrictive and cytotoxic properties of TX may affect the adjacent normal heart muscle. Moreover, TX may directly alter the muscle's electrophysiological properties or, by affecting regional blood flow, alter the electrical stability of the tissue.

Macrophages can also synthesize prostacyclin, which is a compound that has opposing effects—that is, it dilates the blood vessels and regulates the heartbeat. From a therapeutic standpoint, therefore, it is possible that by inhibiting TX synthesis during the



The electrocardiogram demonstrates the electrical activity of the heart and is an invaluable tool for diagnosing heart disease.

healing process, the metabolism of the macrophage might be shifted to initiate the production of the beneficial prostacyclin.

Blood Pressure Used to Measure Behavior Patterns

Because type A behavior (manifested in the hard-driving, time-pressured, competitive personality) has been related to a higher prevalence of coronary heart disease, a study was designed to identify specific behavioral subcomponents among individuals displaying the type A behavior pattern that might clarify this association.

A stress situation consisting of a verbal problem-solving task was administered to type A and type B subjects with and without the incentive of money. Psychomotor performance and physiological responses were measured. Results showed that the monetary incentive affected the performance for type A subjects but not type B subjects. Type A's performed the task more quickly if money was offered, and performances of type B's were not affected by the monetary incentive. Type A subjects, however, responded with increased systolic blood pressure and heart rate regardless of whether money was offered. Type B's showed increased blood pressure and heart rate only when incentives were offered. These data suggest that cardiovascular response may be a more precise method for measuring differences between the two behavioral patterns. This information adds to the understanding of physiologic mechanisms underlying the greater prevalence of heart disease among type A individuals.

Study Describes Risk Factors Associated With Subclinical Cardiac Ischemia and Dysfunction

In the early 1970's, a sample of the offspring of the original population of the Framingham Heart Study was enrolled in a prospective study of cardiovascular disease. After 8 years, followup studies were made of predictors for early heart disease, or subclinical cardiac ischemia and dysfunction (SCID). Electrocardiographic monitoring of ambulatory subjects (age 30 to 69) for 1 hour and exercise testing were performed. Predictors of SCID were found to be cardiac arrhythmias during ambulatory monitoring, or exercise-induced depression in the ST segment of the ECG, or development of arrhythmias. In addition, the study reported that high density lipoprotein cholesterol levels among men were inversely related to SCID and that systolic blood pressure among men and women was positively related to SCID.

These patterns, which are detectable as early as middle age, suggest that risk factors commonly

associated with overt coronary heart disease may also be indicators of early heart disease.

New Data Collected on Risks of Cigarette Smoking

Data from 24 years of followup of the Framingham Heart Study population were used in further study of the impact of cigarette smoking.

Coronary heart disease and peripheral artery disease were related to cigarette smoking in men and women. Cigarette smoking was also significantly related to stroke in men and to cardiac failure in women. Although smoking is related to heart attack and sudden death in both men and women, little relationship was found for angina pectoris.

People under 65 who stopped smoking showed a reduction within 2 years of both heart attacks and coronary mortality and returned to the same risk as that of a nonsmoker. Older people who stopped smoking showed a reduction in fatal heart attacks but no change in their heart attack rate. Smoking filter cigarettes had no effect on risk of heart disease.

Other risk factors for heart disease are recognized, such as high blood pressure and elevated blood cholesterol, but smoking can double the level of risk of other risk factors. Fewer actions can be as beneficial to decreasing heart disease risk as quitting cigarette smoking.

Nutrition Counseling Manual Published

The NHLBI and the American Heart Association have collaborated in the publication of ***Heart to Heart: A Manual on Nutrition Counseling for the Reduction of Cardiovascular Disease Risk Factors.***

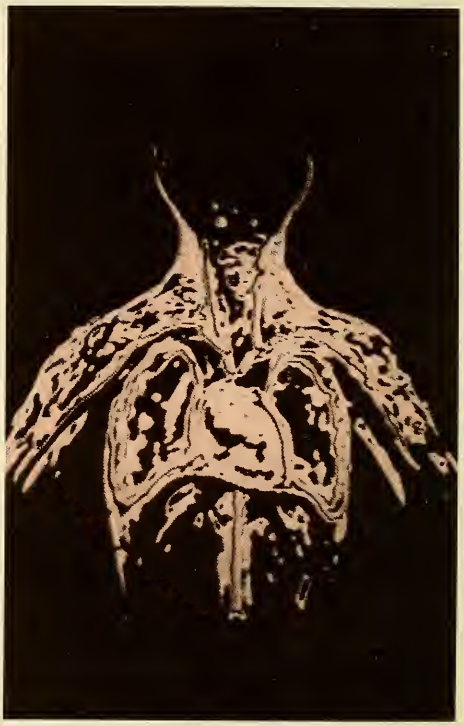
The manual, a result of a series of nutrition counseling workshops that featured presentations by experts in the field, is intended to help counselors of patients with hyperlipidemia, hypertension, and other cardiovascular disease risk factors develop a better understanding of the importance of nutrition in the prevention and treatment of cardiovascular disease. It will also serve as a first step for improving personal counseling skills in on-the-job situations.

PERIPHERAL VASCULAR DISEASE

Abnormalities of blood flow in the arteries or veins other than those supplying the lungs are collectively referred to as peripheral vascular diseases. In the arteries, impeded circulation may result from atherosclerotic obstruction. Venous blood flow is hindered by varicosities and thrombophlebitis. These peripheral vascular disorders are frequently painful and can cause organ damage, skin ulcerations, and gangrene. The formation of a thrombus or clot in the veins may result in pulmonary embolism, a potentially fatal condition in which clot fragments are carried through the bloodstream to the lungs.

Basic Research on Noninvasive Diagnosis Advances

Nuclear magnetic resonance (NMR), a noninvasive means of imaging organs and blood vessels, has been used to detect blood flow and lesions in various peripheral beds. The NMR signals have been obtained from the abdominal aorta, iliac, and femoral vessels of humans. Atherothrombotic protrusions into the lumen and thickening of arterial walls have been detected and confirmed with angiography or computerized tomography scans, and areas of high and low levels of flow and of calcification have been imaged. Investigators have concluded that NMR imaging, which poses no known hazards and does not expose the patient to ionizing radiation, is useful in identifying atherosclerotic disease in many blood vessels.



Nuclear magnetic resonance (NMR) is an innovative, noninvasive diagnostic technique that provides images of organs and blood vessels.

Biofeedback Found Effective in Treatment of Raynaud's Disease

Raynaud's disease is a circulatory disorder characterized by intermittent interruption of the blood supply to the fingertips and toes and sometimes to the ears and nose. Recent research indicates that finger temperature biofeedback appears to be a safe and effective behavioral treatment for this disorder.

In this procedure, patients listen to an electronic tone whose pitch is controlled by their finger temperature, which is a measure of blood flow. They learn to increase their finger temperature by using the tone as a guide. This effect is achieved through a specific physiological mechanism that is unrelated to relaxation. Patients are able to increase their finger temperature outside the laboratory to prevent or abort attacks in cold or stressful situations. This effect has been verified for the first time with physiological recordings made in the natural environment.

At 1-year followup, patients trained with temperature biofeedback had 67 percent fewer attacks than they had prior to treatment. Control groups receiving relaxation treatments failed to show significant improvements in symptoms. This research demonstrates that behavioral procedures, which have no known adverse side effects, can be used to ameliorate the symptoms of one form of peripheral vascular disease.

ARRHYTHMIAS

Arrhythmias, or abnormal heart rhythms, can occur with many forms of heart disease. They may also exist in the absence of recognizable disease. The normal, regular heartbeat results from transmission of electrical impulses within the heart muscle. Interruption or alteration of these electrical impulses results in arrhythmias. Many rhythm disturbances have only a minor influence on life expectancy and cause little disability. Others cause serious symptoms and some are almost instantly fatal. Arrhythmias kill more than one-half of the patients with coronary heart disease and are a major problem in patients with rheumatic heart disease.

Increase of Basic Information About the Beating Heart

The primary pacemaker of the heart is located in the sinoatrial node (SAN), which is a microscopic collection of specialized cardiac muscle fibers responsible for the origin of the cardiac impulse. When this area of the heart is damaged or destroyed, what are the identity, location, and functional characteristics of the subsidiary atrial pacemakers (SAP's) that now regulate the heart rate? Using electrophysiological mapping techniques, investigators showed, contrary to normal assumptions, that the SAP's are located along the sulcus terminalis of the right atrium. In addition, such studies demonstrated that, in contrast to the SAN, SAP activity and propagation depend upon the presence of norepinephrine and are more sensitive than the SAN to acetylcholine and overdrive pacing. These experiments support the concept that SAP activity is a functionally important component in the hierarchy of pacemaker control.

Effect of Insulin on Cardiac and Vascular Tone Described

The (Na^+,K^+)-ATPase pump is a system responsible for active transport of cell substances. It is often coupled to glucose transport and is activated by insulin.

Studies have demonstrated that the number of (Na^+,K^+)-ATPase molecules in the plasma membrane of adipocytes is not changed during activation of this pump by insulin. This observation is in contrast with the situation of the glucose transporter, whose number in the plasma membrane is increased by insulin. It appears, therefore, that the insulin-receptor interaction in responsive cells produces a single signal that has different effects on the plasma membrane. These findings point out the close relationship between the control of ionic homeostasis and glucose metabolism by insulin, and they support the hypothesis that insulin may affect cardiac and vascular tone by its effect on the (Na^+,K^+)-ATPase pump.

Biobehavioral Factors in Arrhythmias Demonstrated

An animal model has been developed for behaviorally induced digitalis-toxic arrhythmias. Results of some experiments show that guinea pigs with a prior exposure to fear conditioning developed digitalis-induced ventricular tachycardia significantly earlier than did controls. This observation suggests that psychological factors should be added to the host of metabolic alterations that can permit the emergence of digitalis toxicity in previously well-controlled patients. Researchers are now working on transferring this biobehavioral model of arrhythmias to other animal models.

Ventricular Arrhythmias Associated With Multiple Factors

Between 1979 and 1982, 1-hour ambulatory electrocardiographic monitoring was performed on 6,021 men and women in the Framingham Heart Study between the ages of 20 and 93. Results showed that

Doctor and nurse discuss management of a patient's ventricular arrhythmia.

under the age of 50, more women than men had irregular heart beats (arrhythmias), but that over age 50, the sex ratio was reversed. In the older participants, coronary heart disease was associated with high-grade arrhythmias, as was expected. Arrhythmias were even more closely correlated with left ventricular enlargement in participants who were classified under one or more of the following groups: high blood pressure, obesity, cigarette smokers, consumers of caffeine and alcoholic beverages, and cardiac drug users. Subjects using the drug propranolol exhibited a significant increase in high-grade arrhythmias. Use of diuretics, however, was not associated with these abnormal rhythms, even after controlling for blood pressure and left ventricular mass.

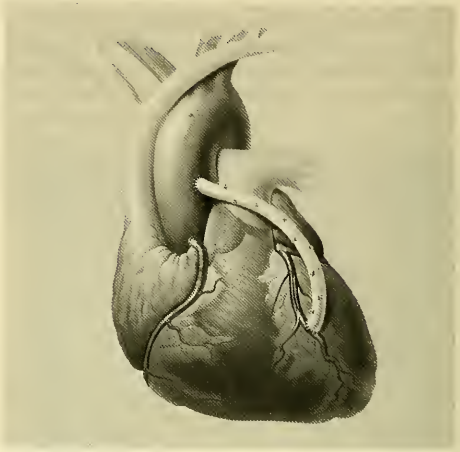
Ventricular Arrhythmias Described in Patients Before and After Coronary Artery Bypass Surgery

Myocardial ischemia is caused by a deficiency of blood supply to an area of the heart muscle, which usually results from obstruction of the coronary arteries. Although little is known about the relationship between myocardial ischemia and ventricular arrhythmias, coronary artery bypass graft surgery has recently been shown to aid in the control of the arrhythmias.

Electrophysiologic studies have been made of a group of 17 patients with severe coronary artery disease who were scheduled to undergo coronary artery bypass graft surgery after prehospital cardiac arrest or after ventricular tachycardia (VT) unassociated with acute myocardial infarction. Before surgery and in the absence of drugs, programmed cardiac stimulation induced ventricular fibrillation (VF) in 4 patients and VT in 11 patients. Antiarrhythmic drugs suppressed the induced VT or VF in 7 of 13 patients in whom they were tried.

None of the patients who underwent coronary artery bypass graft surgery sustained a perioperative myocardial infarction. When studied again after an average of 19 days following coronary artery bypass surgery, 10 patients had no inducible VT or VF, 6 patients had inducible VT, and 1 patient had spontaneous VT. In four patients who manifested electrically inducible VT, the VT was suppressed by antiarrhythmic drug regimens, but three patients continued to manifest electrically inducible VT even when treated with antiarrhythmic drugs. Of the whole group, only 1 patient continued to have VT, and the remaining 16 patients were free of arrhythmias 23 months after surgery.

These studies show that revascularization of the myocardium by coronary artery bypass graft surgery may ameliorate abnormal cardiac rhythm in certain patients.



In coronary artery bypass surgery, a segment of a vein from the leg is grafted onto the obstructed artery, providing a detour around the blockage.

HEART FAILURE AND SHOCK

Heart failure and shock can result from many different diseases. Heart failure can occur when the heart has been damaged so extensively that its ability to pump blood can no longer meet the needs of the body. Chronic heart failure is often accompanied by shortness of breath, accumulation of fluid in the tissues, and swelling of the legs. Shock, a more acutely developing phenomenon, is also characterized by an inability of the heart and peripheral vascular system to maintain adequate blood pressure. Left untreated, it rapidly leads to irreversible tissue damage and death. Shock can be a complication of many disorders such as heart attacks, hemorrhage or other body fluid loss, burns or trauma, and sepsis.

New Information Gained About Contraction of Left Ventricle

The left ventricle is the chamber of the heart that, on contracting, pumps the blood into the general circulation. Researchers have demonstrated that the normal means of stimulating the contraction is a mechanical reflex and not a chemical reflex, as was previously believed. The usual or physiological stimulus for this left ventricular mechanoreflex is an increase or decrease in myocardial contractility.

It has been demonstrated further that obtaining the full response of this reflex requires a beating heart muscle that is capable of increasing its contractility ability in response to the lengthening of the cardiac muscle. Changes in the volume of blood contained in the left ventricle appear to modulate, but not initiate, the mechanoreflex.

Circulatory Shock Affects Cardiac Mechanical Performance

Cardiovascular collapse occurs as a result of shock because of either a failure of the heart to contract effectively as a pump or a deficiency of tone or filling of the peripheral vascular system. During circulatory shock, many measures of cardiac performance change. Since cardiac contractility and the peripheral vascular system are interdependent, a change in one can lead to a change in the other. Most methods of measuring cardiac function are influenced by the status of the peripheral vascular system. In order to understand the mechanisms controlling cardiac performance, investigators use the end systolic pressure-diameter relationship (ES) as a measure of cardiac mechanical performance. The ES can measure cardiac performance independent of the conditions under which the heart is contracting.

Investigators have used two different methods to induce models of circulatory shock in animals. The first model was produced by *Escherichia coli* endotoxin, and the second was induced by blocking the splanchnic artery. The ES was then measured. In both cases, surviving animals exhibited a small decrease in ES, while nonsurviving animals exhibited a significant decrease in ES.

These studies demonstrate that reduction of cardiac contractile performance is a key determinant of shock-induced cardiovascular collapse.

New Drug for Treatment of Cardiac Failure Evaluated

The new drug amrinone is useful in the treatment of congestive heart failure. Its ability to affect the force of muscular contraction was evaluated with the use of cardiac muscle from an animal model of chronic heart failure. Unlike many other cardiotonic drugs, amrinone had little effect on muscle contractility, but rather exerted a marked relaxing action. This finding in consonant with the clinical observation that amrinone is beneficial in the treatment of congestive heart failure, even though it does not increase ventricular contractility. These data demonstrate that the basic lesion or defect in heart failure may be affected differently by drugs whose primary effects are on the force of contraction or whose action influences myocardial relaxation.

A Novel Approach to Reversal of Digitalis Toxicity

Analogs of the cardiotonic drug digitalis are part of the standard therapeutic regimen for treatment of heart failure. The margin between the therapeutic dose and the toxic dose, however, is a narrow one. In very ill patients with advanced degrees of congestive heart failure, this margin of safety becomes even more narrow, and digitalis intoxication can frequently complicate clinical management of these individuals.

Encouraging results of a multicenter trial to test the efficacy and safety of digitalis-specific antibodies, referred to as sheep Fab fragments, in patients with severe, life-threatening digitalis intoxication were recently reported. In the trial, 26 patients were treated with intravenous digoxin-specific Fab fragments. All 26 had an initial favorable response, and none had any adverse reaction to the heterologous protein. For the first time, the specificity of the immune response has been directed successfully toward neutralizing the toxic effects of a drug.

CONGENITAL AND RHEUMATIC HEART DISEASE

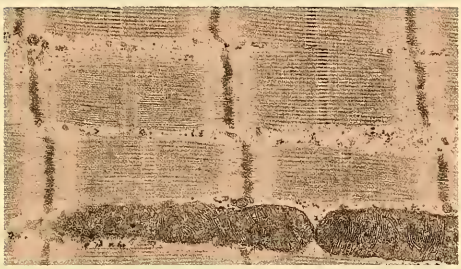
Rheumatic fever, which was once a leading cause of childhood illness, can lead to damage of the heart valves, most often the mitral and aortic valves. The use of antibiotics to treat the streptococcal infections that can lead to rheumatic fever has sharply reduced the incidence of acute rheumatic fever in the United States. However, many adult deaths still occur from cardiac complications (rheumatic heart disease) that can be traced to acute rheumatic fever during childhood.

Congenital heart disease occurs when the heart or the major blood vessels near the heart fail to develop normally before birth. The causes of congenital heart disease are still unknown.

Diffusible Factor Isolated in the Differentiation of Mutant Heart Cultures

During embryonic development in higher animals, cells differentiate to form tissues that perform specific functions. An in vitro organ culture offers a good means of studying abnormalities of tissue function since many in vivo functions can be reproduced in the test tube.

