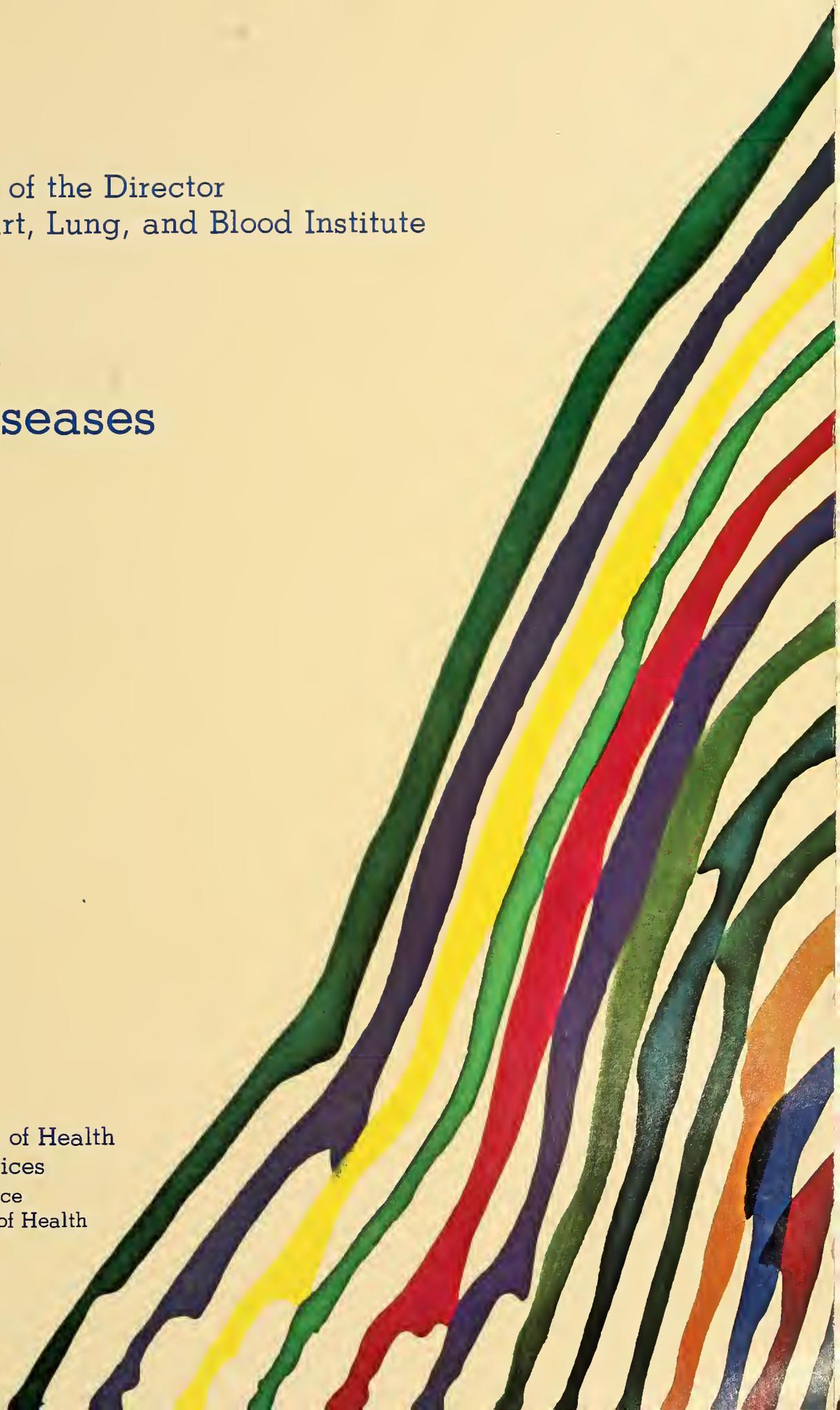


RC
681
N27774
1982
Nov.
v.3

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

Volume 3.
Lung Diseases

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



"Beta Kappa" by Morris Louis is reproduced with the permission of the National Gallery of Art, Washington, D.C. (gift of Marcella Louis Brenner, 1970).

Tenth Report of the Director
National Heart, Lung, and Blood Institute
Ten-Year Review and Five-Year Plan

Volume 3.
Lung Diseases

[Nov. 1982]

U.S. Department of Health and Human Services
Public Health Service
National Institutes of Health
NIH Publication No. 84-2358

Preface

The National Heart, Lung, and Blood Institute is now in its fourth decade, following its original establishment in 1948 as the National Heart Institute, (P.L. 80-655). With a growing awareness of national health problems over the years, such as those reflected in the President's Conference on Heart Disease and Cancer (April 21, 1961) and the President's Commission on Heart Disease, Cancer, and Stroke (December 9, 1964), it was redesignated by the Secretary of Health, Education, and Welfare (now Health and Human Services) as the National Heart and Lung Institute (NHLI) in 1969. The activities of the Institute were expanded in 1972 by the National Heart, Blood Vessel, Lung, and Blood Act (P.L. 92-423) to advance the national attack on diseases of the heart, blood vessels, lungs, and blood. With the passage of the Health Research and Health Services Amendments in 1976 (P.L. 94-278), in which the NHLI was redesignated as the National Heart, Lung, and Blood Institute (NHLBI), the authority was further enlarged to include research on the use of blood and blood products and on the management of blood resources.

The 1972 act was of special significance. The law mandated that the Director of the Institute, with the advice of its Advisory Council, develop a national plan for attacking heart, blood vessel, lung, and blood diseases. The need for the plan evolved from a recognition that isolated approaches were no longer appropriate to the growing magnitude of these public health problems. Twenty-eight task groups of approximately 250 medical and scientific advisors assessed the understanding of these problems and identified new opportunities for initiatives. The effort culminated in the five-volume National Heart, Blood Vessel, Lung, and Blood Program (DHEW Publ. Nos. (NIH) 73-515, 73-516, 73-517, 73-518, 73-519, 73-520, 73-521, 73-522, and 73-524). The needs, goals, recommendations, and strategies presented in the document provided a National Program, which for the past decade has been updated annually and has guided the Institute. The areas of interest include:

- Research on the epidemiology, etiology, and prevention of heart, blood vessel, lung, and blood diseases
- Research on basic cardiovascular biological processes
- Development and evaluation of techniques, drugs, and devices to aid diagnosis and treatment

-
- Programs to develop technological devices to assist, replace, or monitor vital organs
 - Field studies and large-scale tests relating to those diseases
 - Research on blood diseases and the use of blood resources in the United States, including such items as collection, preservation, fractionation, and distribution
 - Education and training of scientists and clinicians
 - Public and professional education programs in all aspects of those diseases
 - Programs to research and study heart, lung, blood vessel, and blood diseases of children.

The 1972 act also requires the Director of the Institute to submit an annual report to the President, for transmittal to Congress, on the accomplishments of the National Program during the preceding year and on plans for the next 5 years.

This five-volume Tenth Report of the Director, NHLBI, which is a 10-year review and 5-year plan, commemorates the 10th anniversary of the National Program. This volume reports on program areas of the Division of Lung Diseases. It begins with an executive summary and a description of the magnitude of the problem related to these diseases. Progress, achievements, and future goals are then reported in the following program areas:

- Structure and function of the lung
- Chronic obstructive pulmonary disease
- Pediatric pulmonary diseases
- Fibrotic and immunologic interstitial lung diseases
- Respiratory failure
- Pulmonary vascular disease.

The volume concludes with a discussion of research training and development.

Volume 1 serves as an executive summary of the other four volumes. Volume 2 reports on the program areas of the Division of Heart and Vascular Diseases, and volume 4 reports on programs of the Division of Blood Diseases and Blood Resources. The final volume contains a discussion of important companion issues, including international programs and program coordination and liaison.

The process by which these volumes were developed was modeled after the one used in 1972 for the National Program. Members of working and review groups were drawn from the NHLBI staff, the National Advisory Council and advisory committees, the extramural scientific community, the community of health providers and health consumers, and the general public.

Foreword

The Division of Lung Diseases of the National Heart, Lung, and Blood Institute serves as a focal point within the Institute for planning and conducting a coordinated research and personnel development program for all diseases of the respiratory system with the exception of lung cancer and infectious diseases of the lung, which are within the purview of the National Cancer Institute and the National Institute of Allergy and Infectious Diseases, respectively. The programs of the Division of Lung Diseases, which were identified in 1972 in accordance with the requirements of the National Heart, Blood Vessel, Lung, and Blood Act of 1972 (P.L. 92-423), are included in six major categories, which are viewed in this volume: structure and function of the lung, chronic obstructive lung diseases, pediatric pulmonary diseases, fibrotic and immunologic interstitial lung diseases, respiratory failure, and pulmonary vascular diseases.

This 10-year review and 5-year plan was prepared by the Pulmonary Diseases Advisory Committee with assistance from additional scientific consultants. Each section of the volume concludes with a specific listing of members of the community who participated. The contributions of all who worked so hard to develop this report are gratefully acknowledged by the Division of Lung Diseases.

The reports generated by the scientific consultants were edited by staff of the Division of Lung Diseases: Zakir Bengali, Ph.D., Dorothy Gail, Ph.D., Hannah Peavy, M.D., Sri Ram, Ph.D., Everett Sinnett, Ph.D., Richard Sohn, Ph.D., Hugh Stamper, Ph.D., Bitten Stripp, Ph.D., and Carol Vreim, Ph.D. Mrs. Barbara Liu prepared section 9, "Research Training and Development." Dorothy Gail, Ph.D., and Hannah Peavy, M.D., in collaboration with Thomas J. Thom from the Division of Heart and Vascular Diseases, prepared section 2, "Magnitude of the Problem."