It is known that during development of the vertebrate heart, exposure to anterior endoderm is required for the occurrence of normal cellular differentiation and for induction of contractile function. With the use of heart cultures, it was shown that normal embryonic hearts of the Mexican salamander beat vigorously, whereas mutant hearts failed to beat; but when mutant hearts were cultured in the presence of the anterior endoderm from normal developing hearts, the mutant hearts began to beat vigorously within 12 to 24 hours. Electron microscopy revealed that these hearts contained numerous normal muscle fibers called myofibrils.



The heart muscle, or myocardium, is composed of numerous muscle fibers that contract to carry out the pumping action of the heart.

A diffusible substance isolated from the organ cultures seems to be responsible for transforming the nonfunctioning embryo heart to a functioning heart. The substance is now being characterized. While much research is needed to establish the structure and function of this factor, it offers a new approach to the study of nonfunctional heart tissue. It is possible that such a substance could act to cause differentiation of heart tissue during the process of healing after a myocardial infarct. In addition, characterization of the substance may eventually help to explain the control of gene expression in higher animals.

CARDIOMYOPATHIES AND INFECTIONS OF THE HEART

Cardiomyopathies include a variety of lesions of the heart muscle. In many cases their cause is unknown; however, some are secondary to systemic disease. Known factors include toxic substances, viral infections, alcohol, immunologic phenomena, nutritional deficiencies, muscular dystrophy, and a number of rare diseases. These diseases cause enlargement of the heart, heart failure, irregularities of the heart rhythm, and (occasionally) sudden death. The condition may be acute, or chronic and progressive. Infections of the heart may affect the heart muscle (myocarditis), its lining and valves (endocarditis), or its exterior surface (pericarditis).

New Information for Diagnosing Hypertrophic Cardiomyopathy

Between 1979 and 1982, 1,620 persons of the Framingham Heart Study, 3,309 of their offspring, and spouses of the offspring participated in a study of the heart disorder termed hypertrophic cardiomyopathy (HCM). Although HCM is a clinically important cause of sudden death, little is known about its epidemiology or its echocardiographic characteristics.

Markers for HCM include disproportionately increased interventricular septal thickness (DST) and systolic anterior motion (SAM) of the mitral leaflet. The two abnormalities were found in 32 (2 percent) of the 1,620 subjects and in 9 (0.3 percent) of the offspring population. None of the offspring had SAM, whereas 13 (0.8 percent) of the 1,620 "parents" had the abnormality and 8 (0.5 percent) had both DST and SAM. Clear signs of cardiac disorders other than HCM were found in 10 (24 percent) of the 41 subjects.

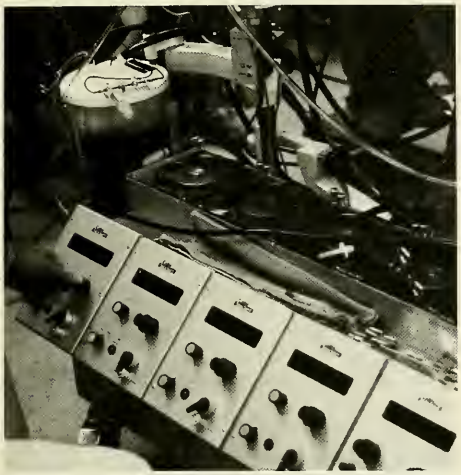
In this study, data showed that DST, SAM, and HCM are not rare (especially in the elderly), are often associated with other cardiovascular disorders, and often tend to masquerade as other cardiac disorders.

Immunologic Basis for Cardiomyopathy Described

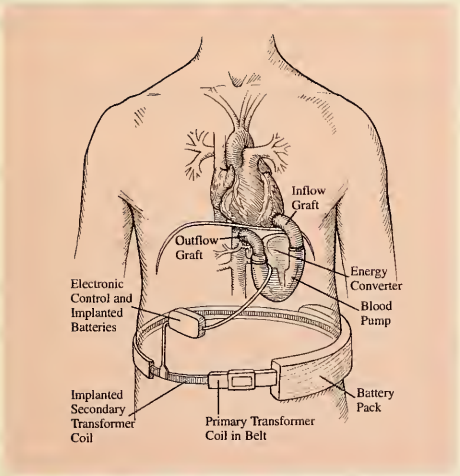
Coxsackieviral myocarditis can result from the immune response to virus infection of the heart rather than from direct virus-mediated myocardial cell lysis. The virus-induced antigens on myofibers that invoke the immune response are not virion antigens, but are probably virus-specific noncapsid antigens or neoantigens. Clinical and epidemiological evidence as well as results from the murine model of the disease suggest that autoimmunity to myocardial cell antigens may cause heart damage. In the murine model, a cytolytic T lymphocyte that reacts specifically with uninfected myocardial cells was isolated. Investigators believe that suppressor cells play an important role in preventing or ameliorating the disease.

CIRCULATORY ASSISTANCE

Efforts are continuing to develop and improve mechanical devices to assist the pumping action of the heart or to replace it entirely. These devices range from those used for short periods of time until the heart can recover from an acute insult to a totally implantable permanent "artificial heart." Heart-lung machines have been used for 30 years and allow surgical repair of cardiac lesions while the heart is temporarily arrested. Left ventricular assist devices and intra-aortic balloons are used for short periods until injury or dysfunction is repaired and normal circulation is restored. A practical artificial heart requires solution of problems relating to biomaterials development, mechanical failure, anatomic compatibility, power generation, blood clotting, and infection.



The heart-lung machine takes over the work of the heart and lungs oxygenating tasks, permitting open-heart surgical repair.



Left ventricular assist devices pump blood through the body until the heart muscle heals.

Low Level Shear Stress and Platelet Aggregation

Ongoing research is focused on the aggregation of blood materials flowing through natural and artificial conduits. It is known that platelets and white blood cells aggregate when they are exposed to shear stress, which occurs as these blood cells pass through blood vessels. Investigators have sought to determine whether the platelet aggregation at low levels of shear stress is initiated by metabolites released upon cell disintegration or by the mechanical effects of the shear stress itself. To answer this question, researchers employed two methods of assessing cell destruction: measuring the release of radioactive chromium from a labeled cell and measuring the enzymes released by a destroyed cell. Very low levels of stress were applied, at which no cell destruction occurred, as evidenced by no detectable release of radioactive chromium. The researchers then added an enzyme system to block the action of adenosine diphosphate (ADP), which promotes cell aggregation, and also excess of adenosine triphosphate (ATP), to further block cell aggregation. Under these conditions, no cell aggregation occurred. Some aggregation occurred if no ATP was added.

These findings suggest that low levels of shear stress induce platelet aggregation and that the process is mediated by ADP. Shear stress itself, in a process that is separate from the effects of cell destruction, may alter the platelets in a way that promotes cell aggregation. This information may be of value in the design of devices to aid the circulation.

New Ways to Study Surfaces of Assist Devices

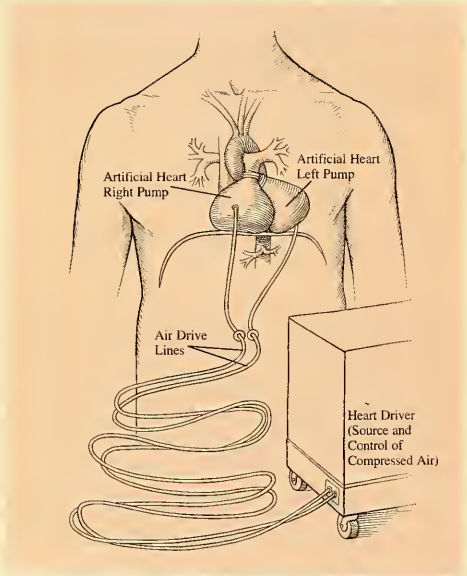
In the development of polymers that form the smooth lining of assist devices, knowledge is needed about the pattern of adhesion of cells or proteins to such surfaces. The use of angular methods has refined the techniques of x-ray photoelectron spectroscopy in probing polymeric surfaces and has allowed more specific chemical analysis of the uppermost surface of polymer films. The technique has also been applied to adsorbed protein films to demonstrate that proteins adsorb in a patchy fashion to discrete areas rather than uniformly across the surface, as had been assumed. Increased sensitivity of other polymeric surface analytic methods, such as total internal reflectance fluoroscopy (TIRF) and

Fourier transform infrared (FTIF) spectroscopy, permits detection of adsorption of micromolar amounts of proteins onto surfaces. Methods are now being developed with these techniques to characterize the conformation of the adsorbed protein and any change from its native configuration.

These methods may be important in the manufacture of polymeric materials that are used for cardiac replacement devices and other prosthetic devices to be inserted in the circulatory system.

First Cardiac Replacement Device Implanted in Man

Dr. Barney Clark, who suffered from cardiomyopathy, a primary heart disease possibly resulting from an earlier viral infection, consented to an experimental procedure of uncertain duration. An air-driven cardiac replacement device was implanted in Dr. Clark on December 2, 1982. His experience marked the first step towards a more practical and permanent device for circulatory assistance. He was linked by two plastic lines to a 375-pound console that controlled the action of his device. Five days after implantation, Dr. Clark experienced a series of seizures and was semiconscious for reasons that remain unclear. A week later, a valve in the left ventricle failed, and the left ventricle was replaced for a second time, the first having occurred during the initial surgery.



The artificial heart sustained life for Dr. Barney Clark for more than 3 months.

In spite of these setbacks and ongoing lung and kidney dysfunction, Dr. Clark continued to make progress and exhibited return of central nervous system function. He was able to sit, stand, and walk with a walker. Using a modified bicycle, he could exercise while sitting in a wheelchair. He remained relatively stable until 3 months later when he developed circulatory collapse as a result of systemic infection due to bowel infarction. The device, which beat more than 12 million times, was in good condition, and examination revealed that there was no evidence of clotting complications.

LUNG DISEASES

Improved effectiveness of diagnosis, treatment, and prevention of pulmonary diseases is the ultimate goal of the research in the lung diseases program. The National Program encompasses six major areas related to lung disorders. Research is conducted on the structure, function, and development of the lung and respiratory passages; on the diagnosis and treatment of the chronic obstructive pulmonary diseases, including emphysema, chronic bronchitis, and asthma; on pediatric pulmonary diseases such as respiratory distress of newborns, cystic fibrosis, and bronchiolitis; the mechanisms of occupational and immunologic lung diseases; on improved management of pulmonary hypertension and pulmonary edema; and on the causes of and effective treatment for respiratory failure. As research advances occur that offer potential for disease prevention and treatment, programs of education for health professionals and the lay public are developed and implemented. Following is a description of program highlights and scientific accomplishments of the past year, arranged by program area.

STRUCTURE AND FUNCTION OF THE LUNG

To prevent, diagnose, and treat lung diseases, a basic understanding of the structure and function of the normal lung is required. This understanding has gradually been developed and expanded by basic research in such disciplines as molecular biology, biochemistry, immunology, endocrinology, and cell biology. Investigations of lung structure and function contribute to understanding the causes and processes that affect the course of lung diseases. With insights into fundamental mechanisms, it is possible to detect subtle structural and functional changes that characterize and early phase of a disease before clinical symptoms are manifest. Such insights also offer possibilities for therapy and, in some instances, prevention of lung diseases.

Performance of World Class Endurance Runners Limited by Muscles, Airways

The factors that limit the performance of athletes have long been the subject of speculation among physiologists. Decades ago, it was theorized that man was physiologically incapable of running a mile in under 4 minutes, and yet it has been done repeatedly in the past 10 years. Training is, of course, of paramount importance in improving performance. The heart and circulatory system show well-documented effects of training that result in improved delivery of oxygen and essential nutrients to the working muscle. It has always been assumed, however, that the capacity of the healthy respiratory system far exceeds any demands that may be placed on it, even under the most severe stress of exercise.

A recent study of some internationally ranked milers and marathon runners has called this assumption into question. In both mock and real competition, these runners allowed blood and expired air to be sampled as they ran. These studies were complemented by more controlled laboratory studies involving running on a treadmill as well as by laboratory studies of animal models. The results indicate that the respiratory system may limit the performance of these athletes in at least two and possibly three different ways.

During exercise, the capacity of the system to move air in and out of the lungs appears to be stressed up to (and beyond!) the limits of ventilation measured at rest. These limits are imposed by the inherent collapsibility of the airways during exhalation; once collapse occurs, a more vigorous effort does not increase flow. The fact that the exercising athletes exceeded the maximum flows measured at rest may indicate a widening of the airways induced by exercise. Still, it appears that maximum flows are being reached, which imposes a limit to performance.

Blood measurements showed a pronounced but variable drop in oxygen levels shortly after exercise began. This drop is never seen in untrained volunteers during exercise. Although the limits to ventilatory flow may explain some of this drop, it may also be true that blood flowing through the lung capillaries of the athletes is traveling too fast to achieve equilibrium with the air in the alveoli.

In the athletes, the respiratory muscles, particularly the diaphragm, appear to be operating at levels close to those that would produce fatigue. The drop in blood oxygen may well be traceable to this cause as well, since studies in patients with severe chronic obstructive pulmonary disease indicate that they will tolerate a drop in blood oxygen rather than ventilate at an intensity that could lead to fatigue and total failure of the diaphragm. This situation may also be true for world class runners who push themselves to the limits of human performance.

During exercise, the capacity of the respiratory system to move air in and out of the lungs appears to be stressed up to (and beyond!) the limits of ventilation measured at rest.

Biochemistry of Adult Human Lung Surfactant Classified

Pulmonary alveolar surfactant is a mixture of lipids and proteins synthesized in alveolar type II cells and secreted into the alveoli and air passages. This substance reduces the surface tension of pulmonary fluids and thus contributes to the elasticity of lung tissues. Although there have been many studies of the lung surfactant system in experimental animals, there is almost no direct information concerning the biochemical composition of adult human surfactant.

In a recent study, researchers purified surfactant from specimens of macroscopically normal lung tissue obtained from 50- to 70-year-old males after pneumonectomy or lobectomy for localized bronchogenic carcinoma. The results demonstrated that surfactant with a characteristic lipid and protein composition can be readily isolated from surgically excised human lung tissue. Adult human surfactant, like all other surfactant studied, contains the lipid dipalmitoylphosphatidylcholine as the major component. There were, however, some biochemical differences from the surfactants isolated from other species.

An understanding of the biochemical composition of normal human lung surfactant is fundamental to the study of the surfactant system in adult respiratory distress syndrome and other pathologic conditions of the human lung. This study is especially timely in view of the recent attempts to use artificial and synthetic surfactants in the prevention and treatment of neonatal respiratory distress syndrome. It is apparent that the success of these efforts is dependent on a thorough understanding of the role and significance of all functional components of the human surfactant system.

Oxygen Toxicity Increased by Dietary Deficiency of Protein or Amino Acid

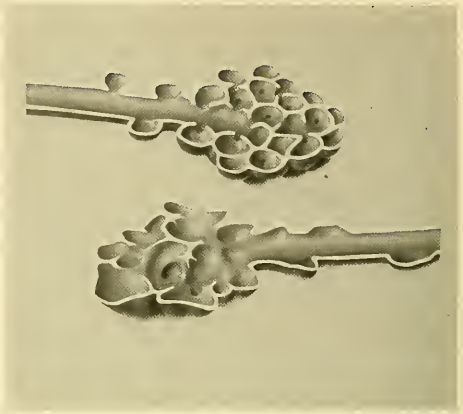
Patients with acute or chronic pulmonary diseases, who are most likely to require treatment with high concentrations of oxygen in an intensive care or postsurgical setting, are often unable to maintain an adequate food intake. Consequently, these patients often demonstrate protein and caloric malnutrition. Studies of the possible relationships between hyperoxia and nutritional deficiencies have been undertaken in animal models, and deficiencies of nutrients such as vitamin E, selenium, and copper have been implicated in reduced tolerance to oxygen.

In a recent study of rats, the physiological effects of oxygen in conjunction with a low protein diet were investigated. The results showed that a limited protein diet increased toxicity to oxygen. Neither a limited caloric diet nor fasting had such an effect. The increased susceptibility to oxygen toxicity did not seem to be explained by alterations in protective enzymes. Toxicity, however, was prevented by supplementing the low protein diet with the sulfur-containing amino acids, cysteine, cystine, or methionine. Additional cysteine added to a nondeficient diet did not significantly increase tolerance to oxygen above normal levels. The potentiation of oxygen toxicity by dietary restriction of protein was found to be associated with a failure to increase the production of glutathione (a tripeptide coenzyme found in most cells that protects the cell against oxidant-induced injury) during exposure to oxygen.

These findings have clinical implications for patients receiving high concentrations of oxygen in an intensive care or postsurgical setting. An ability to generate glutathione in response to hyperoxia may be an important indication of the tolerance to high oxygen concentrations of a patient whose levels of glutathione may be compromised by protein-deficient diets. This possibility suggests that sulfur-containing amino acid supplements may be useful for limiting toxicity to oxygen for patients receiving protein-deficient diets.

CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Research on chronic obstructive pulmonary disease leads to a better understanding and management of chronic bronchitis, emphysema, and asthma. Chronic bronchitis is a persistent inflammation of the lungs, characterized by recurrent coughing and excess mucus in the airways. Emphysema is a disease in which the thin walls of the alveoli (air sacs) lose their elasticity and tear. These diseases are associated



Normal alveoli (above) have a distinctive honeycomb appearance; emphysematous alveoli (below) become thickened, and passageways are plugged with mucus.

with certain risk factors such as cigarette smoking, and in some cases with genetic determinants such as a deficiency of a particular enzyme. Asthma, a disease characterized by bronchoconstriction, can be precipitated by a wide variety of poorly understood factors such as allergic reactions, infections, emotional disturbances, exercise, cold, and environmental pollutants. Advances are being made in understanding the basic chemical processes that cause progressive, debilitating destruction of the lung tissues. Information is accumulating on the cellular origin and biochemical characterization of the generation, release, structure, and function of the chemical mediators that appear to be associated with the development of airway obstruction.

Critical Macrophage Functions Inhibited by Mucus

The normal tracheobronchial tree contains a thin, presumably discontinuous layer of mucus, which is probably absent in peripheral airways. In diseases such as asthma, characterized by hypersecretion of mucus, increased quantities of mucus extending into

peripheral airways become evident. Furthermore, airway mucus plugs from children with asthma have been shown to contain large numbers of entrapped macrophages, which are a type of blood cell that functions as a scavenger. The presence of abnormally abundant, thick mucus has been assumed to prevent efficient cleansing of the lung by physical and mechanical processes. The result is colonization and infection of lung tissue by bacteria and other organisms.

Recent biological studies show that mucus inhibits the activity of the macrophages. In a study of macrophages of sheep airways, it was found that mucus inhibited phagocytosis and protein synthesis, but when the mucus was separated by centrifugation into sol and gel phases, protein synthesis was unaffected by the gel phase but was markedly inhibited by the sol phase. Both phases significantly inhibited phagocytosis.

Although the exact mechanisms underlying these inhibitory actions are unclear, the different effects of the whole mucus and its sol and gel phases suggest that the physical effects of mucus are probably minimal but that the chemical nature of its components may be important to its ability to inhibit phagocytosis. Furthermore, inhibition of protein synthesis and phagocytosis seems to be caused by different fractions of the mucus. These studies show that the excessive mucus secreted in some diseases may exert profound biological effects on a variety of defense functions of the lung.

Asthma Self-Management Programs Disseminated in Cooperation With the Volunteer Sector

Between 5 and 15 percent of all American children have asthma. It continues to be the leading chronic disease causing school absenteeism. It can disrupt family life, and it often keeps a child from participating in daily activities. Exercise is frequently curtailed for fear of its precipitating an asthmatic attack. Yet attacks can often be prevented, or their severity reduced, if the patient takes greater responsibility for managing his or her condition. Such responsibility includes adhering to the medical regimen, avoiding allergens, and taking preventive action in case of an attack.

Recognizing the need for educating asthmatic children and their parents in managing asthma, the NHLBI supported the development of three model educational programs to teach children with asthma and their parents how to deal with the condition. After the program, the children were more self-reliant and lost fewer days from school, and their families were less anxious. There is also evidence of decreased use of emergency rooms among children who were frequently taken there during an attack. The projects were conducted in three very different settings—a middle-class outpatient population, a Health Maintenance Organization population, and an inner-city black-Hispanic popuiation.

Children with asthma can be taught to manage their condition.

The NHLBI is working with the American Lung Association to make these programs widely available to hospitals, clinics, voluntary associations, physicians, nurses, and health educators. To inform people in local communities about the availability of asthma education programs that can be implemented by a health professional, the Institute has cohosted one pilot asthma self-management workshop with a local chapter of the American Lung Association, which taught health professionals in the region how to implement an asthma program. Several more pilot workshops will be conducted, and the workshop will be replicated nationwide. It is expected that these workshops will form the basis for a regional network of health professionals who are interested in asthma. This partnership between the NIH and the voluntary sector is developing into an important, effective, and mutually beneficial mechanism that could improve the health of many asthmatic patients.

No Reversal of Decline Observed in Pulmonary Function of Low-Tar Cigarette Smokers

Ever since tar in cigarette smoke was associated with cancer, efforts have been made by the tobacco industry to develop a "safer" cigarette by reducing the tar content, especially by attaching various kinds of filters. Smokers turned to low-tar cigarettes with the understandable expectation that all health hazards of smoking would be reduced. Although it is theorized that reduction in the tar content of cigarette smoke may

lower the incidence of some cancers, recent studies indicate that it does not necessarily protect smokers from a decline in their pulmonary function.

To evaluate the pulmonary effects of the tar content of cigarettes, investigators compared longitudinally the pulmonary function of 1,355 men, including smokers of cigarettes of varying tar contents, ex-smokers, and men who never smoked. Pulmonary function declined most rapidly in current smokers. A faster decline was observed in former smokers than in those who had never smoked. Furthermore, those who smoked 20 or more low-tar cigarettes a day registered the lowest levels of pulmonary function, and these values declined even more during further followups. More important, in persons who smoked low-tar cigarettes, pulmonary function declined at the same rate as in those men who smoked cigarettes with higher tar content.

This study reaffirms the importance of quitting cigarette smoking, which remains the single most effective way to prevent the development of chronic obstructive pulmonary disease.

Increased Workload of Diaphragm Observed in Emphysema

Fatigue and inefficiency of respiratory muscles contribute to respiratory failure in patients with emphysema. The diaphragm, the chief respiratory muscle, must work increasingly harder to move air through obstructed passages. The disease process itself results in overinflation of the lungs, which alters the position of the diaphragm and causes shortening of the muscle fibers. Shortened muscle fibers contract with less force than stretched fibers. In addition, patients who are undernourished as a result of their COPD have reduced muscle mass. The increased respiratory workload imposed by disease leads to hypertrophy of the respiratory muscles and to other adjustments.

Recent animal studies provide some information about compensatory mechanisms that develop in respiratory muscles as a result of emphysema. They confirmed that starvation reduces diaphragmatic muscle mass and contractile force. In animals with elastase-induced emphysema, muscle structure, but not the mass of the diaphragm, showed alterations; the diaphragm as a whole became thicker and shorter. Individual fibers increased in size, and there was a reduction in the number and length of the subunits (sarcomeres) of which the muscle fiber is composed, similar to changes seen in limb muscles subjected to working for long periods of time in a shortened position. In animals, shortened diaphragmatic muscle fibers were seen to contract more rapidly, with the result that the rate of respiratory air flow was increased. These compensatory adaptations allowed the diaphragm to function more efficiently in its altered position.

Similar structural changes conceivably occur in humans with chronic obstructive pulmonary disease and help augment the mechanical effectiveness of the diaphragm. This understanding of respiratory muscle function should help evaluate therapies for strengthening respiratory muscles in the management of patients with COPD.

Release of Toxic Oxygen Metabolites Increased in Cigarette Smokers With Elevated White Blood Cell Count

The polymorphonuclear leukocyte (PMN), a type of white blood cell, is capable of causing tissue injury by several mechanisms, including the release of proteolytic enzymes and the generation of unstable oxygen metabolites. Various studies have confirmed that the numbers of PMN's and other inflammatory cells increase in the lungs of cigarette smokers. Cigarette smoke also stimulates the oxidative metabolism of these cells, which induces them to release highly unstable oxygen metabolites that cause cell death. Furthermore, these reactive oxygen metabolites may inactivate antiproteases in the lung, with the result that the harmful effects of PMN-derived proteases go unchecked.

A recent study of polymorphonuclear leukocytes from cigarette smokers whose white blood cell counts were higher than 9,000 showed a 50 percent increase in the release of potentially toxic oxygen metabolites. This effect was not observed in nonsmokers with similar counts nor in smokers and nonsmokers with counts of less than 9,000.

It is well-known that only a small fraction (10 to 15 percent) of smokers get emphysema or bronchitis. It will be interesting to see if this specific group of smokers, whose white blood cell count is greater than 9,000, is more susceptible to tissue-damaging effects of cigarette smoke, eventually leading to chronic lung disease. This possibility needs to be verified in further studies.

PEDIATRIC PULMONARY DISEASES

Lung disorders of infants or young children include respiratory distress syndrome (RDS),* cystic fibrosis, and bronchiolitis. Respiratory distress syndrome of the newborn is seen in premature infants

*The entity RDS is no different from hyaline membrane disease (HMD), and the terms are often used interchangeably.

who lack the ability to produce alveolar surfactant; alveolar collapse (atelectasis) commonly results. Cystic fibrosis is a genetically determined disease characterized in the lung by abnormal mucous secretion, and infection and progressive lung malfunction frequently occur during childhood. Bronchiolitis is an acute airway obstruction in young children, and it is increasingly being associated with adult occurrence of asthma, chronic bronchitis, and emphysema. Research in this program area has led to a marked decline in the mortality rate from respiratory distress syndrome of the newborn. Basic laboratory investigations are increasing the understanding of the normal cellular regulation of mucous secretion, water movement, and ciliary motion and how these processes are altered in cystic fibrosis.

Improved methods of ventilatory assistance for newborns with pulmonary problems have led to marked decrease in mortality.

Additional Benefit of Antenatal Steroid Therapy Demonstrated in Preventing Respiratory Distress Syndrome

Initial studies in 1968 suggested that lung maturation might be accelerated by pharmacological means. It was reasoned that the lung, because of its embryonic origin as an outgrowth of the foregut, might be an analog of the developing intestinal tract and that the maturational effect of corticosteroids observed in intestinal enzyme systems could conceivably be employed in accelerating maturation of the lung's surfactant system. Subsequent animal and clinical studies of corticosteroids and lung maturation supported this hypothesis.

A collaborative multicenter clinical trial on the effectiveness of dexamethasone in preventing neonatal respiratory distress syndrome confirmed that corticosteroids indeed can accelerate the functional maturation of the lung. This finding was evidenced by a lower incidence of RDS among infants whose mothers received dexamethasone compared with infants whose mothers received a placebo. A recent long-term followup study showed that no detectable growth, physical, motor, or developmental deficiencies within the first 3 years of life can be attributed to this therapy.

Necrotizing enterocolitis (NEC) is another serious disorder in newborns. It is characterized by areas of necrosis in the small and large intestines that sometimes can become perforated and lead to peritonitis. NEC occurs most frequently among premature infants, and the worldwide increase in incidence of NEC may be related to the survival of smaller, more premature infants who previously would have died because of a lack of respiratory support systems. The average incidence is currently estimated to be 24 cases per 1,000 admissions to neonatal intensive care units, which in the United States represents 4,000 cases annually. Mortality is high (about 29 percent), and NEC is the single most common surgical emergency of newborn infants.

An analysis of the incidence of neonatal complications other than RDS in the more than 700 infants born in the collaborative clinical trial showed that the incidence of NEC was approximately 60 percent lower among infants whose mothers had received dexamethasone than among infants whose mothers received the placebo. The significantly lower incidence of this disorder among infants exposed to dexamethasone is of considerable clinical importance. The reason for the lowered incidence is not currently known. Since hypoxia and RDS are commonly associated with NEC, it is possible that prevention of RDS is responsible for the lowered incidence of NEC. It is also possible that dexamethasone has a maturational effect on the intestinal wall that prevents necrosis from occurring. This possibility is supported by the finding that even in the infants who developed RDS the incidence of NEC was lower if these infants had been exposed to dexamethasone.

Cause of Lung Disease in Cystic Fibrosis Suggested

The basic mechanism of the defect in the genetic disease cystic fibrosis (CF) is still undefined, but recent studies suggest the possibility that it may be characterized by functional abnormalities in the airway epithelium, which is the covering of the surfaces of the airways.

In normal individuals, this epithelium regulates the volume and composition of the airway secretions through active ion transport mechanisms. The airway secretions become thicker or thinner depending on the direction of flow of water and ions across the epithelium. Secretions become thicker when epithelial cells absorb water and ions, and they become thinner when they release water and ions.

Children with cystic fibrosis undergo inhalation therapy to loosen pulmonary secretions and treat infection.

With the use of isolated nasal epithelium, scientists measured the transport and movement of key ions (sodium and chloride), and made comparisons for CF patients, parents, siblings of patients (heterozygotes), healthy individuals, and patients with pulmonary diseases other than cystic fibrosis. Results showed that there may be a disturbance in this critical regulatory function of the airway epithelia in CF patients. Interestingly, this function in heterozygotes was the same as that in normal individuals. This observation suggests that the malfunction in CF patients may be secondary to the disease process rather than a direct consequence of the defective gene.

In addition, studies with chemicals that alter active ion transport led to the conclusion that CF epithelium is apparently defective in chloride permeability. This defect could lead to decreased water content in airway secretions and to thickened mucus, which are characteristics of cystic fibrosis and a precursor of pulmonary infections. Agents that can modulate active ion transport therefore become valuable candidate drugs for CF therapy. Studies of the efficacy, toxicity, and modes of delivery of these agents will be an important area of research in the coming years.

Corrective In Utero Fetal Surgery for Congenital Malformation of the Lungs Demonstrated in Experimental Animals

In about 1 of every 5,000 live births, a congenital malformation of the lungs results from diaphragmatic hernia. Over 60 percent of such infants soon die despite an absence of other major congenital abnormalities and despite aggressive efforts to provide oxygenation and control pulmonary hypertension. In fact, the mortality from this defect has not declined appreciably since 1853, when the first patients with diaphragmatic hernia were reported.

Since it is now possible to diagnose diaphragmatic hernia in utero with the use of ultrasonography, the idea of repairing this fetal lesion is very attractive. Considerable experimentation in animal models, however, is needed before such a feat can be achieved. It has recently been possible in nonprimate animal experiments to induce and repair hernias in fetuses. Animals that were delivered at term after repair lived from 4 hours to 123 days, whereas the unrepaired animals died within 20 minutes.

Morphologic analyses have indicated that diaphragmatic hernia markedly alters normal lung development and results in underdevelopment of the lung, which appears very solidly structured and shows poor airsack development. Type II cells are abnormally abundant, but the mechanism by which external compression of the lung increases the number is not understood. A striking feature in diaphragmatic hernia observed in the animal studies, which has not been previously stressed, is the paucity of capillaries in the walls of the alveoli. If this finding is confirmed by detailed morphometric analyses now in progress, it will provide a possible explanation for the severe pulmonary hypertension associated with diaphragmatic hernia.

In addition, in utero repair of the diaphragmatic hernia markedly improved not only the survival of the animals but also caused a reversal of the abnormal structural development. It is anticipated that human fetal surgery may be possible if these studies can be successfully repeated in nonhuman primates.

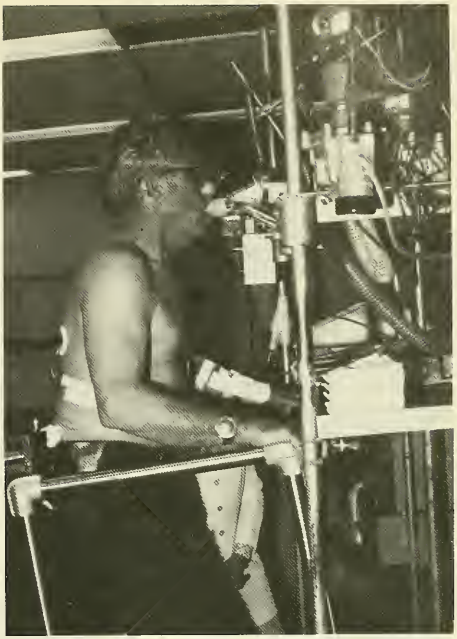
OCCUPATIONAL AND IMMUNOLOGIC LUNG DISEASES

Several lung diseases are characterized by immunologic and fibrotic responses that result in the proliferation of connective tissue or scar formation. Among the factors that induce these responses are exposure to occupational coal dust, silica, and asbestos in the environment; viral and bacterial infections; diseases of the connective tissue such as rheumatoid arthritis, lupus, and scleroderma; radiation damage; and exposure to substances like molds and dust that initiate hypersensitivity reactions. Diseases characterized by pulmonary fibrosis and by immunologic reactions include pneumoconiosis, sarcoidosis, diffuse hypersensitivity pneumonitis, farmer's lung, and bronchial asthma.

Because of its complexity and inaccessibility, the lung was one of the last organs to receive the attention of immunologists. The recent widespread use of

fiberoptic bronchoscopy has facilitated clinical evaluation of airway and interstitial lung diseases by permitting safe retrieval of secretions and cells from the airways and alveoli. The immunologic functions and mechanisms of action of these cells in lung injury are now being elucidated. In addition, occupational epidemiology studies are continuing to identify the etiology and risk factors of these lung diseases.

Exposure to coal dust during mining operations has been linked to development of coal workers' pneumoconiosis.



Monitoring respiratory health with a pulmonary function test.

Interstitial Lung Diseases Evaluated by Bronchoalveolar Lavage

Bronchoalveolar lavage (BAL) is a relatively noninvasive, nonsurgical method for obtaining cells and soluble components from the lower respiratory tract of normal and diseased lungs. Small quantities of normal saline are instilled into the lung and immediately withdrawn by aspiration. This technique has been performed in humans for approximately 10 years and is used in conjunction with fiberoptic bronchoscopy.

At present, only one interstitial lung disease, primary pulmonary histiocytosis X, can be diagnosed with reasonable accuracy by ultrastructural study of the cell pellets from BAL fluid. With the remaining interstitial lung diseases, two major inflammatory or cell patterns have emerged—a lymphocytic pattern and a polymorphonuclear leukocytic pattern. In diseases such as sarcoidosis and hypersensitivity pneumonitis, the primary cell found in the lavage fluid is the lymphocyte, while in idiopathic pulmonary fibrosis (IPF) and the interstitial lung diseases associated with collagen-vascular disorders, primarily polymorphonuclear leukocytes are found.

BAL is also proving useful in the diagnosis and management of infection secondary to acquired immune deficiency syndrome. In patients with bleeding complications, BAL is used to document pneumocystis carinii pneumonia, which is by far the most common pulmonary complication of AIDS.

Patterns of lung cells and soluble products are being identified in BAL studies of patients with interstitial lung diseases. Although the overlap in these patterns limits the diagnostic value of BAL at the present time, the technique is a powerful and exciting research tool, and with better standardization and with further studies, it has the potential of becoming a routine method for the clinical diagnosis and management of interstitial lung disease.

Study of Surface Antigen Leads to Better Understanding of Macrophage Turnover in the Lung

Alveolar macrophages function in the primary defense against inhaled particulate matter as scavenger cells that keep the lung surfaces clean and sterile. They also participate in inflammatory responses both as phagocytes and as secretors of various substances

that have been identified as contributing to the pathogenesis of diseases such as pulmonary fibrosis and emphysema. Because of their role both in lung defense and in lung disease, the alveolar macrophages have been the focus of studies to identify the processes of their origin and maturation.

Alveolar macrophages were recently found to contain a surface antigen that could be used as a marker for their origin and age. The antigen was found exclusively on alveolar macrophages and could not be induced in nonpulmonary macrophages. Development of a monoclonal antibody specific for the alveolar macrophage surface antigen and use of the antibody in cell sorting studies have led to a better understanding of macrophage turnover in the lung. In animals, this antigen seems to reflect the age of the cells. When new macrophages arrive in the alveoli, they have little antigen on their surface, but as they mature, an increasing amount of the antigen is acquired. The quantity of surface antigen present on macrophages provides a unique tool for isolating and studying alveolar macrophage subpopulations. Studies of antibody binding and particle uptake suggest that the antigen may also be involved in the phagocytic process. Cell sorting is now being used in the study of drug-induced fibrotic lung disease in animals to determine if macrophage turnover is abnormal in fibrotic lung disease.