The decade of the 1970's provided numerous research accomplishments that bring us closer to the goals of effective treatment and prevention of respiratory diseases. Although this report notes many of the important contributions that have been made, it is not intended to be inclusive, nor is it intended to suggest that the work that has been acknowledged is the most important. Nevertheless, we hope that the report will prove of

interest, and we feel confident that it will set the stage for further progress and accomplishments related to all diseases of the respiratory system.

Suzanne S. Hurd

Suzanne S. Hurd, Ph.D.

Contents

Preface	iii
Foreword	vii
1. Executive Summary	1
2. Magnitude of the Problem	7
3. Structure and Function of the Lung	31
4. Chronic Obstructive Pulmonary Disease	93
5. Pediatric Pulmonary Diseases	131
6. Fibrotic and Immunologic Interstitial Lung Diseases	169
7. Respiratory Failure	191
8. Pulmonary Vascular Diseases	217
9. Research Training and Development	247

Figures

1	Prevalence of Selected Chronic Respiratory Conditions, 1980	8
2	Percent Distribution of Deaths From Lung Diseases, 1978	18
3	Percent Change in Death Rates for the Leading Causes of Death, United States, 1968 to 1978	28
4	Changes in Age-Adjusted Death Rates for COPD for 1968 to 1978	29
5	Concepts of Control of Respiration in 1972	46
6	Concepts of Control of Respiration in 1981	49
7	Electron Micrograph Showing the Aggregated Surfactant and the Type II Cell.	66
8	Electron Micrograph of the Air-Blood Barrier of the Lung.	72
9	Mortality From Neonatal Respiratory Distress Syndrome	135
10	Child Receiving Oxygen Via Specially Developed Nasal Cannulae	143
11	Pulmonary Academic Award, Growth of Program, 1971 to 1982	269
12	Postdoctoral Research Trainees: MD-PhD Distribution, 1971 to 1981	277
13	DLD Manpower Programs: MD-PhD Distribution, 1979 to 1981	278

Tables

1	ICD Codes for Lung Diseases.	9
2	Estimated Economic Costs of Selected Lung Diseases; U.S., 1979	11
3	Mortality Trends for COPD; U.S., 1950 to 1980.	13
4	Number of Deaths From Selected Lung Diseases; U.S., 1978	15
5	Number of Deaths for Which Selected Lung Diseases Represent Underlying or Contributing Cause of Death; U.S., 1978	17
6	Mortality From the 10 Leading Causes of Death; U.S., 1981	17
7	Number of Short-Stay Hospital Discharges and Hospital Days for Selected Lung Diseases; U.S., 1979.	19
8	Number of Physician Office Visits for Selected Lung Diseases; U.S., 1979	21
9	Prevalence and Prevalence Rates for Selected Chronic Lung Conditions: Total and for Persons Limited in Activity; U.S., 1979	23
10	Disability Days for Selected Chronic Lung Conditions; U.S., 1979	24
11	Lung Host Defenses to Airway Challenges.	79
12	Conditions Associated With a Disorder in the Ventilatory Control System	156
13	Respiratory Disorders Associated With Pulmonary Hypertension	229
14	Personnel Shortage in Pulmonary Diseases, 1972	248
15	Clinical Training Programs, 1971 to 1972	249
16	Research Trainees, 1971 to 1972.	250
17	Division of Lung Diseases Personnel Development Program, Number of Positions Funded Directly by Institutional Grants, 1970 Through 1981.	253

Tables (continued)

18	Division of Lung Diseases Personnel Development Program, Number of Institutional Grants, 1970 Through 1981	255
19	NRSA Program, 1975 Through 1981, Number of Postdoctoral Trainees.	257
20	NRSA Program, 1975 Through 1981, Distribution of Physician Trainees by Specialty	257
21	NRSA Program, 1975 Through 1981, Distribution of Basic Scientist Trainees by Discipline	258
22	Lexicon of NRSA Disciplines.	259
23	NRSA Program, 1975 Through 1981, Distribution of Trainees by National Program Area.	260
24	NRSA Program, 1975 Through 1981, Trainees in Structure and Function of the Lung	261
25	NRSA Program, 1975 Through 1981, Trainees in Pediatric Pulmonary Diseases	262
26	NRSA Program, 1975 Through 1981, Trainees in Chronic Obstructive Pulmonary Disease.	263
27	NRSA Program, 1975 Through 1981, Trainees in Fibrotic and Immunologic Interstitial Lung Diseases	264
28	NRSA Program, 1975 Through 1981, Trainees in Respiratory Failure.	265
29	NRSA Program, 1975 Through 1981, Trainees in Pulmonary Vascular Diseases.	266
30	Pulmonary Training Programs, 1970 to 1981.	276

1. Executive Summary

Contents

EXECUTIVE SUMMARY.	1
BASIC RESEARCH	1
DIAGNOSIS.	3
PREVENTION	3
MANAGEMENT	5
RESEARCH TRAINING.	5

1. Executive Summary

Diseases of the lungs are among the leading causes of sickness and death in the United States. Bronchitis, asthma, and respiratory infections are among the common causes of absence from work; and because of their prevalence, chronic lung diseases, typified by emphysema, chronic bronchitis, asthma, and some occupational disorders, impose severe strains on the welfare and economy of the United States. In addition, pneumonia and pulmonary edema are frequent causes of death of patients with a wide variety of diseases that originate in organs other than the lungs.

During the past decade, important strides have been made in preventing and coping with some of these disorders. In the eight sections of the report that follows, these accomplishments are described in detail. An overview of some of the important advances is presented here. For convenience, they are presented in five categories: basic research, diagnosis, prevention, management, and research training.

Basic Research

New concepts and techniques in the basic sciences, particularly in cell and molecular biology, have greatly furthered research on the lungs and led to fresh understandings and new avenues for exploration. For example, the ability to isolate, purify, and culture lung cells, coupled with the technique of bronchoscopy, has reoriented and revitalized the study of the lung defense mechanisms, such as the immune and secretory mechanisms, and of the processes of lung injury and repair. These research areas, of major biologic interest in themselves, are also of potentially fundamental and practical importance for coping with chronic bronchitis, emphysema, cystic fibrosis, the respiratory distress syndromes, interstitial lung disease, and hypersensitivity disorders.

Morphologists have pioneered the exploration of the biology of the many cells found in the lung. Lung growth and development have begun to be explored with particular reference to factors that influence lung maturation and defense functions. Another fundamental concern of morphologists is to quantitatively relate the impairment of lung function, as measured by physiologic

techniques, to the anatomical derangements that result from inflammation and scarring.

Biochemists, in collaboration with physiologists, have moved forward along several fronts, examining the nature of mucus and surfactant and the mechanisms involved in bronchoconstriction and in the protection of the lungs against oxygen poisoning. Particularly noteworthy is the progress in describing the metabolism and function of the various pharmacologic mediators, as well as surfactant, the extraordinary lipid-protein substance that lines the gas-exchanging surfaces of the lungs and enables the lungs to function efficiently in the healthy individual. A deficiency or abnormality of the surfactant, as in adults and children with respiratory distress syndrome, may have disastrous consequences.

Among the new vistas opened during the past decade is the exploration of the nonrespiratory functions of the lungs. This research has disclosed the importance of the lungs in processing blood-borne substances that come into contact with pulmonary endothelium. The implications of this insight are monumental: first, the lungs have been found to play an important role in the overall body economy by providing vital substances such as converting enzyme that is central to the regulation of blood pressure; second, studies of the cells lining the pulmonary blood vessels have provided invaluable clues to the interactions of the vessel wall with blood constituents. This information is relevant to the processes leading to clotting and arteriosclerosis.

Physiologists have made progress in many areas. One is in the control of breathing in normal individuals and in patients with abnormalities of the lungs or chest wall or with sleep disorders. New discoveries have clarified the determinants of normal and abnormal patterns of breathing. How the lungs protect themselves by clearing mucus and debris has become much more intelligible. The concept of fatigue of the respiratory muscles has been clarified and examined in novel ways. This advance has led to a better understanding of the role of respiratory muscle fatigue in disability and death in a variety of clinical and experimental pulmonary disorders, and has promoted the development of strategies for its earlier detection and for the prevention of its untoward consequences. Disturbances of fluid and solute balance in the pulmonary circulation seem to underlie many devastating clinical disorders, and this knowledge has enabled improved approaches to management. Geneticists have turned increasing attention not only to heritable disorders but also to predispositions to disease, particularly emphysema, asthma, and certain types of occupational lung disease. These examples illustrate the impact of advances in basic science on clinical investigations, diagnosis, and management.

Diagnosis

A continuing goal of chest physicians has been the early detection of lung disease so that interventions can be effected before the stage of irreparable damage is reached. In this regard, a landmark innovation was the flexible fiberoptic bronchoscope, a remarkable tool for the diagnosis and management of diseases of the airways and lungs. Also, during the past decade, a considerable effort was spent in developing and perfecting noninvasive techniques: spirometry has been standardized and simplified; techniques for monitoring blood gases through the intact skin have been developed; new devices have become available to monitor chest movements and breathing patterns with minimal disturbance to the patient; and sleep laboratories have materialized in joint efforts involving chest physicians, physiologists, and neurologists. Radioactive materials administered in minute and harmless doses have been applied noninvasively in diverse ways for diagnosis. Noteworthy among these are ventilation-perfusion scans for pulmonary emboli, and gallium scanning to detect inflammatory or cancerous processes not disclosed by conventional chest x-rays. A major breakthrough leading to improved care of prematurely delivered infants was the ability, using relatively simple methods, to detect whether the fetus lacks pulmonary surfactant by analyzing the amniotic fluid before birth.