Contractile Protein of Pulmonary Tissue and Cells Altered in Fibrosis

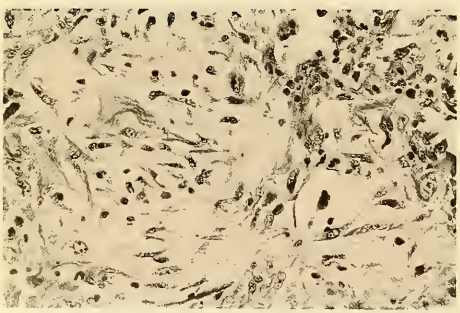
In pulmonary fibrosis, the lung tissue progressively loses its elasticity, which results in decreasing ability to expand the lungs and increasing difficulty in breathing, and ultimately death from a lack of oxygen. Despite a considerable amount of research on pulmonary fibrosis, the advances in elucidating the disease process have been few. Recent efforts have been made to study the distribution and turnover of contractile proteins in lung tissue, with the goal of determining how their activity is affected in pulmonary fibrosis.

A significant proportion of the lung is composed of cells with an abundance of actin microfilaments. Actin is a contractile protein usually found in muscle cells, and its abundance in nonmuscle lung cells may explain the substantial contractile capability of lung tissue.

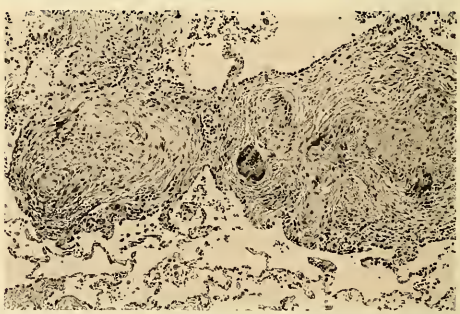
Recent biochemical analysis of normal lung tissue showed that about 10 percent of extractable protein consisted of actin that differed from muscle cell actin. Approximately 70 percent of the lung actin was in a form known as F-actin, and the remainder was in a form called G-actin. In drug-induced fibrotic lung tissue from animals, there was an increase in contractility, which was associated with an increase in the size of the microfilaments in cells. Biochemical analysis of this fibrotic lung tissue revealed that the total amount of extractable actin was the same as that seen in normal lung tissue, but the ratio of the F and G forms of actin had changed. There was a significant increase in the F form and a commensurate decrease in the G form. These results provide evidence for a mechanism of localized control of lung function as well as a new aspect of interstitial lung disease that may prove fundamental to its understanding.

Possible New Technique for Measuring Sarcoidosis Disease Activity Developed

Sarcoidosis, which occurs predominantly in individuals between 20 and 40 years of age, is a multisystem granulomatous disease of unknown etiology. In about 90 percent of cases, some degree of thoracic involvement can be detected by a chest x-ray. The most common complaints in about 40 percent of symptomatic cases are respiratory. Active pulmonary sarcoidosis is characterized as a high-intensity alveolitis with granuloma formation, increased antibody production (hypergammaglobulinemia), an increased



Lung tissue from animals with drug-induced pulmonary fibrosis shows developing intra-alveolar fibrosis.



Micrograph shows granulomatous inflammation of the lung that occurs in sarcoidosis.

number of antibody secreting cells (B lymphocytes), and a large number of activated T lymphocytes.

This heightened immunologic host response has been the focus of a number of recent studies to determine the mechanisms that are involved. The hypergammaglobulinemia found in sarcoid patients can be detected in the blood as well as at the site of disease, such as the lung. It was concluded in earlier studies that the majority of antibody, specifically immunoglobulin G (IgG) seen in bronchoalveolar lavage fluid, originated in the blood and was deposited at the site of disease by transudation from the serum. Recent evidence indicates that this may not be the case and that IgG production can take place at the site of disease and "spill over" into the blood, which produces the serum hypergammaglobulinemia seen in these patients. If these new findings are confirmed and expanded, it may be possible to use IgG levels in BAL as a reliable measure of disease activity. This hypothesis is particularly attractive since IgG determinations are easily performed and are in wide use.

The role of T lymphocytes in sarcoidosis is also under investigation. These cells can function as helper cells in modulating sarcoid granuloma formation by secreting chemotactic factors that attract monocytes (the "building blocks of the granuloma") to the alveoli. In addition, they are capable of mediating the hypergammaglobulinemia of sarcoidosis patients by activating normal B cells, which results in the presence of more immunoglobulin-secreting cells. Activated T cells also release interleukin-2 (IL-2), which in turn can cause activated T cells to proliferate. A recent study has suggested that in pulmonary sarcoidosis the amount of IL-2 released by the lung T cell was directly related to the activity of the disease in pulmonary sarcoidosis. Thus the T cell appears to be the key cell in the heightened immune responses seen in sarcoid patients.

RESPIRATORY FAILURE

Adult respiratory distress syndrome (ARDS) is a condition of acute respiratory failure that results from a variety of causes. Respiratory failure occurs as a consequence of many types of pulmonary and nonpulmonary acute and chronic disorders, when alveolar ventilation is insufficient to provide adequate gas exchange. It is among the most common causes of death from postoperative and other major traumas, and it occurs also in late stages of such chronic disorders as emphysema and chronic bronchitis.

Respiratory failure can be successfully treated if it is recognized early and therapy is instituted promptly. Research is focusing on an understanding of the pathways that are common to the diseases or injuries that lead to ARDS. The effects of cellular components of the blood, blood proteins, and products of vascular and pulmonary cells are being actively investigated. Through clinical research, more effective means of patient management are being sought.

Early Detection of ARDS Facilitated by Presence of Blood Protein

Adult respiratory distress syndrome is a form of lung failure that occurs as a complication of trauma or a variety of diseases. Marked improvements in the outcome of this condition, which is associated with a high mortality rate, could conceivably be made if its onset could be detected earlier than is now possible.

Results of a recent study involving 100 patients with ARDS indicated that substantial changes occurred in factor VIII, which is one of the blood proteins involved in the blood clotting system. This protein is composed of three components, factor VIII:C (the "coagulant" factor), factor VIII:CoF (the "von Willebrand" factor), and factor VIII:antigen, which is involved in the aggregation of blood platelets and their attachment to the walls of blood vessels. The study showed that the levels of all the factor VIII components increased in these ARDS patients but that the increase in factor VIII:antigen was much higher. This pattern of change appears to be unique to ARDS patients. Although factor VIII:antigen increases somewhat in patients with liver and kidney disease, it does so in proportion to increases in the other factor VIII proteins. In the same study, it was also found that the chemical structure of the factor VIII:antigen from the ARDS patients, as characterized by its behavior when placed in an electrical field, was abnormal.

Because these changes seem to be specific and were seen in patients even with only mild cases of ARDS, they may represent useful sensitive indicators for the early detection of this disorder.

Bacterial Infection Contributes to the Progression of Lung Injury

Patients dying of ARDS frequently have bacterial infections of the abdominal cavity and the lungs. Recent studies suggest that bacterial infections may be a much more important factor in determining the outcome of ARDS than was previously suspected. Clinical studies have shown that infection occurred in 98 percent of nonsurviving patients and in only 62 percent of survivors. The infections were also associated with clinically important impairment of other major organs or systems, including the kidneys and the central nervous system. In animal studies, lung damage was twice as great in the presence of a bacterial infection than in its absence.

The presence of infection may offer an explanation, in part, for the progression of ARDS. One of

the early events thought to bring about lung damage is an abundance of the protein C5a, which normally participates in the body's defense against invading organisms. It is very likely that superimposed infection greatly augments the production of C5a and the subsequent lung damage. These results suggest that more effective control of infection in ARDS patients should lead to a significantly improved outcome.

Effectiveness of Steroid Treatment Determined by Etiology of ARDS

It is estimated that in the United States, there are approximately 150,000 new cases of ARDS each year. In spite of advances in modes of ventilatory support and oxygen therapy, the mortality rate for ARDS still exceeds 50 percent. Even though steroid drugs have been the most common intervention for treating ARDS patients, the effectiveness of steroids remains controversial.

Recent animal studies suggest that the effectiveness of steroids may be related to the etiology of the disease. Animals with either oleate-induced lung injury or acid aspiration-induced lung injury were studied with and without steroid pretreatment. Oleate produced an injury similar to that of fat embolism syndrome, and acid-induced injury was similar to the acute lung injury produced by gastric aspiration, which is a common cause of ARDS with a very high mortality rate.

In the oleate group, steroid pretreatment improved survival, increased arterial oxygenation, decreased edema fluid, and induced proliferation of type II lung cells. The beneficial effect of steroids was thought to be due to the proliferation of alveolar type II cells, which preserved the gas exchange areas of the lung. The acid-induced injury was unaffected by steroid pretreatment, and the conclusion was drawn that steroids offer no protective effect against acid aspiration. The primary difference seen in the two types of injuries is that the acid-aspiration injury caused complete destruction of the basement membrane, which is the "scaffolding" to which the cells lining the blood vessels and the air sacs are attached. In the oleate-induced injury, the basement membrane remained intact.

These findings suggest that the effect of steroids is dependent upon the agent of injury and may explain the contradictory reports of the effects of steroid therapy in human ARDS.

PULMONARY VASCULAR DISEASE

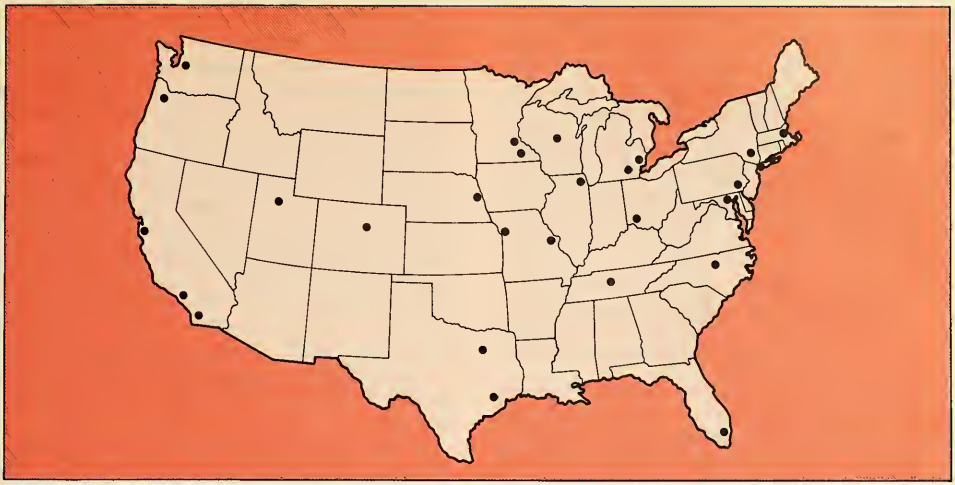
Pulmonary vascular diseases include cor pulmonale, pulmonary hypertension, and pulmonary edema. Cor pulmonale refers to enlargement of the heart due to an increased workload of the right ventricle resulting from conditions that affect the pulmonary circulation. Pulmonary hypertension is characterized by elevation of pulmonary arterial pressure above normal levels. Such a condition is considered primary when it is found in the absence of cardiac or pulmonary diseases and secondary when it is associated with these diseases. Pulmonary edema is a pathologic state in which there is abnormal extravascular storage of fluid in the lung. There is not yet enough information about the disorder for its early detection.

Although reliable data on the incidence and prevalence are not yet available, the difficulty of diagnosis appears to be the primary problem in managing these diseases successfully, since they are characteristically asymptomatic up to the point of irreversibility. Much of the research has been focusing on the mechanism of these disorders in animal models. Elucidation of the role of formed elements of the blood, hormones, and metabolites is resulting from ongoing investigations. The search for reliable noninvasive diagnostic techniques also is continuing.

A New Systematic Approach to Knowledge About Pulmonary Hypertension Established

Primary pulmonary hypertension is a synonym for pulmonary hypertension of unknown cause. It results from the arteries within the lungs becoming diseased, although the factor or factors responsible for the condition have not been described. It is a catastrophic disease that can affect people of all ages, including children and young adults. The prognosis is poor, and death usually occurs within a few months to a few years following diagnosis. Because the disorder is sporadic, no single medical center has been able to accumulate data on a significant number of patients, and clinicians have been able to clarify only a very few of its characteristics.

To obtain and analyze data on the etiology, natural history, pathogenesis, diagnosis, and treatment of this disorder, the NHLBI has established a patient registry on primary pulmonary hypertension. The registry, which includes children of over 1 year and adults who have pulmonary hypertension of unknown etiology, is now in full operation, with 35 participating clinical centers and a data and coordinating center. As of this writing, 124 cases have been submitted. Through the registry, new insights into the etiology and pathogenesis of the disease are expected, from which new strategies should evolve for its early detection and treatment. The information is also expected to lead to improved management of the more common types of pulmonary hypertension of known



Primary pulmonary hypertension patient registries are located at 35 participating medical centers.

cause, such as those associated with emphysema and chronic obstructive lung disease.

Ibuprofen Offers Possible Protection Against Acute Lung Injury

Mortality in humans with the clinical diagnosis of adult respiratory distress syndrome remains at 50 to 60 percent in spite of advances in modes of ventilation and in the technology for acquiring clinical data. ARDS patients with persistent pulmonary hypertension (increased pulmonary vascular resistance) and persistent severe hypoxemia (low oxygen in the blood) have particularly high mortality.

In the past 10 years, there has been a marked increase in understanding the pathophysiology of acute lung injury. Data from experimental animals suggest that some of the vascular and airway abnormalities resulting from acute lung injury are brought about by metabolites of arachidonate, which are prostaglandin-like compounds, and by interactions of these metabolites with leukocytes. It has been shown in animal models of ARDS that cyclooxygenase products of arachidonate are released from the lungs following acute lung injury coincident with pulmonary vascular constriction and airway constriction, and that both of these constrictor responses are affected by drugs that inhibit cyclooxygenase. Such drugs also significantly improve oxygenation of the blood after acute lung injury.

At least four potent inhibitors of arachidonate cyclooxygenase (aspirin, indomethacin, meclofenamate, and ibuprofen) are now used in humans to treat other diseases.

Cyclooxygenase inhibitors have been found to block or lessen the pulmonary hypertension, hypoxemia, and increased levels of arachidonate metabolites associated with acute lung injury. Results of animal experiments of ARDS, however, indicate that the effects of ibuprofen differ from the effects of other cyclooxygenase inhibitors. Ibuprofen also diminishes or prevents the production of pulmonary edema. The mechanism of how ibuprofen exerts this protective effect in acute lung injury is unclear. It may be related to a direct effect of ibuprofen on inhibiting leukocyte function, such as generation of toxic oxygen radicals, or it may act as a free radical scavenger as well as an inhibitor of cyclooxygenase activity. These observations suggest that cyclooxygenase inhibitors, especially ibuprofen, may be beneficial in treating ARDS.

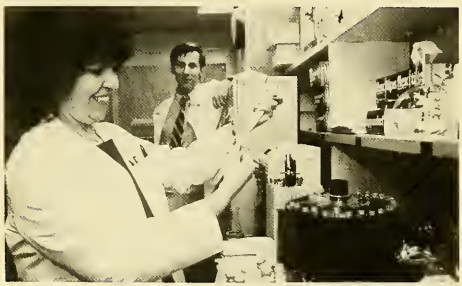
Use of Cyclosporin A Suggested in Immunosuppressive Therapy for Lung Transplant Recipients

Transplantation of lungs has been shown to be technically feasible, both in animal experiments and in human patients. A major obstacle to the use of this operation in patients with end-stage pulmonary disease is the behavior of the body's immune defense mechanisms, which reject the grafted lung. Attempts to suppress this response have included radiation, antimetabolite drugs such as azathioprine, large doses of steroids, and antilymphocyte serum. None of these agents alone or in combination has successfully prevented rejection for more than a few weeks.

Results of recent animal experiments suggest that the drug cyclosporin A, which is derived from a fungus, is much more effective in preventing rejection than are other available agents. Of 12 animals that were given cyclosporin A following lung transplantation, 4 survived from 1 to 14 months without any evidence of rejection. In four others, rejection occurred, but it was successfully suppressed by giving a steroid drug. These results, which have been hailed as an advance in immunosuppressive therapy, may offer promise for treating recipients of human lung transplants.

BLOOD DISEASES AND RESOURCES

The blood diseases and blood resources program plans and supports research on the causes and treatment of genetic and acquired disorders of the blood, and it is also responsible for developing and overseeing procedures that will ensure an adequate and safe supply of high quality blood and blood products.



Blood samples are analyzed in a hematology laboratory to detect the presence of blood diseases.

The program is organized into four areas: bleeding and clotting disorders, red blood cell disorders, sickle cell disease, and blood resources. Within each of these areas, investigations encompass the spectrum of medical research, from basic laboratory findings to applications for clinical medicine. Because the functions of the blood are so closely related to heart, lung, and blood vessel diseases, increases in understanding blood disease mechanisms and treatment benefit all the program areas of the NHLBI.

BLEEDING AND CLOTTING DISORDERS

Bleeding disorders and clotting disorders are closely interrelated. Both represent failures of normal maintenance of blood fluidity within the blood vessels. Normal clotting is a protective mechanism to prevent bleeding that results from trauma. When it occurs abnormally, tissue damage is the inevitable result. In contrast, excessive bleeding into surrounding tissues or outside the body can result from hemophilia and other acquired or inherited abnormalities of the hemostasis system.

When excessive bleeding or clotting occurs in small blood vessels and capillaries (collectively termed the microcirculation), tissues and cells are deprived of essential oxygen, energy, regulating hormones, and nutrients, and noxious waste products are not removed effectively. Bleeding and clotting in the microcirculation are contributory or primary mechanisms in hypertension, stroke, diabetes, infectious and inflammatory disease, autoimmune disease, host-graft rejection, cancer, sickle cell anemia, drug toxicity, mismatched blood transfusion, liver disease, and nephritis.

A basic understanding of blood coagulation is critical to the reduction of disability and death from bleeding and clotting disorders. Research during the past year has increased the understanding of the mechanism of blood clotting and the contribution of the blood vessel wall and of the formed elements of the blood to the process. Advances in genetic engineering and the development of monoclonal antibodies have contributed to a more complete comprehension of the blood clotting process. As a result, clinical applications are becoming a reality.

New Information About Cellular Interactions

Over the past several years, the focus of hemostasis research has shifted from the characterization and study of the interaction of the soluble clotting factors and inhibitors to the interplay of these factors with the blood cells and the blood vessel wall. This shift has occurred as a result of advances in the understanding of cell physiology and receptor biology. There is now a greater awareness of the cellular activity that precedes coagulation and is followed by hemostasis, immune reactions, and tumor cell growth.