With the recognition that tests on resting subjects can supply only limited information about pulmonary performance, exercise testing was modified beyond simple monitoring of the electrocardiogram to the definition and assessment of physical performance. One novel application of exercise testing has been to uncover latent asthma, a condition that may be undetected in the resting individual predisposed to bronchospasm.

Prevention

A dedicated effort has been made during the past decade to promote prevention of lung disease. One direction was the identification of risk factors. Another was the intensification of mass education through the repeated reaffirmation of the preeminent role of cigarette smoking in causing chronic bronchitis and emphysema on the one hand and cancer of the lung on the other. Criteria for immunization against influenza were developed to protect victims of pulmonary disease and those with poor resistance to pulmonary infection from the potentially lethal effects of this viral infection. A clinical trial was undertaken to evaluate the benefits and risks of antenatal administration of dexamethasone in the prevention of neonatal respiratory distress syndrome.

In the search for mechanisms by which cigarette smoking causes emphysema, a particularly useful approach proved to be the study of a type of emphysema caused by a genetic deficiency in a normal blood constituent (alpha-1-antitrypsin). This fruitful research has led to a new and testable hypothesis concerning the pathogenesis of emphysema; that is, an imbalance between normal blood constituents, proteases (elastases) on the one hand, and inhibitor substances on the other. This new approach not only holds the prospect of identifying genetically vulnerable individuals but also may lead to new therapeutic measures through replacement of the missing or deficient substances.

The availability of simple, valid, and standardized tests for repeatedly evaluating lung function is an important tool for uncovering evidence of early and reparable lung injury, and for applying preventive measures. Standardization of spirometry, coupled with mass education of physicians and individuals at risk, particularly cigarette smokers and those exposed to occupational inhalants, has proved to be of great value in early detection of disease and intervention in individuals who are neither symptomatic nor disabled.

The past decade has also witnessed greater understanding of lung diseases related to the working place. In addition to occupational disorders stemming from prolonged and inordinate exposure to certain dusts and fumes, the entity of hypersensitivity lung diseases has emerged. As a consequence of the increasing clarification of the nature of the diverse occupational disorders, more effective preventive measures have been applied.

Right ventricular failure secondary to pulmonary hypertension frequently complicates serious disorders of the lungs and respiratory apparatus. An intensive effort has been launched to uncover mechanisms of pulmonary hypertension with particular reference to elucidating its pathogenesis and possible approaches to therapy. Special impetus has been given to this research by the advent of potent vasodilators, which may be useful in preventing or ameliorating right ventricular overload.

A major pulmonary illness (in addition to chronic bronchitis and emphysema) that underscores the need for prevention is pulmonary embolism. Heightened awareness of risk factors, improved strategies for early detection (ventilation-perfusion scans and refinements in angiography), and effective anticoagulants have improved the prevention and management of this life-threatening disorder during the past decade.

Detailed discussions of prevention activities are integrated into the discussions of particular program activities.

Management

Probably the most spectacular advances in managing pulmonary disease are exemplified by the life-assist devices in the intensive care unit and the recent revolution in critical care. Mechanical assist devices, tailored to the needs of desperately ill patients, including prematurely born infants with insufficiently developed lungs, have made it possible to cope with clinical syndromes that were unmanageable 10 years ago. Noteworthy among these are the neonatal respiratory distress syndrome, which is linked primarily to prematurity, and the adult respiratory distress syndrome, a final common pathway of a variety of nonpulmonary disorders, such as shock, peritonitis, and pancreatitis. The new devices have also greatly simplified the postoperative management of patients with lung trauma and surgery as well as patients with obstructive airway disease who are either too fatigued or too disabled to breath on their own.

Less dramatic, but important for ambulatory patients with chronic obstructive pulmonary disease (COPD), were clinical trials, such as the one that demonstrated the greater value of continuous (24 hours) rather than nocturnal (12 hours) oxygen therapy. Also, appreciation of the abnormalities in ventilatory control during sleep in certain individuals has led to effective prophylactic measures that ensure proper breathing and gas exchange. Self-management and educational programs have improved the quality of life in patients with obstructive airway disease. Patient management has also been greatly enhanced by progress in understanding and in disseminating information about the proper use of therapeutic agents. The clarification of how bronchodilators exert their effects and the determination of appropriate aminophylline dosage by quantification of its blood levels in asthmatics have added a new dimension to the therapy of obstructive airway disease and of asthma in particular. The use of corticosteroids in treating the respiratory diseases in general and the adult respiratory distress syndrome in particular is being evaluated. Oxygen toxicity, especially as it results from the therapeutic use of oxygen in children and adults, is now better understood. Inroads have been made into providing proper nutritional support for individuals suffering from lung disease. Newer advances in the understanding of secretion in airways are being applied to therapeutic interventions in chronic bronchitis and in cystic fibrosis.