Using in vitro cell culture techniques and animal models, many investigators are now studying the function and interactions of the vascular and leukocytic cells in hemostasis. Advances are now being made in the understanding of the influence of the hemostatic system not only in hemorrhagic and thromboembolic diseases, but also in the neoplastic, infectious, and inflammatory diseases. These studies are focusing on the stimulatory and regulatory mechanisms of the cells, and their surface receptors, synthesis, and secretions.

It has been shown in vitro that the monocyte-macrophage secretes more than 50 peptides, including procoagulant factor, prothrombinase, and fibronectin. Investigators have demonstrated that the endothelial cell synthesizes and secretes fibrinolytic activators and inhibitors that are involved not only in dissolution of fibrin clots but also in macrophage activation, neoplastic transformation, tissue repair, ovulation, and embryo implantation.

Continuation of such investigations should lead to a greater understanding of the function of cellular secretions in hemostasis, immune reactions, and tumor cell growth.

New Evidence for Role of Lymphocytes and Monocytes in Thromboembolic Disease

For many years, the blood platelet has been thought to be the most important of the various blood cells involved in clotting. Recent research, however, has revealed that other blood cells as well as the cells that line blood vessel walls have an important function in clot formation and the cessation of bleeding.

Interior lining of blood vessels plays a role in clotting.

Advances have been made in delineating the cellular pathways that initiate the clotting response, including the modes of triggering the T class of lymphocytes to elicit a response, and in identifying and phenotyping the T cells that appear to instruct human monocytes to synthesize tissue factor, which is a protein that serves as a cofactor for factor VII in the initiation of coagulation through the so-called extrinsic pathway.

This pathway is central to the widespread clotting disorder that occurs in blood vessels during bacterial infection and endotoxemia, and it may be the basic pathway by which viruses, antigens, and immune complexes trigger thromboembolic disease. If subtle differences in cell surface molecules can be observed in reponses of this pathway, the information may lead to an explanation of how coagulation along blood vessel walls is initiated during aging or spontaneous mutation of cells.

New Human Endothelial Cell Culture Technique Developed for Basic and Clinical Research

Although bovine endothelial cells have been studied widely because of the ease with which they can be serially subcultured, little progress had been made in the serial subculturing of human endothelial cells. A significant advance was recently reported in the cultivation of both human umbilical vein endothelial (HUVE) cells and endothelial cells from adult human blood vessels. Supplementing the standard culture media of endothelial cells (Medium 199, 20 percent fetal bovine serum, and endothelial cell growth factor) with heparin resulted in enhanced proliferation, increased doubling times, and increased life span of human endothelial cell cultures that can be serially subcultivated. Using this culture technique, scientists for the first time established 11 cloned HUVE cell strains and 4 human abdominal aorta endothelial cell strains. Although the mechanism by which heparin promotes human endothelial cell proliferation is unknown, these results suggest that heparin-like substances may play an important role in the regulation of cell growth in normal and injured vessels. With this new culture technique, research involving human endothelial cells can be facilitated and expanded. In addition, this cell system may prove valuable for various clinical applications, such as in vitro testing of vasoactive agents and the coating of artificial graft materials.

Relationship of Platelet-Derived Growth Factor to Oncogenes Described

Although genes to produce platelet-derived growth factor (PDGF) are found in most human cells, PDGF is normally produced only by the platelet. It has long been known that platelet-poor plasma supports poorly, if at all, growth of fibroblasts, smooth muscle cells, and glial cells, although malignant or virally transformed cells in culture lack responsiveness to specific growth factors and behave as if the cells were already fully stimulated. The factor in

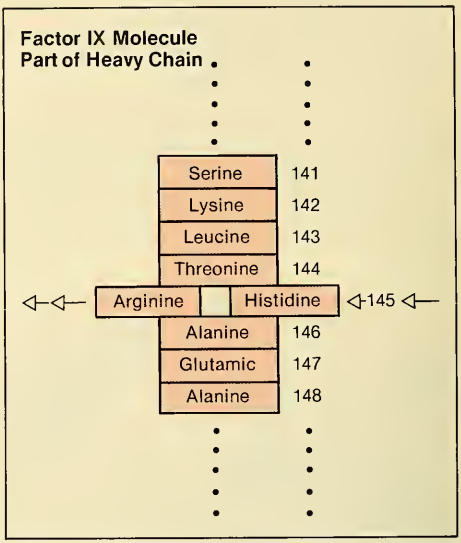
plasma (PDGF) that is necessary for this growth-promoting activity has been isolated, characterized, and sequenced. The recent announcement of the amino acid sequence of PDGF led to the serendipitous discovery that there was an 87 percent homology between the sequence of this protein product and a piece of genetic material from a virus that can cause cancer in animals, the oncogene *sis*. The demonstration that the transforming protein of simian sarcoma virus and a platelet-derived growth factor are derived from the same or closely related cellular genes strongly sugests that the way in which this *onc* gene transforms cells may involve the constitutive expression of a protein with functions similar to those of a factor that is active transiently during normal cell growth. It is now believed that oncogenes are derived, in whole or in part, from cellular genes that had somehow been incorporated by the viruses during the course of infection. The findings about PDGF are the first in which an identified *onc* gene has been shown to correspond to a cellular gene encoding a protein of known physiological function. The oncogene theory for the development of human cancers was given a new dimension very recently when it was announced that the oncogene *myc* is turned on by growth factors, including PDGF. Since the growth factor PDGF acts on receptors located on the surfaces of cells and the protein product of the *myc* gene is located in the nucleus, it is suggested that two potential oncogenes might act on one another in malignant transformation. These results support the growing view that transformation generally requires the activation of at least two oncogenes in a possible cascading hierarchy.

Factor VIII Gene Produced by Recombinant Techniques

The isolation of a cDNA fragment for human factor VIII was recently reported. This is the first step in isolating the genomic DNA for this important clotting factor and its subsequent expression in in vitro systems. The availability of a biologically active recombinant DNA-produced factor VIII product could have a substantial impact on the treatment of the approximately 12,000 patients with hemophilia A in this country. Such a product would be free of viral contamination, which currently poses a major risk for the transmission of hepatitis and possibly AIDS. Knowledge of the structure of factor VIII, its structure-activity relationships, and the ability to genetically engineer an active fragment could theoretically allow the synthesis of a therapeutic product that would not be antigenic and could be used to treat the 15 percent of hemophiliacs who develop inhibitors (antibodies) to factor VIII.

Molecular Basis of Hemophilia B Defined

Hemophilia B, or Christmas disease, is a bleeding disorder characterized by a deficiency in the factor IX molecule of the coagulation system. Although abnormal factor IX molecules have been isolated and studied, the precise molecular defect has not been identified. Two recent developments, however, have significantly advanced the understanding of this disease, and they illustrate the level of molecular investigation now possible for other hemostatic disorders characterized by an abnormal protein.



Molecular biology techniques have permitted determination of the amino acid sequence in an abnormal factor IX molecule.

A portion of the factor IX DNA has been isolated, and attempts are now being made to go directly to the genome. In complementary studies, the defect in an abnormal factor IX (termed factor IX:Chapel Hill) has been identified and correlated with a single-base substitution. This factor IX molecule was isolated from a patient with mild hemophilia B and has been shown to be defective only in its ability to be activated by factors XI and VII. Amino acid sequence studies have now shown that the defect is a substitution of histidine for arginine at position 145, and this has been related to a base change of CGT to CAT in the DNA sequence. This change results in the inability of the molecule to be activated to factor IXa; however, when the cleavage is accomplished in vitro, the factor IXa formed is active.

This information provides new insight into structure-function relationships in abnormal factor IX that will aid in understanding both the defect causing this bleeding disorder and the normal factor IX activation process. New microsequencing techniques, the ability of monoclonal antibodies to selectively remove trace proteins, and advances in genetic technology will enable study at the molecular level of other normal and abnormal proteins.

Advances in Genetic Engineering Applied to Study of the Structure of Normal or Abnormal Clotting Proteins

Most of the clotting factors and fibrinolytic enzymes appear to be synthesized by the liver; yet little is known about the regulation of synthesis of many of them. Recent advances in genetic technology are now enabling the study of not only synthetic regulatory mechanisms but also the gene products and aberrations that are responsible for hereditary clotting and bleeding disorders.

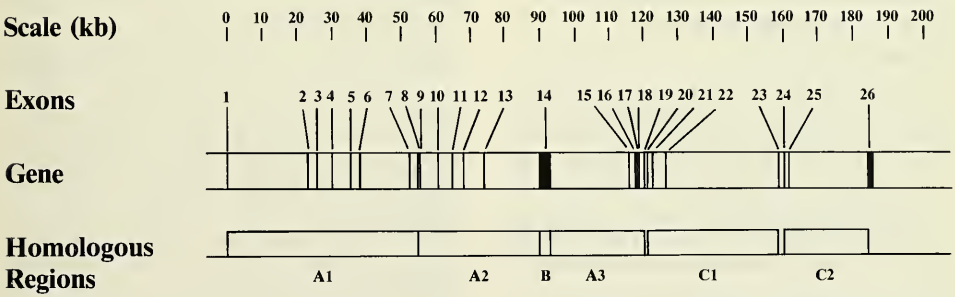
Many components of the clotting and fibrinolytic system are now being studied with the use of recombinant DNA and cloning methods. The genes for the three chains of fibrinogen from murine, human, and bovine plasma have now been cloned. These genes are now being sequenced and studied structurally for information about regulation and control. Thus far, it has been determined that the three genes for the three chains are distinct, although the gene products show a high degree of similarity. Their synthetic processes are highly coordinated in the liver, with a simultaneous increase in messenger RNA and all the protein subunits.

Other proteins for which the genes have been isolated and partially sequenced include human and bovine prothrombin, human and bovine factor IX, antithrombin III, plasminogen, and tissue plasminogen activator. It has been shown that factor IX is synthesized as a preproenzyme with a gene sequence similar to the gene sequence that codes for prealbumin.

Of great interest and importance is the factor VIII gene. Using sequence data to make peptide probes, several commercial laboratories are attempting to clone this gene. Availability of a functional factor VIII produced by cloning would have a major impact on treatment of hemophilia. Plasma fractionation to obtain the factor would no longer be necessary.

The goal of this effort is to clone complementary DNA and the natural genes of clotting and fibrinolytic proteins. Individually cloned complementary DNA's can be used to monitor the expression of the various genes that are involved. Cloned complementary DNA can also make it possible to study the structure of messenger RNA for these proteins as to sites of initiation, signals of termination, and other properties of their regulation. Further, isolation of complementary DNA and genomic clones will enable the study of gene structure and perhaps the development of a strain or strains of bacteria or mammalian cells capable of producing and secreting functional proteins.

Map of Human Factor VIII Gene



Source: Nature: Vol. 312, p. 327.

Genetic engineering technology has produced maps of the genes responsible for production of clotting factors.

Use of Monoclonal Antibodies in Structure-Function Studies

Monoclonal antibodies are now known to have an exquisite sensitivity for use in the study of functions of various molecules and cells and for differentiating the correlation of these functions with peptide sequence and tertiary structure. The technique has recently been applied to the study of von Willebrand factor. The number of monoclonal antibodies now available will allow investigators to build a model system in which the specific mutation of von Willebrand's disease variants can be determined and permit a molecular classification of the disease. It is now possible to produce a new animal model of von Willebrand's disease by infusion of a monoclonal antibody. The reagents have also provided information for identifying the functional structures that are involved in von Willebrand factor binding to platelets, to factor VIII, and to subendothelium.

Diagnosis With the Tool of Monoclonal Antibodies

The potential uses for monoclonal antibodies as a diagnostic tool are numerous. It was recently reported that Bernard-Soulier syndrome and Glanzmann's thrombasthenia, which are two congenital platelet disorders respectively associated with deficiencies of platelet membrane glycoproteins GPIb and GPIIb/IIIa, can be diagnosed specifically and accurately with appropriate monoclonal antibodies. In addition, advances in the early diagnosis of thrombotic disorders are imminent, with the use of antibodies to activate peptides of the clotting enzymes and specific enzyme-inhibitor complexes.

Interactions Among Platelets, Collagen, and von Willebrand Protein Demonstrated by Laboratory Model

Normal cessation of bleeding and clot formation depends on complex interactions among platelets, the wall of the blood vessel, and von Willebrand factor (vWF) (factor VIII:R, or factor VIII:Ag). Von Willebrand's disease is a congenital bleeding disorder in which these interactions are faulty. Von Willebrand factor is found in platelets and is the antigen that has been used to identify endothelial cells (factor VIII: Ag).

An in vitro model has been developed that tests platelet-collagen-vWF interactions. It is based on the observation that formaldehyde-fixed, washed human platelets adhere to collagen filaments in suspension. The rate of adherence is affected by the presence of certain forms of von Willebrand factor, and it appears that platelets and von Willebrand factor have different binding sites along the collagen.

Scientists using this simple laboratory model now have a new approach to studying the complex interrelationships of the clotting mechanism. Once the normal process is understood, it may be possible to manipulate the model to mimic disease states. Such experiments should provide insights into the development and treatment of thrombosis and atherosclerosis.

Proteins C and S Clotting Activity Described

Protein C and protein S are the only known vitamin K-dependent proteins that contribute to the inhibition of blood coagulation and to the stimulation of fibrinolysis, or the dissolution of clots.

Investigators have shown that thrombin activates protein C (a serine protease zymogen), which then rapidly inactivates factor Va and factor VIII. Although thrombin in an in vitro system is a feeble activator of protein C, perfusion of the myocardium with protein C in the presence of thrombin elicits a potent anticoagulant activity, which has been identified as activated protein C. With the use of cultured endothelial cells, it has been found that the activation of protein C in the presence of thrombin is the result of a cofactor bound to the endothelial surface. This cofactor, termed "thrombomodulin," has been purified. It is composed of a single polypeptide chain with a molecular weight of 75,000. Other investigators have demonstrated that both the anticoagulant activity and the proteolytic activity associated with active protein C are stimulated by a second vitamin K-dependent protein, protein S. Activation is dependent upon the binding of both proteins to phospholipid vesicles. Animal studies have demonstrated that intravenous infusion of activated bovine protein C causes a marked rise in fibrinolytic activity.

It now appears that when thrombin is generated in the circulation, it arrives seconds later in a capillary bed, where virtually all the thrombin binds to endothelium. This thrombin bound to thrombomodulin begins to activate protein C, which binds to protein S and phospholipid vesicles and then circulates and scavenges traces of activated factor V and factor VIII, and provokes the release (most likely from the endothelium) of the fibrin-dependent plasminogen activator. Further investigation of the potent anticoagulant and fibrinolytic properties of these proteins should enhance the understanding of the regulation of hemostasis and the treatment of thromboembolic diseases.

Blood Products Replaced by Hormones

The replacement of blood products by hormones is now an alternative for some hemophiliacs as well as for chronic renal disease patients with prolonged bleeding time. Danazol, an impeded androgenic hormone, was found to increase plasma levels of factor VIII and factor IX in hemophilia A and hemophilia B. Another hormone, I-deamino-8-D-arginine vasopressin (DDAVP), which has been available for several years for use in treatment of milder forms of hemophilia A and von Willebrand's disease, has been investigated more extensively in an effort to elucidate its mode of action. These studies have led to a greater understanding of the release of factor VIII from storage sites and also of the physiological importance of the multimeric forms of the von Willebrand factor. Since DDAVP increases plasma levels of factor VII and factor XII and also decreases the prolonged bleeding time associated with chronic renal failure, alternatives to plasma therapy now exist. These alternatives avoid the disadvantages inherent in the use of plasma derivatives, which include risk of exposure to viral hepatitis and other plasma-transmitted diseases, exposure to immunologic alterations from plasma proteins, a lack of uniformity, high costs, and a drain on the Nation's blood supply.

Trace Plasma Proteins Isolated and Purified

The availability of monoclonal antibodies has made it possible to isolate trace plasma proteins in a pure form, among which are factor V and coagulant factor VIII (VIII:C). These two proteins had heretofore resisted purification in a number of laboratories. Factor VIII:C usually copurifies with von Willebrand factor. Only in the last several years has it been proved that these are two distinct proteins rather than a multifunctional factor VIII molecule with both sets of activities. Both bovine and human factor V have now been isolated by affinity methods that make use of monoclonal antibodies. Efforts are now being made to use these antibodies in the preparation of a concentrate of human factor V, for emergency replacement therapy in a few factor V-deficient individuals when they are in need of hemostatic protection in a surgical procedure. Antibodies are also available to factor VIII:C from human and porcine plasma, and it is conceivable that they will provide purified factor VIII:C free of unrelated von Willebrand factor (sometimes referred to as factor VIII:R or factor VIII:Ag), which may be of therapeutic use.

Noninvasive Methods Used to Identify Fibrin Clots

A clinically important problem is the detection of the existence and location of deep venous and coronary artery thrombi. The use of antibodies to detect fibrin deposits in vivo has been complicated by the cross-reactivity of these antibodies with fibrinogen, which is the circulating precursor. A potentially significant advance was made when a synthetic heptapeptide from the amino terminus of the beta chain in fibrin was used to produce monoclonal antibodies that bind specifically to fibrin even in the presence of plasma concentrations of fibrinogen. These antibodies have been tested successfully for their binding to human fibrin-coated disks in a chicken ex vivo circulatory model. Such findings may lead to better methods for thrombus identification.

Therapy for Venous Thrombosis Improved

Significant progress is continuing not only in the treatment of thrombosis but also in its diagnosis and prevention. A major finding discussed in the *11th Report of the National Heart, Lung, and Blood Advisory Council* was that plasminogen activator is released from endothelial cells and, subsequently, activates plasmin(ogen) (the clot-lysing enzyme) only at in situ fibrin clots and does not destroy other coagulation factors (as do streptokinase and urokinase). Recently, several research centers have concentrated on the production of large amounts of plasminogen activator and similar products for the treatment of thrombosis. From this research, plasminogen activators have been synthesized from cell cultures, and at least three commercial laboratories are in the process of producing tissue plasminogen activators from recombinant DNA techniques. It is expected that the product will be available for clinical trials within the next several months. Research funded by the NHLBI has contributed to the awarding of several patents in this area. Other potential clot-lysing agents are being investigated, such as components of snake venoms. With these new advances, it is anticipated that the therapy of venous thrombosis will be markedly improved within the next few years and may no longer be a life-threatening condition.