Research Training

Progress in the areas described above would not have possible without concurrent development of professional and scientific personnel in the pulmonary field. During the past decade, new

programs to develop medical school faculty and upgrade curricula have helped make chest diseases an attractive choice of subspecialty of many young physicians. In the area of the basic sciences, investigators from a wide variety of disciplines have brought their expertise to bear on studies of the lung. Post-graduate research training programs have expanded to accommodate increasing numbers of basic and clinical researchers, and innovative programs for young investigators have provided opportunities for trainees to develop and establish academic careers in pulmonary research. The current supply of highly trained personnel bodes well for continued progress in the decade ahead.

Presented above are only a few examples of accomplishments in the categories of basic research, diagnosis, prevention, and management of lung diseases. They illustrate major directions and accomplishments of the past decade with respect to the totality of lung disease and indicate potential areas of exploration for the decade ahead.

2. Magnitude of the Problem

Contents

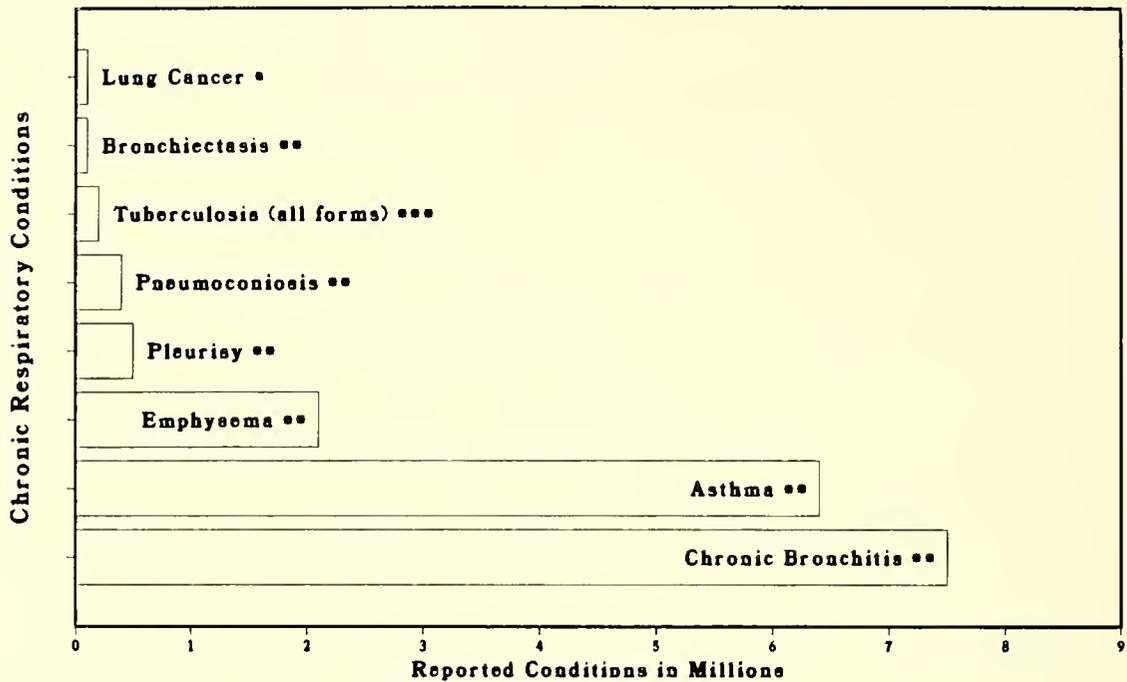
MAGNITUDE OF THE PROBLEM.	7
ECONOMIC COSTS.	12
SIZE AND SCOPE.	14
Diseases of the Airways	14
Pneumonias.	25
Neonatal Pulmonary Disorders.	25
Disorders of the Pulmonary Circulation.	25
Interstitial Lung Disorders	26
Lung Cancer	26
TRENDS IN MORBIDITY AND MORTALITY	27
CONTRIBUTORS.	30

2. Magnitude of the Problem

Lung diseases are among the leading causes of death and disability in the United States. About 1 in every 5 persons has some chronic respiratory problem. An estimated 16 million persons have chronic bronchitis, emphysema, or asthma, and each year there are about 100 million cases of influenza, pneumonia, or acute bronchitis. As the underlying cause, nearly 240,000 deaths are attributed to lung diseases each year, and these diseases are a contributing cause to perhaps that many additional deaths. Thus, lung diseases cause 1 of every 8 deaths and play a role in 1 of every 4 deaths.* These diseases are present among infants, children, and adults, and each year they account for approximately 2.5 million hospital discharges, 21 million days of hospital care, and 25 million visits to physicians. In the total population, chronic obstructive pulmonary disease and asthma are especially prevalent, afflicting nearly 10 million and 6.5 million persons respectively. The prevalence of selected lung diseases in the U.S. population is shown in figure 1.