Clot Formation After Total Hip Replacement Prevented

Patients who undergo total hip replacement surgery are at high risk of developing clots in the deep veins of the leg. Low doses of aspirin have been

shown to decrease the incidence of such clot formation, especially in male patients. To develop better methods of preventing thrombosis, a small study was conducted of patients over the age of 40 who were undergoing total hip replacement, in which the effects of two different doses of aspirin were compared with the effects of external pneumatic compression plus dextran.

Thus far, the results of the study show that for female patients, external pneumatic compression plus dextran has been better than aspirin in preventing clots, and that for male patients, this method offers substantial promise. Preliminary figures also suggest that a very low dose of aspirin is not more effective in females or males.

The study needs to be repeated with a larger population to establish statistically significant differences. A determination of the efficacy of the combination of external pneumatic compression and dextran, and an evaluation of the lower dose of aspirin are important issues in the prevention of venous thromboembolic disease.

A Continued Search for Improved Heparins

The present commercial preparations of heparins, which are obtained from animal sources, are quite diverse in their chemical structure and actions. They produce many side effects, can be antigenic, and must be administered parenterally. Extensive research is now being conducted to determine their anticoagulant moieties, their action on other body functions, and techniques for the production of synthetic heparin fragments that are safe and can be administered orally.

Oral Heparin Suggested for Treatment of Thromboembolic Disease

Heparin is a substance that is widely used as an anticoagulant in the treatment and prevention of thrombosis. It is safe and effective, but because of its chemical and pharmacokinetic properties, it must be administered by injection.

A heparin ammonium ion complex has recently been developed that is an effective anticoagulant in experimental animals. Additional heparin complexes are being developed, and they are being tested in animals for effectiveness and toxicity. With continued promising results, clinical investigations will be needed.

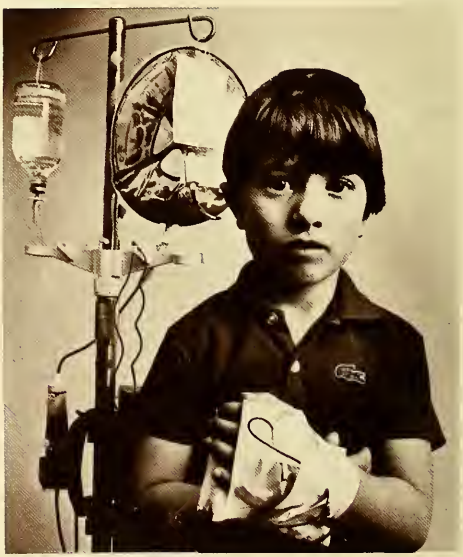
The availability of an effective oral preparation of heparin would be a major achievement in the treatment of thromboembolic diseases. Oral anticoagulant therapy would be less expensive, and the hazards and discomfort of parenteral administration of heparin would be eliminated.

RED BLOOD CELL DISORDERS

Red blood cell disorders include: Cooley's anemia (thalassemia), which is a genetic disorder affecting hemoglobin molecules that makes the red cells very fragile and results in anemia, bone abnormalities, impaired growth, and tissue iron overload; red blood cell membrane and enzyme disorders; aplastic anemias; hemolytic anemias; and disorders of oxygen transport. Scientists are striving to increase information about the factors that control erythropoiesis, which is the production of red blood cells by the bone marrow; to elucidate the structure and function of the red blood cell membrane; and to explain intracellular metabolism. Comprehension of disease mechanisms is made possible through an understanding of the normal function of red blood cells. Such an understanding will lead to the prevention, control, and more effective treatment of red blood cell disorders.

New Study of Therapy for Iron Overload in Cooley's Anemia

Cooley's anemia (beta-thalassemia) is a hereditary blood disease in which adult hemoglobin is either diminished or absent in the red blood cells. Although the disease is not widely prevalent in the United



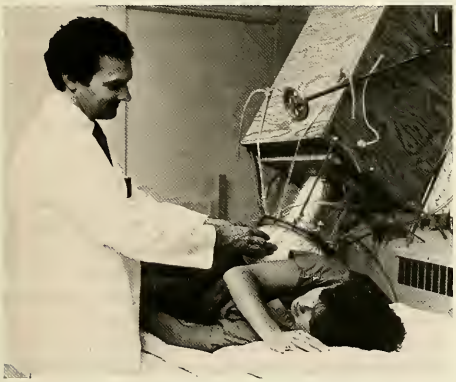
Cooley's anemia patient receiving red blood cell transfusion.

States, it is a catastrophic illness that can be classified as an "orphan disease." Patients with the disease die in early childhood unless they receive frequent blood transfusions. These repeated transfusions, however, cause an accumulation of iron in vital organs, which often results in congestive heart failure. Unless the iron is removed, patients die as teenagers. Current therapy consists of improved methods of blood transfusions and daily subcutaneous administration of deferoxamine over a 10-hour period to remove toxic iron. This therapy is expensive—more than $8,000 a year for each patient.

If therapy with transfusions and deferoxamine is not begun before the age of 10, cardiac abnormalities are not prevented, reversed, or arrested. A study of a group of patients in whom therapy was begun at an earlier age, however, seems to show maintenance of normal heart function. An additional followup of these young patients is needed to determine if this therapy further favorably alters the lifetime course of the disease.

Noninvasive Method Developed to Measure Iron Stores

The repeated transfusions necessary to treat patients with thalassemia, including Cooley's anemia, result in a buildup of iron. A safe, accurate, noninvasive assay technique has been devised to monitor the levels of stored iron in these and other patients who may develop iron overload.



The prototype of a newly developed device is used to measure, noninvasively, the amounts of iron stored in the liver.

With a specially designed superconducting quantum interference device (SQUID), it has been possible to measure iron stored in the liver and to observe human cardiac magnetic fields. Results show that human hepatic iron content can be measured by exploiting the unusual magnetic properties of ferritin and hemosiderin. These iron storage compounds are easily detectable because they increase a magnetic field, whereas most other biologic materials decrease a magnetic field.

In patients studied to date, this technique has been superior to such indirect techniques as measurement of serum ferritin and transferrin saturation. When compared to chemical measurements performed on biopsy specimens, the magnetic method shows close agreement over a range of iron concentrations up to 30 times normal. For persons with increased iron stores, measurements by magnetic techniques are equal to chemically determined values, plus or minus 15 percent.

Although designed for hepatic measurements, the SQUID has also been used for initial observations of cardiac magnetic properties. Cardiac studies are complicated by the proximity of the lungs, the generally lower values of iron concentration found in the heart, the much smaller mass of iron-bearing tissue, and the motion of the heart. This project has developed the first clinical diagnostic procedure using superconduction technology.

Gene for Erythropoietin Cloned

For a number of years, basic research in hematopoiesis and clinical research in treatment of certain anemias was impeded by the lack of purified preparations of the hormone erythropoietin. From 1977 to 1980, the NHLBI sponsored research on purification of erythropoietin that resulted in a long-standing program of distribution. This program has recently been terminated because of the availability of commercial preparations. Attempts at biochemical methods of purification, however, have met with limited success. The commercial products are impure and unsuitable for use in humans.

It has been recently reported that the gene for erythropoietin has been cloned and expressed in vitro. The protein product appears to have biologic activity. This advance will permit more detailed biochemical studies of the hormone, the development and application of sensitive radioimmunoassays, and potentially a new therapy for patients with anemia of chronic renal failure.

Clinical Advances Result From a New Assay for Erythropoietin

Erythropoietin is a hormone produced by the kidney in response to an increased need for oxygen by body tissues. Its primary function is to stimulate the production of red blood cells. Purification of the hormone rapidly led to the development of an assay method that enabled scientists to study in detail the

molecular and cellular mechanisms of red blood cell differentiation.

The sensitivity of the assay has facilitated important clinical investigations, such as understanding the anemia associated with renal failure in adults and children and determining whether erythropoietin has clinical value in treating this form of anemia; determining the etiology of erythrocytosis; understanding how maternal diabetes alters the production of blood cells in the developing fetus; relating cord-blood erythropoietin levels to bilirubin production (a cause of jaundice) in infants of diabetic mothers; understanding anemia in premature infants; and assessing the effects of oxygen inhalation in sickle cell anemia patients.

The erythropoietin assay may eventually become a standard clinical test to aid in the determination of the causes of anemia.

Success of the Erythropoietin Distribution Program

For over 20 years, the NHLBI has provided human urinary erythropoietin to hundreds of qualified scientists throughout the world. This scarce hormone is responsible for stimulating the production of red blood cells. The program was undertaken to encourage and foster research on erythropoiesis at a time when few investigators were involved. As a result of these efforts, the field has blossomed. The availability of commercial sources of human erythropoietin has led to a decision to discontinue the erythropoietin distribution program as of January 31, 1984.

SICKLE CELL DISEASE

Sickle cell disease is a chronic condition characterized by accelerated destruction of red blood cells and resulting in acute and chronic damage to various body organs. These clinical manifestations are caused by the presence of an abnormal hemoglobin (Hb S) leading to crescent-shaped, "sickled" red cells. Sickled red cells have difficulty traversing the small blood vessels and tend to occlude them. The occlusions impair circulation, which causes tissue damage and painful crises. A hereditary disorder, sickle cell disease can markedly shorten life. Milder symptoms and greater longevity are encountered in certain genetic variants of sickle cell disease (Hb S-C disease, Hb S-thalassemia).

Sickled red blood cells block blood flow in capillaries.

Understanding sickle cell disease requires basic research at the cellular and molecular level, a search for genetic and environmental factors that may determine its incidence, the creation of improved methods of diagnosis and management, and delineation of strategies for prevention and treatment. Programs of information, education, screening, and counseling are being devised and widely implemented to increase the awareness and understanding of the disease by the general public, by patients and their families, and by health care professionals.

New Method Developed to Assess Splenic Function in Sickle Cell Disease

It has long been recognized that children with sickle cell disease have a high mortality rate in early life. The predominant cause of death among these children is overwhelming infection from *Streptococcus pneumoniae*. This problem has persisted, with no apparent change in survival rates.

This increased susceptibility to overwhelming infection is related in large measure to a loss of splenic function in the first 3 years of life. In the past, spleen scans using ^{99}mTechnitium colloid (^{99}mTC) were the primary technique for assessing splenic function. A noninvasive approach has now been established that is sensitive and that correlates with the accuracy of findings by spleen scans.

Splenic function has been assessed in over 2,000 patients with the use of ^{99}mTC scans and of the enumeration, with interference-phase contrast microscopy, of "vesiculated" red blood cells. The presence of more than 3 to 5 percent of vesiculated red cells correlates with functional hyposplenia as defined by ^{99}mTC scans. Delineation of spleen function by hemoglobin genotype reflects the relative susceptibility, based on the percentage of vesiculated red cells, to overwhelming infection.

This technique is sensitive, economical, and expeditious, and it provides semiquantitative information. More importantly, it affords clinicians a reliable noninvasive procedure to measure splenic function and affords the opportunity for early protective intervention.

Time and Cost of Prenatal Diagnosis of Sickle Cell Disease Decreased

The abnormal hemoglobin molecule present in sickle cell anemia results from the substitution of the amino acid valine for glutamic acid at position 6 of the beta hemoglobin chain. Recent developments in DNA technology have made it possible to diagnose sickle cell anemia by analysis of DNA from fetal cells obtained by amniotic fluid. Initially, the test required a culture of the amniotic fluid, which was a lengthy and costly process. Collection of fetal cells also posed some risk to the fetus. The assay was based on the demonstration that a particular enzyme could recognize the DNA base change responsible for the amino acid substitution in the beta chain of sickle cell globin. Since the enzyme splits DNA at the specific point of the mutation, it was theorized that this enzyme assay could be used to test all couples at risk. However, the test lacked specificity and required an amount of DNA that necessitated culturing amniotic fluid cells.

Recently, an assay using a different enzyme has successfully diagnosed prenatal sickle cell anemia. Because it does not require amniotic cell culture, the time for diagnosis is reduced from 5 weeks to 2 weeks, with a considerable reduction in cost.

Fetal Hemoglobin Production Increased With 5-Azacytidine

Fetal hemoglobin includes the alpha chains found in all adult hemoglobins and also gamma chains. Fetal hemoglobin is generally not synthesized after birth. However, if synthesis could be stimulated, cells with fetal hemoglobin could successfully perform the oxygenation functions that are impaired in sickle cell disease and Cooley's anemia. Scientists have therefore been studying ways to preserve the high levels seen in the fetus and young children or to reverse the "switch" to adult hemoglobin.

On the basis of the results of animal studies, clinicians have recently treated several severely ill sickle cell or Cooley's anemia patients with 5-azacytidine. Within 3 to 5 days after administration, there was a rapid increase in F-cell production, which lasted for approximately 30 days. These changes were accompanied by a transient increase in fetal hemoglobin (Hb F) per F cell, increased percent Hb F and percent F cells, increased total hemoglobin, and an increase in the patient's mean corpuscular volume of erythrocytes. Although no toxic side effects have occured, a major concern about this drug is its mutagenic and carcinogenic potential. Although these preliminary findings do not permit conclusions about clinical efficacy, they are considered an exciting link between theory and therapy.

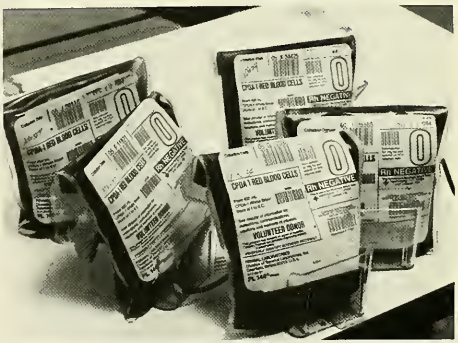
Enzyme Inhibitor Makes Possible Oral Administration of 5-Azacytidine

Administration of 5-azacytidine has been reported to increase the level of fetal hemoglobin in sickle cell anemia and alpha-thalassemia, but unfortunately, the drug has to be administered by injection because it is inactivated by the enzyme cytosine deaminase when it reaches the gastrointestinal tract.

Tetrahydrouridine is a potent inhibitor of cytosine deaminase, and it has been administered to experimental animals, along with 5-azacytidine. The results of these studies indicate that 5-azacytidine is effective orally when administered in this fashion. In addition, lower doses of 5-azacytidine can be used to achieve elevations of fetal hemoglobin similar to those seen with higher doses administered by injection.

BLOOD RESOURCES

Blood resources for the Nation are essential for surgery and for the effective treatment of many diseases. Whole blood is made up of formed elements dispersed in a fluid medium, plasma, and consists of red cells that deliver oxygen, platelets that stop bleeding, and white cells that fight infection. Plasma contains such useful products as albumin, immunoglobulins, and clotting factors.



Red blood cells, separated from volunteer-donated whole blood, are often used for transfusion to treat anemia.

The safety and availability of blood and blood products are critically important. Research in this program area is focused on the safety of transfused blood products, particularly with the incidence of transfusion-transmitted hepatitis and the potential involvement of chronic transfusions in the transmission of acquired immune deficiency syndrome; improvement of methods of separating, preparing, and

preserving blood components and derivatives; development and clinical trials of blood substitutes; elucidation of the structure and functions of blood group antibodies and antigens as a means of eliminating transfusion reactions; and improved management of the supplies of high-quality blood and blood products and blood substitutes so that they are available when and where they are needed.

Simian Acquired Immune Deficiency Syndrome Transmitted Through Blood

The discovery of a simian disease (SAIDS) that mimics certain aspects of human acquired immune deficiency syndrome has provided the scientific community with a potentially invaluable animal model to study this syndrome.* SAIDS is characterized by a profound acquired immune deficiency involving both T- and B-cellular components of the immune system. The disease is accompanied by the emergence of a spectrum of opportunistic pathogens similar to those in human patients. Epidemiologic studies of SAIDS suggest that close intimate contact is a key element in transmission.

Recently, SAIDS was transmitted to normal rhesus monkeys by inoculation with heparinized whole blood or plasma from diseased monkeys. The specimens were passed through filters of 0.45 micrometer pore size before inoculation. A retrovirus has been isolated from the plasma of monkeys with SAIDS. Retrovirus infection is known to cause leukemia, lymphomas, and solid tumors in several species of animals and T-cell malignancies in humans, and it has also been shown to result in immune deficiency in cats infected with feline leukemia virus. The retrovirus from the plasma of SAIDS monkeys has been purified and inoculated into several animals. Efforts are now being made to characterize this agent and to determine its role, if any, in the etiology of SAIDS.

Transmission of Acquired Immune Deficiency Syndrome Studied in Chimpanzees

The similarity of patterns of transmission in AIDS and in hepatitis B and hepatitis non-A, non-B suggested that the chimpanzee model, so valuable in hepatitis research, might also serve to prove the existence of a transmissible agent in AIDS. Using the chimpanzee model, investigators supported by the NHLBI are now attempting to demonstrate the presence of a transmissible agent in the plasma or lymphocytes, or both, of AIDS patients. If bloodborne tranmission is documented, stored plasma and lymphocytes can serve as the starting point for viral isolation, biophysical characterization, and serologic analysis of the presumed agent.

*Between the time this report was submitted and the time of publication, research on AIDS advanced considerably. These advances will appear in the *Twelfth Report of the Director, NHLBI.*

Immunologic Status of Frequently Transfused Patients Studied

The acquired immune deficiency syndrome epidemic continues to be a major public health problem that affects primarily certain high-risk groups—namely, homosexual men, intravenous drug abusers, Haitians, and patients with hemophilia. The clustering of AIDS among users of commercial clotting factor concentrates suggests that the disease may be transmitted to hemophilia patients through these infusions. In addition, heavily treated hemophilia patients without clinical evidence of AIDS have shown alterations of the immune system similar to the alterations observed in AIDS patients.

Some recent investigations have revealed that patients with thalassemia and sickle cell anemia who are receiving transfusions of washed red cells have normal immune function or immune markers whereas patients with hemophilia who receive commerical factor VIII concentrates have a high frequency of immunoregulatory defects. In addition, several investigators have reported alterations in immune markers in patients with sickle cell disease. Also of great interest is the finding that a significant number of the hemophiliacs tested had antibodies to cell membrane antigens associated with human T-cell leukemia virus (HTLV). Antibodies to HTLV were not detected, however, in thalassemia major patients, sickle cell disease patients, and controls. Further analyses will be made of blood specimens from additional thalassemia and sickle cell disease patients, and hemophiliacs treated with cryoprecipitate will also be studied. This project will provide useful information on the incidence of immunoregulatory defects among patients requiring frequent transfusions of blood and blood products.