*The difficulties of obtaining entirely reliable morbidity, mortality, and disability statistics are well known. A number of lung diseases, for example, are underrepresented because different but associated diseases are more commonly reported as the underlying cause of death. Despite shortcomings of the data, the estimates in this report provide the best available measures of the national economic burden, mortality, morbidity, and disability due to respiratory diseases. In general, each of these measures is more likely to understate than exaggerate the magnitude of the problem.

The data discussed in this report are on lung diseases of the program areas of the Division of Lung Diseases: chronic obstructive airway diseases such as chronic bronchitis, emphysema, asthma, and cystic fibrosis; fibrotic and immunologic interstitial lung diseases including those caused by inhalation of noxious dusts and gases; pediatric pulmonary diseases; and pulmonary vascular diseases such as pulmonary hypertension, pulmonary edema, and pulmonary embolism (table 1). Data on diseases outside the Division program such as lung cancer, tuberculosis, pneumonia, and influenza are included for perspective.



- National Cancer Institute Estimate
- National Health Interview Survey Estimate
- Centers for Disease Control Tuberculosis Case Registration Data

Figure 1. Prevalence of Selected Chronic Respiratory Conditions, 1980

This morbidity (condition of illness)* and mortality not only affects the quality of life in the United States but also has a significant impact on the nation's economy as well.** In 1979, the economic cost of lung diseases amounted to an estimated \$29 billion measured in terms of health expenditures (\$7 billion), wages lost due to illness (\$10.5 billion), and potential wages lost due to premature death (\$11.7 billion) (table 2). There are

*Morbidity is measured by incidence, prevalence, physician office visits, hospital discharges, days of hospital care, and disability days (restricted activity days, work-loss days, days lost from school, and bed days).

**Economic costs are measured in terms of total direct expenditures for health care combined with estimated cost of lost productivity attributed to these diseases.

Table 1. ICD Codes for Lung Diseases

Disease Category	ICDA-8 Code No.	ICD-9-CM Code No.
Diseases of the Airways		
COPD*		
Chronic Bronchitis	490, 491	490, 491
Emphysema	492	492
COLD*	519.3	496
Asthma	493	493
Cystic fibrosis	273.0	277.0
Bronchiectasis	518	494
Acute bronchitis and bronchiolitis	466	466
Pneumonias		
Pneumonias with organism unspecified or manifestations of other infectious diseases	484-486	484-486
Bacterial pneumonia	481, 482	481, 482
Mycoplasma pneumonia	483	483
Mycotic pneumonia	113, 114, 115, 117.3	039, 114, 115, 117.3
Viral pneumonia (includes influenza pneumonia)	470-474, 480	480, 487
Neonatal Pulmonary Disorders		
RDS (including hyaline membrane disease)	776.1, 776.2	769
Immaturity, unqualified	777	765
Asphyxia of the newborn	776.9	768

*The term "chronic obstructive pulmonary disease" (COPD) is often used to encompass both chronic bronchitis and emphysema; chronic obstructive lung disease (COLD) has frequently been used. In this report, COLD is used to refer only to category 519.3 in the ICDA-8. The COLD disease entity categorized as 519.3 in ICDA-8 is not necessarily the same as that used for chronic obstructive pulmonary disease, not elsewhere classified, categorized as 496 under ICD-9-CM, but they are roughly equivalent.

Table 1. ICD Codes for Lung Diseases (concluded)

Disease Category	ICDA-8 Code No.	ICD-9-CM Code No.
Disorders of the Pulmonary Circulation		
Cor pulmonale	426	415.0
Pulmonary edema**	519.1	518.4
Pulmonary embolism	450	415.1
Interstitial Lung Disorders (by etiology)		
Chronic interstitial pneumonia	517	515
Granulomatous diseases including sarcoidosis	135, 441.6, 446.3	135, 446.4
Occupational lung diseases	515, 516.0--2	495, 500-506
Tuberculosis	011, 012, 019.0	011, 012
Lung Cancer		
Cancer of bronchus and lung	162.1	162.2-.9

**Excludes pulmonary edema related to heart failure.

Sources: Eighth Revision International Classification of Diseases, Adapted for Use in the United States; U.S. Department of Health, Education, and Welfare, Public Health Service Publication No. 1693, 1969; and The International Classification of Diseases, 9th Revision, ICD-9-CM; U.S. Department of Health and Human Services; DHHS Publication No. (PHS) 80-1260; September, 1980.