New Antibody Screening Test Developed to Detect Platelet Antibodies

After transfusion, clinically significant destruction of platelets can occur in the presence of antibodies of many different specificities. Methods exist to detect such antibodies in vitro, but they are impractical because they lack sensitivity, speed, and simplicity.

A new thrombocytotoxic antibody test has been developed, which is simple, fast, and sensitive. In addition, it requires only very small quantities of reagents. The test has the potential for use in large-scale screening of transfusion recipients.

New Field of Transfusion Medicine Encouraged

During the last two decades, significant changes occurred in many areas related to blood resources. Treatment evolved from simple—but not always safe—transfusion of whole blood for emergency replacement, to the use of multiple blood components and derivatives for a large number of acute and chronic complex disease states. Sophisticated technology that permits the collection of specific components from the circulation also allows for the selective removal of excessive components and protein complexes from the circulating blood of patients. A great gap has developed, however, between the rapidly expanding knowledge base in this field and its clinical use by trained physician-investigators. Few medical schools are providing systematic instruction in transfusion-related problems, and there is a general lack of formal mechanisms in which knowledgeable professionals coordinate teaching, research, and clinical responsibilities in this field.

To remedy this gap and to highlight transfusion medicine as a discrete discipline in academic medicine, the NHLBI has initiated an award program that is intended to encourage the development of effective multidisciplinary curricula in transfusion medicine through the continuum of medical education, to attract and develop faculty, students, and promising young physicians and scientists in the field, and to facilitate the exchange of information and educational techniques in the research, medical, and blood service communities. In response to the first announcement, 35 applications were received, and five awards were made during the first year of the program.

Chapter 4
The National Program: Future Directions

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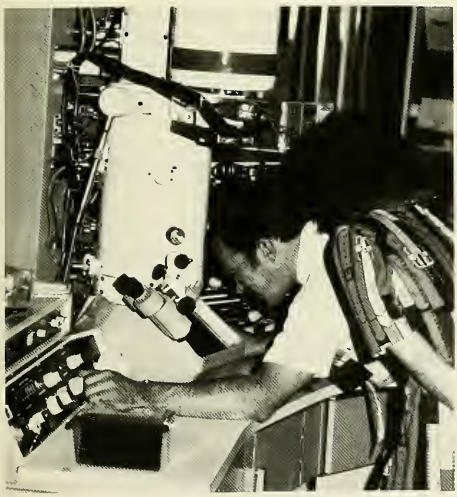
HEART AND VASCULAR DISEASES

Multidisciplinary heart and vascular disease research programs seek to expand the biomedical community's knowledge of the fundamental mechanisms of diseases of the heart and blood vessels. Clinical trials provide the opportunity to apply and evaluate research results in the treatment and prevention of cardiovascular disease. Understandings resulting from the new biology are thus ultimately translated into practical applications for disease management. Research plans for each of the 10 program areas are described below.

Arteriosclerosis

To improve diagnosis, treatment, and prevention of arteriosclerosis and its consequences, it is necessary to obtain a better understanding of the basic processes involved in this disorder. Toward that end, future research goals are to:



Electron microscopy permits visualization of intracellular structures.

- Elucidate further the basic pathogenetic mechanisms of atherosclerosis at the tissue, cellular, and molecular levels, using all suitable mechanisms and techniques, including those of cellular and molecular biology.
- Increase knowledge of the causal mechanisms and associated risk factors that play important roles in atherogenesis.
- Improve comprehension of the natural history of arteriosclerosis in all vascular regions in humans, utilizing innovative methods of research, and reassessing, with modern techniques, older studies.
- Improve understanding of the epidemiology of arteriosclerotic disease, data-gathering capability and analytic methods, and improve the predictive capability for all populations.
- Develop improved minimally invasive and noninvasive methods for detection of atherosclerosis in various regions of the vascular system.
- Expand investigations to ascertain the effectiveness of therapeutic interventions to reduce or prevent atherosclerosis.
- Elucidate the roles of behavior as they relate to the etiology, pathogenesis, treatment, and prevention of arteriosclerosis and related diseases.

Hypertension

Research goals targeted towards understanding the etiology and pathogenesis of hypertension and improving treatment and prevention will include:

- Conduct further fundamental research on the etiology and pathogenesis of hypertension, including investigations of neural, humoral, genetic, and environmental factors, with emphasis on interdisciplinary approaches.
- Investigate, in all age groups, the influence of familial, genetic, and environmental factors in the determination of blood pressure levels in order to establish the relative importance of the

multiple factors that contribute to the development of high blood pressure.

- Continue to develop and refine noninvasive technologies for measurement of blood presure and other relevant parameters related to hypertension that can be used as needed for the evaluation of the health status of persons with high blood pressure.
- Continue to improve pharmacological and nonpharmacological methods for the long-term management of hypertension, and evaluate for each their relative roles in terms of benefits and risks; and continue to study the benefits and risks of blood pressure reduction in elderly individuals with systolic hypertension.
- Continue to improve the control of high blood pressure in the population, especially in segments of the population where the disease is prevalent, through demonstration and educational activities.
- Continue research and development programs that attract and sustain high-caliber hypertension research investigators to maintain progress against this disease.

Cerebrovascular Disease

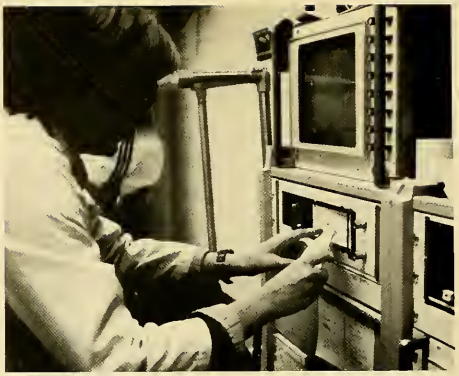
As a means of decreasing the incidence of stroke through studies of the pathology and pathogensis of cerebrovascular disease and its prevention, research goals are to:

- Improve the fundamental understanding of the nature of lesions of the vessels of the head and neck that lead to stroke, with a view towad improving the diagnosis, prediction, treatment, and prevention of cerebrovascular disease.
- Conduct further epidemiological studies of risk factors of cerebrovascular disease.

Coronary Heart Disease

A primary mission of the program is to develop improved therapy, rehabilitation, diagnosis, understanding, and prevention of the mechanisms that result in symptomatic coronary heart disease. The major goals of the program are to:

- Improve the understanding of the fundamental pathogenetic mechanisms involved in coronary heart disease and its various manifestations, including sudden death.
- Develop and refine methods for use in diagnosis and in estimating prognosis in patients with asymptomatic and symptomatic coronary heart disease.



New laboratory technology permits sophisticated diagnostic methods for coronary heart disease.

- Develop and refine medical and surgical interventions for the treatment of acute coronary events and chronic ischemic heart disease.
- Identify factors that are involved in the pathophysiology of coronary heart disease and the transition from latent to overt CHD.
- Improve the rehabilitation of patients with coronary heart disease.
- Enhance methods to reduce or prevent new and recurrent myocardial infarction.
- Continue to support research on the mechanisms underlying arrhythmias in myocardial ischemia.
- Continue development of reliable methods of studying the coronary collateral circulation in humans and the factors influencing its development.
- Elucidate profiles of individuals at enhanced risk of first myocardial infarction and of postmycardial infarction sequelae in order to develop means of risk reduction in these groups.
- Study the phenomenon of silent myocardial ischemia and its prevalence and significance.

Peripheral Vascular Disease

To improve the prevention, diagnosis, therapy, and understanding of the mechanisms causing peripheral arterial and venous diseases, program goals are to:

- Promote fundamental research on the nature, etiology, and pathogenesis of disorders of the peripheral arteries, veins, and lymphatics.
- Develop further and refine methods to diagnose peripheral vascular disease.

Arrhythmias

To diagnose, manage, and prevent arrhythmias and other electrical disturbances of the heart, anticipated research will:

- Identify further the fundamental electrophysiologic mechanisms of normal and ischemic myocardium and their relationship to arrhythmias and sudden death.
- Develop and refine methods useful in identifying individuals in all age groups at risk of arrhythmias and sudden death.
- Improve the understanding of the role of the nervous system in the pathogenesis of cardiac rhythm abnormalities.
- Develop and refine medical and surgical interventions to reduce or prevent sudden death in high-risk populations.
- Encourage multidisciplinary studies of cardiac rhythm in both the normal and diseased heart.

Heart Failure and Shock

The mission of this program is to minimize heart failure associated with and following heart attack by enhancing the survival of damaged heart muscle as well as that associated with hypertension or with valvular disease by improved treatment and prevention. Planned research projects are to:

- Improve the understanding of the basic mechanisms and the natural history of heart failure and shock.
- Improve the techniques for the clinical detection, treatment, and prevention of heart failure and shock.

Congenital and Rheumatic Heart Diseases

To understand better the causes of congenital heart disease, to improve diagnosis and therapy, and to rehabilitate patients with these diseases, especially newborns, research goals are to:

- Improve the understanding of the genetic and environmental factors involved in the pathogenesis of various congenital cardiac malformations.
- Develop and refine methods for accurate diagnosis and curative or palliative therapy for patients with congenital heart disease.
- Explore the fundamental etiology and pathophysiology of valvular heart disease.
- Develop and refine medical and surgical interventions for valvular heart disease.

Cardiomyopathies and Infections of the Heart

The research goal in this program area is to:

- Develop and refine methods to prevent, diagnose, and treat the various cardiomyopathies and infections of the heart.

Circulatory Assistance

The primary research objective in this program area is to:

- Develop effective, safe, and reliable cardiac assist and total cardiac replacement devices for partial or total assumption of heart function.

LUNG DISEASES

Elucidation of the basic biological mechanisms, in health and disease, of the various types of lung cells will lead to a better understanding of how to diagnose and manage the lung disorders that afflict millions of Americans. The future directions for research supported by the NHLBI are outlined under the six National Program areas that it encompasses.

Structure and Function of the Lung

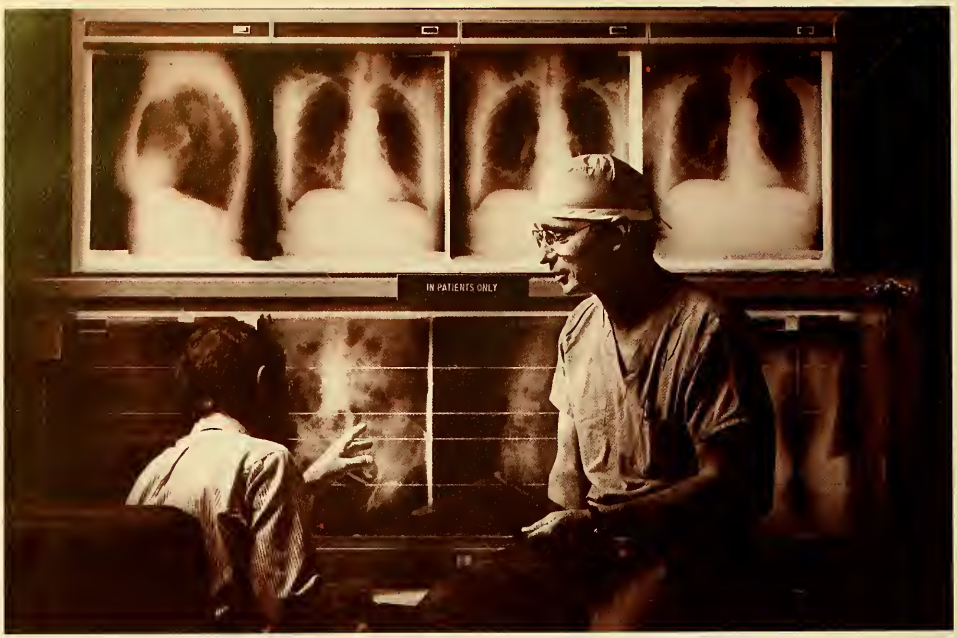
Research goals are to:

Lung Cell Biology

- 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.

Ventilatory Function

- Improve the understanding of gas exchange and transport from the environment to the cell, of utilization of oxygen at cellular and subcellular levels, and of alterations in gas exchange and transport associated with various stresses such as exercise, high altitude, hyperbaria, and endogenous disturbances.
- Elucidate respiratory macro- and micromechanics in normal and disease states and of respiratory and circulatory interactions.
- Improve the understanding of the roles of chemical, mechanical, and neural factors in control of normal ventilation during selected states and situations such as sleep, exercise, and high altitude.



Lung x-rays facilitate diagnosis of pulmonary diseases.

Nonventilatory Lung Function

- Elucidate the metabolic activities of the lung, including the surfactant system and the defense functions of the lung against exogenous insults and endogenous disturbances.

Growth and Development of the Lung

- Increase the understanding of the ventilatory and nonventilatory functions of the immature respiratory system and their response to endogenous and exogenous insults.

Chronic Obstructive Pulmonary Disease

Increased understanding, improved management, and prevention of chronic obstructive pulmonary disease wll be gained by research goals to:

- Elucidate basic mechanisms involved in structural and functional derangements associated with the onset and progression of chronic bronchitis and emphysema.
- Identify presymptomatic stages, critically assess current therapeutic measures, and develop more effective regimens.
- Further understand individual risk factors, their interactions, and their roles in the etiology and pathogenesis of these disorders.
- Elucidate underlying mechanisms in bronchoconstriction, and develop more effective measures to ameliorate or prevent the brochoconstrictor response in asthma.

Pediatric Pulmonary Diseases

Further research progress in the area of pediatric pulmonary diseases will be stimulated by studies to:

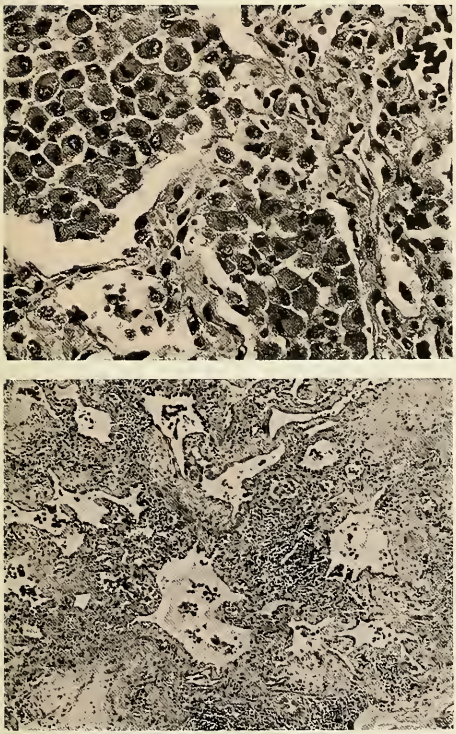
- Improve detection, management, and prevention of neonatal respiratory disorders and their sequelae.
- Identify the basic mechanism(s) of the defect in cystic fibrosis that leads to pulmonary disease.
- Characterize the early pathogenetic changes of cystic fibrosis through study of structural and functional derangements in the lung.
- Improve management of cystic fibrosis through critical assessment of current modes of therapy and development of new regimens.
- Increase the understanding of the pathophysiologic features of bronchiolitis and the

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

Occupational and Immunologic Lung Diseases

Research goals that will lead to the development of better methods for the detection, prevention, and treatment of occupational and immunologic lung diseases are:

- 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 and improve the management of these diseases by the identification of etiologic agents and other risk factors, early detection of disease, and development and improvement of therapeutic regimens.



Early idiopathic pulmonary fibrosis (upper photo) showing inflammation and early fibrosis; late-stage idiopathic pulmonary fibrosis (lower photo), loss of alveolar spaces, and severe inflammation and fibrosis.

Respiratory Failure

Reduction in death and disability from respiratory failure will be achieved through a better understanding of acute lung injury. Specific objectives are to:

- Elucidate intrinsic structural, biochemical, and physiological mechanisms of acute lung injury that lead to respiratory failure.
- Improve management of acute respiratory failure by developing measures to detect, arrest, or reverse degenerative changes following lung injury.

Pulmonary Vascular Disease

Continuing inquiry into the pathophysiology of pulmonary edema, pulmonary hypertension, and pulmonary thromboembolism will:

- Elucidate the mechanisms controlling fluid and solute exchange and hemodynamics in the normal and diseased pulmonary circulation.
- Improve the management of pulmonary vascular diseases through the development of noninvasive diagnostic techniques and are effective therapeutic regimens.

BLOOD DISEASES AND RESOURCES

The basic functions and the development of blood cells are becoming clearer as methods of the new biology are being applied. Recombinant DNA techniques, for example, can be used to study blood coagulation and fibrinolytic proteins. Planned research directions in the four blood diseases and resources program areas are outlined below.

Bleeding and Clotting Disorders

As a guide for future research into thromboembolic disorders, platelet disorders, and hemorrhagic disorders, anticipated goals of investigation into bleeding and clotting disorders are to:

- Elucidate the roles of soluble clotting factors and inhibitors, platelets and their secreted products, and the blood vessel wall in the hemostatic mechanism.
- Explore the interactions of the components of the clotting system and other body defense systems.
- Develop and test anticoagulants, platelet inhibitors, and thrombolytic agents to prevent and treat clotting disorders.

- Develop new knowledge of platelet function in human disease.
- Improve diagnostic techniques and develop more specific therapies for platelet disorders.
- Develop a better understanding of the genetic and pathologic mechanisms underlying hemophilia and other bleeding disorders, and characterize the coagulation factors involved.
- Develop improved diagnostic techniques and better therapies for hemorrhagic disorders.

Red Blood Cell Disorders

To develop and support activities to reduce the morbidity and mortality caused by disorders of the red blood cell so that ultimately they can be prevented, research goals are to:

- Elucidate the structure, function, and rheologic properties of the red blood cell membrane during acquired and congenital hemolytic disorders.
- Clarify the metabolic and transport systems of the erythrocyte in health and disease.
- Develop better understanding of normal erythropoiesis.
- Apply knowledge of normal erythropoiesis to diseases of abnormal bone marrow function, with the specific objective of diagnosis, treatment, and prevention of nonneoplastic hematopoietic disorders.
- Elucidate the structure and function of hemoglobin and the globin genes in health and in the various hemoglobinopathies.
- Develop improved techniques for the diagnosis, treatment, and prevention of the thalassemia disorders, with particular emphasis on Cooley's anemia.

Sickle Cell Disease

Reduction of both morbidity and mortality from sickle cell disease will be achieved through research and development at both the fundamental and clinical levels; the initiation and expansion of community education, screening, and counseling programs; the education of medical and allied health professionals; and the improvement of care for patients with sickle cell anemia.

Specific long-range objectives of the sickle cell disease program are to:

- Elucidate the pathophysiology of sickle cell disease at both the cellular and molecular levels by investigating the structure and function of the sickle hemoglobin polymer, flow properties of the red cells, kinetics of polymerization, and the role of the erythrocyte membrane.
- Clarify genetic and environmental determinants that control the synthesis of fetal hemoglobin (Hb F) in erythroid ceils, with the ultimate goal of augmenting Hb F in human erythrocytes.
- Increase the understanding of impaired immune function and increased susceptibility to infections, and improve methods for their prevention and treatment.
- Develop new and improved methods of diagnosis.
- Create effective therapeutic agents for the treatment of sickle cell disease.
- Promote understanding of the clinical and psychosocial aspects of sickle cell disease and develop approaches to management.
- Increase the awareness and understanding of sickle cell disease by the general public, patients and families, and health care professionals through information, education, screening, and counseling programs.

Blood Resources

To assure the efficient use of, and access to, an adequate supply of high-quality blood and blood products for everyone in need, the NHLBI plans to develop and support activities in five subprogram areas. Their specific goals are to:

Blood Component Therapy and Blood Derivative Therapy

- Improve methods for separation, preparation, and preservation of blood components and derivatives.

Safety of Blood Therapy

- Determine if acquired immune deficiency syndrome is transmitted by blood, and, if so, develop means to prevent such transmission.
- Prevent morbidity and mortality from transfusion-transmitted hepatitis and other transfusion-associated infections.

Immunohematology

- Elucidate the structure and functions of blood group antibodies and antigens, the Rh complex of red cells, and red cell antibody and complement interactions as a means of eliminating hemolytic and nonhemolytic transfusion reactions.

Blood Substitutes

- Develop and test the safety and efficacy of substitutes that perform certain functions of blood so that they can be used as supplements to natural blood or blood products.

Blood Resource Management

- Aid nationwide and regional efforts to enhance access to an adequate supply of high-quality blood, blood components and derivatives, and blood substitutes for everyone in need.

Chapter 5
Resource Allocation

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The National Heart, Lung, and Blood Institute is the focal point of the Federal Government's investment in the National Heart, Blood Vessel, Lung, and Blood Diseases Program, mandated in 1972 and expanded in 1976 to include blood resources. In response to these mandates, the Institute's programs have grown over the past 11 years, and now include, in addition to the fields encompassed by the 1972 National Program, the following areas of responsibility: lung diseases, sickle cell disease, clinical trials, high blood pressure education, blood diseases, national research and demonstration centers, blood resources, blood banking, and prevention, education, and control programs.

Earlier chapters of this report have discussed how the Institute's balanced program of research activities has made progress in improving the health of the Nation in the areas of the Institute's concern and how the Institute plans to sustain the momentum of its programs during the coming year. This chapter discusses the allocation of the Institute's resources in support of continued research and in the development of qualified investigators.

In the spring of 1982, the National Heart, Lung, and Blood Advisory Council expressed its concern for the future of biomedical research and research training in light of fiscal trends in the preceding years. In particular, the Council felt that if trends were to continue, the number of funded research project grant applications might fall below 25 percent of those approved, and the viability of the research program supported by the NHLBI might be undermined, especially by reducing investigators' opportunities to initiate and complete timely research programs and by deterring promising persons from entering research careers and academic medicine.

In response to this concern, the Council scheduled four public briefing meetings in the late winter and early spring of 1983, to be held in Washington, D.C., San Francisco, New Orleans, and Chicago. The purpose of these meetings was to inform biomedical scientists, administrators, volunteer health organizations, and the public about possible strategies for achieving and maintaining a balance of program mechanisms and for protecting the number of research grants awarded by the Institute.

Short- and long-term strategies were discussed at the meetings, and two different—not necessarily conflicting—points of view emerged: the first seeks to keep the largest number of laboratories in operation and to fund the largest number of qualified scientists working in them; the second envisions full funding for projects of scientific merit, through existing and improved processes, at the risk of delaying or losing some excellent projects.

Regardless of these differing points of view, many participants in the meetings felt that the adequacy of funding at the Federal level had never been appropriately addressed, and that it should be. Of special concern to some attendees was the small number of physician investigators. One suggestion was to fix the level of support for a given area (for example, biomedical research) at a percentage of the Nation's total health expenditure. A fixed rate of 4 to 5 percent, which is less than industry invests in research and development, would represent a conservative level.

The NHLBI remains committed to supporting a balanced program of research and prevention activities and to investing in the development of highly trained biomedical investigators, so that the momentum of progress against heart, blood vessel, lung, and blood diseases will not falter. In response to the concerns expressed by the National Advisory Council and by the participants in the public briefing meetings, the Institute is currently in the process of developing new techniques to ensure that research opportunities are fully exploited.

Maintaining Research Support

In 1972, the year in which the National Heart, Lung, Blood Vessel, and Blood Act was passed, the Institute's appropriation was $232.6 million. In 1983, the Institute's appropriation rose to approximately $624 million. Table 12 provides NHLBI-projected resource allocations for the National Program for fiscal year 1985 through fiscal year 1989. These funding levels reflect expansion in the Institute's program responsibilities and include resources necessary to keep pace with anticipated inflation. The estimates of future needs are based on NHLBI professional

Table 12—Projected Resource Allocation for the National Program, 1985 to 1989* (dollars in millions)

	Fiscal Year				
	1985	1986	1987	1988	1989
Extramural Research Programs					
Heart and vascular diseases	$405.4	$445.9	$490.5	$539.5	$593.5
Lung diseases	114.8	126.3	138.9	152.8	168.1
Blood diseases and resources	119.9	131.9	145.1	159.6	175.5
Prevention, education, and control programs	71.9	79.1	87.0	95.7	105.3
Research manpower development	63.1	66.9	70.9	75.2	79.7
Construction	6.6	9.8	13.5	17.6	22.4
Total extramural research programs	$781.7	$859.9	$945.9	$1,040.4	$1,144.5
Intramural research	65.9	69.9	74.0	78.5	83.2
Research management and support	43.9	46.5	49.3	52.3	55.4
TOTAL, NHLBI	$891.5	$976.3	$1,069.2	$1,171.2	$1,283.1

*Dollar values represent professional judgment by NHLBI and not official administration policy. These tabulations give the primary thrust of activities, even though the activities generally involve more than one subprogram.

judgments and do not reflect competing priorities within the Department or the administration.

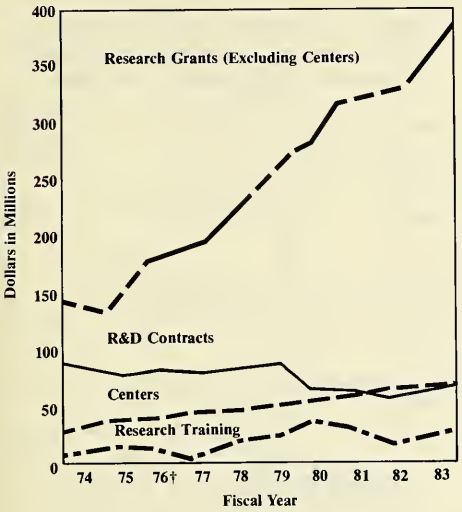
Figure 5 shows the trends in extramural research funding for the NHLBI for fiscal years 1974 to 1983 by grants, contracts, centers, and training. Funding of research grants increased from $148.3 million in 1974 to $384.4 million in 1983; specialized research centers increased from $31.2 million to $65.5 million; contracts decreased from $90.9 million to $61.1 million; and research training funding increased from $19.4 million to $26.6 million.

Table 13 compares NHLBI funding for 1974 and 1983 by budget mechanism and shows the dollars obligated in 1983 to research grants, centers, training, contracts, intramural research, and research management and support. This table reflects the Institute's efforts to preserve a full range of funding mechanisms for fundamental and clinical research, clinical trials, and demonstration, prevention, education, and training programs.

To meet its mandated responsibilities, the Institute's resources must keep pace with inflation and with advances in sophisticated scientific methodologies. Figure 6—NHLBI obligations in current and constant dollars, 1974 to 1983—shows the increase for extramural research in current year dollars from $290 million in 1974 to $538 million in 1984. In addition to inflation as measured by the standard cost-of-living scale, medical costs—including costs for biomedical research—have risen, leaving only a small real dollar value increase despite relatively large increases in the Institute's responsibility.

During this same period, the Institute has received an increasing number of meritorious research proposals. Figure 7—NHLBI competing research project grants: applications reviewed, approved, and awarded, 1974 to 1983—shows the more than 68 percent increase in current year applications reviewed (from 1,501 in 1974 to 2,519 in 1983) and 89 percent increase in applications recommended for approval

Figure 5—Trends in Extramural Research Funding: Research Grants,* Centers, Research and Development Contracts, and Research Training (Dollars Funded), NHLBI, 1974-1983



*Includes Research Career Programs
†Excludes Transition Quarter

(from 1,117 in 1974 to 2,110 in 1983). The increase in the disparity between approved and funded awards is also evident. In 1974, there were 662 awards among the 1,117 approved applications (59 percent). In 1983, 748 awards were made among the 2,110 approvals (35 percent). Figure 8—NHLBI competing research project grants: percent funded, 1974 to 1983—graphically displays the decline of funded projects.

Qualified Investigators

To attract promising investigators into research and academic careers, the Institute provides research training and career development opportunities. In the last decade, the Institute has implemented an array of training programs to ensure an adequate pool of researchers in the many scientific areas covered by its mandate. The programs have provided maximum flexibility and steady support in times of administrative and fiscal changes. Career development mechanisms used by the Institute include:

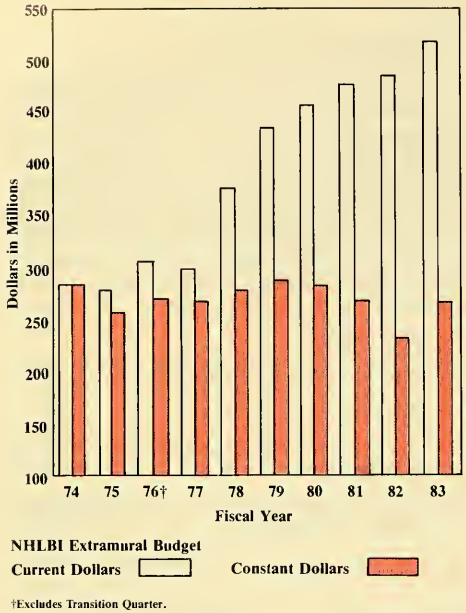
- Fellowships.
- Training grants to institutions.
- Minority training programs.
- Programs to bridge the transition from training to independent research.
- Career development programs for clinicians and academic investigators.

Table 13—NHLBI Actual Obligations by Budget Mechanism for 1974 and 1983

	1974		1983	
	$ Millions	Percent	$ Millions	Percent
Research grants	148.3	45	384.4	62
Centers	31.2	10	65.5	10
Training	19.4	6	26.6	4
Contracts	90.9	28	61.1	10
Subtotal extramural	289.8	89	537.6	86
Intramural laboratory and clinical research, and research management and support	36.4	11	86.5	14
Total	326.2	100	624.1	100

- Faculty traning and curriculum development for minority institutions or areas of science that are in need of additional investigators.

Figure 6—NHLBI Extramural Obligations in Current and Constant Dollars, 1974-1983



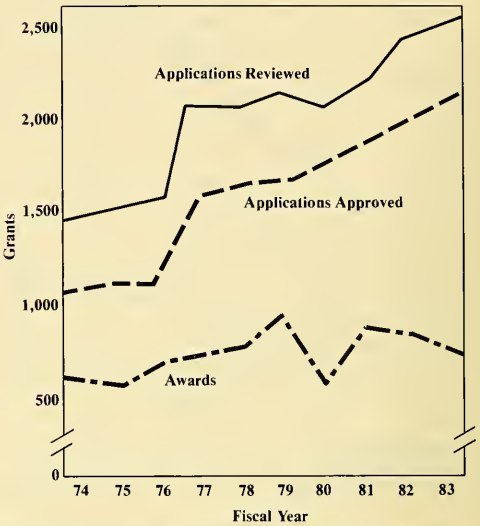
†Excludes Transition Quarter.

Figure 9—dollars expended by NHLBI on career development, fellowships, and training, 1974 to 1983—graphically displays funding in these areas.

Despite nearly level funding in terms of constant dollars for training and career development, the Institute has succeeded in training an increased number of individuals by adjusting program specifications to fiscal realities. Figure 10—full-time training positions for career development, fellowships, and training, 1974 to 1983—shows an increase in full-time equivalents from 1,357 in 1975 to 1,940 in 1983.

The National Research Service Award (NRSA) Act of 1974 repealed previous NHLBI training authorities. Earlier fellowships and training programs were phased out and replaced by awards to individuals, as well as awards to institutions, which in turn select and train postdoctoral, and in some cases predoctoral, candidates in specific research areas. Programs sponsored under the NRSA include Postdoctoral Individual Fellowships, National Research Service Awards for Senior Fellows, and Minority Access to Research Career (MARC) Awards for Faculty Fellows as individual awards. Institutional Fellowships include the Minority Hypertension Research Development Summer Award, long-term institutional awards, and Health Professional Student Short-Term and Summer Research Training.

Figure 7—NHLBI Competing Research Project Grants:* Applications Reviewed, Approved, and Awarded, 1974-1983



*Includes research project grants, new investigator awards, research program projects, and small business innovation research grants, which began in fiscal year 1983. Reflects release of fiscal year 1973 impounded funds.

Source: Division of Research Grants, NIH.

The Institute has also implemented career development awards to bridge the transition between training and independent research, programs to develop outstanding research capability and to expand the experience of clinicians and investigators beyond specific research projects, and programs for special needs such as curriculum development and correction of personnel shortages. These career development programs include the Research Career Development Award (RCDA) Program, Special Emphasis Research Career Awards (SERCA) in Diabetes Mellitus, Academic Invesitgator Awards, and Clinical Investigator Awards.

In addition to NRSA programs and career development programs, the Institute participates in or supports other related activities that develop investigators. Such activities include training workshops, minority biomedical research support,

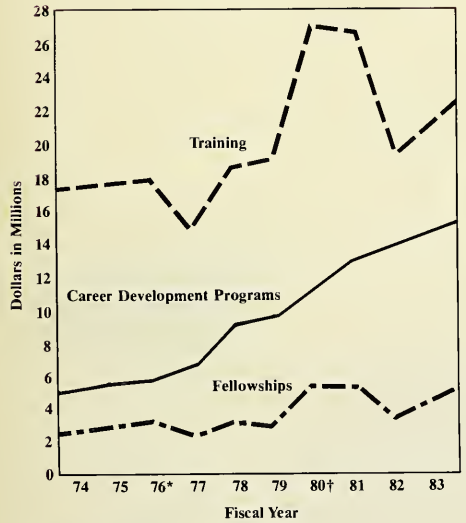
Figure 8—NHLBI Competing Research Project Grants: Percent Funded, 1974-1983

the extramural associates program, the young investigator award, staff fellowship programs, and the medical staff fellowship program.

Through the support of research training and development, career development, and other training-related activities, the Institute continues to participate, with other Federal entities, academic institutions, private industry, and other organizations, in the training of the Nation's future biomedical and behavioral scientists.

As existing opportunities for advances in research are exploited, a new wave of researchers, experienced in currently evolving techniques and methodologies, will be needed to spur the continued advance of knowledge against heart, blood vessel, lung, and blood diseases. Each of these areas has its special needs in research personnel. In recent years, the Institute has put considerable effort into ensuring that a new generation of researchers will be available to continue this work. The advances attained over the past 11 years in the treatment and prevention of heart and vascular diseases have been achieved in large part by investigators working in the rapidly expanding fields of biochemistry, biotechnology, cellular and

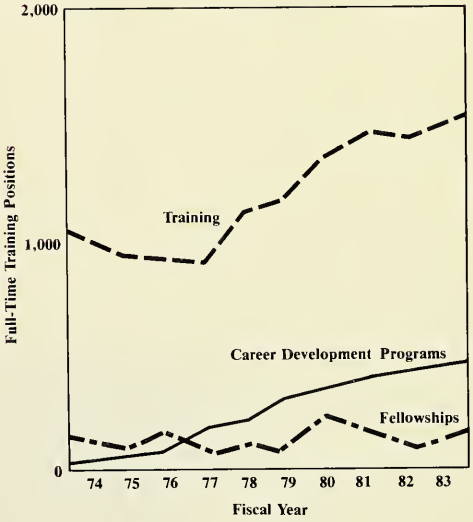
Figure 9—Research Training and Career Development Obligations, 1974-1983



* Excludes Transition Quarter.

† Stipend increase occurred in fiscal year 1980.

Figure 10—Number of Trainees (Full-Time Training Positions) for Research Training an Career Development Programs, 1974-1983



molecular biology, and enzymology. The need for basic researchers trained in the newest knowledge in these fields and adequately focused on the processes of atherogenesis, hypertension, and coronary heart disease is acute.

In the past 11 years, the field of pulmonology had to be rebuilt from the decline that followed the conquest of tuberculosis several decades ago. The requirement for more researchers in this virtually new field is critical, especially because, among the diseases in the purview of the NHLBI, only morbidity and mortality due to lung diseases continue to increase.

Research in blood diseases is achieving a new threshold of understanding of basic biochemical, molecular, and genetic processes. This understanding represents the frontiers of knowledge in these fields. At the same time, the Institute's mandate to manage the Nation's blood resources requires personnel trained to a new level of expertise: the transfusion medicine scientist is becoming a professional reality and a practical necessity if greater efficiency in blood resources management is to be achieved.

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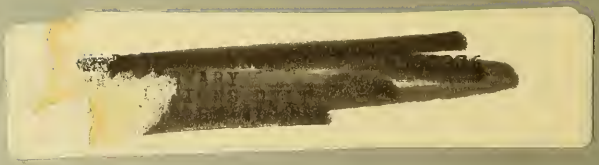

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