Table 2. Estimated Economic Costs of Selected Lung Diseases
 United States, 1979
 (dollars in millions)

Disease Category	Direct Health Expenditures*				Indirect Costs		TOTAL
	Hospital Care	Physicians and Other Care	Drugs and Medical Sundries		Morbidity	Mortality	
COPD	\$1,315	\$731	\$274		\$1,969	\$2,209	\$6,498
Chronic bronchitis	338	513	192		303	217	1,563
Emphysema	180	57	22		1,666	692	2,617
COLD	797	161	60		---	1,300	2,318
Asthma	665	552	207		788	180	2,392
Acute bronchitis and bronchiolitis	442	240	90		368	64	1,204
Influenza	107	207	78		6,298	58	6,748
Active tuberculosis	142	16	6		35	168	367
Viral pneumonia	79	10	4		61	97	251
Mycotic pneumonia	31	8	3		11	---	53
Other pneumonia	134	166	62		636	2,381	3,379
Lung cancer	1,084	368	14		324	6,580	8,370
TOTAL	\$3,999	\$2,298	\$738		\$10,490	\$11,737	\$29,262

*Direct expenditures for costs of nursing home care by diagnoses are not available.

**Data not available.

Source: Prepared by the National Heart, Lung, and Blood Institute; data from the National Center for Health Statistics and the Health Care Financing Administration.

no measures to quantify social costs or human suffering associated with these diseases.

As indicated in table 3, the age-adjusted death rate due to COPD continues to increase although the rate of increase has delined in recent years. During the same period, there has been a steep decline in mortality from neonatal respiratory distress syndrome and other diseases relating to immaturity of the newborn. Except for an increase in the prevalence of COPD, there appear to be no increases for other major lung diseases for which national prevalence is measurable. There is less certainty about trends for measures of morbidity from other lung diseases.

Economic Costs

The term "economic costs of a disease" is used to designate estimates of the benefits that would accrue annually to the national economy if the disease were eliminated or controlled. Morbidity and mortality contribute to these costs.

The total estimated economic cost of the selected lung diseases listed in table 2 in 1979 was \$29.3 billion.* Direct costs, which include expenditures for hospital care, for physicians' and other health professionals' services, and for drugs and medical sundries, amounted to an estimated \$7 billion. Because nursing home care costs are not available by diagnoses, direct costs are underestimated. Indirect costs amounted to an estimated \$22.2 billion in 1979, one-half of which was due to morbidity and one-half to mortality. Indirect morbidity costs, which are measured in terms of lost earnings, exclude losses to employers. Indirect mortality costs include not only lost earnings in 1979, but all future earnings, discounted to 1979, that persons who died would have earned during their expected remaining lifetime.**

*In an effort to provide more reliable estimates, the lung disease categories are limited to the more common diseases.

**This is a "net effective discount rate" of 4 percent. That is, it adjusts for future inflation at 6 percent and for a rise in productivity of 2 percent per year in order to have future earnings measured in 1979 dollar value.

Table 3. Mortality Trends for COPD*
United States, 1950 to 1980

Year	Number of Deaths	Unadjusted Death Rate per 100,000 Population	Age-Adjusted Death Rate per 100,000 Population
1950	3,157	2.1	NA
1955	5,616	3.4	2.8
1960	12,426	6.9	5.6
1965	23,432	12.1	9.4
1970	33,011	16.3	12.2
1975	41,100	19.3	13.5
1980**	53,310	24.0	15.5

*Chronic bronchitis, emphysema, and COPD (excludes asthma). ICD/6 and 7 codes 501-502, 527.1 (1949-1967); ICD/8 codes 490-492, 519.3 (1968-1978); and ICD/9 codes 490-492, 494-496 (1979-).

**Provisional statistics.

NA: Not available.

Source: National Center for Health Statistics.

The estimated economic costs of chronic obstructive pulmonary disease in 1979 is at least \$6.5 billion (table 2).[†] Direct costs represent \$2.3 billion. This estimate includes \$1.3 billion for hospital care, \$731 million for physicians' and other health professionals' services, and \$274 million for drugs and medical sundries. Indirect costs for COPD amount to an estimated \$4.2 billion, of which \$2 billion are for morbidity and \$2.2 billion are for mortality.

Asthma cost the nation an estimated total of \$2.4 billion in 1979 (table 2). Acute bronchitis and bronchiolitis represented about \$1.2 billion that same year.

[†]This total includes figures for chronic bronchitis, emphysema, and COLD, ICDA-8 codes 490-492, 519.3.

Size and Scope

Data in tables 4 and 5 show the importance of lung diseases as the underlying, contributing, or immediate cause of death in 1978. Chronic obstructive pulmonary disease and allied conditions represented the fifth leading cause of death in 1981 (table 6) and accounted for 3 percent of all deaths. During the same year, influenza and pneumonia were the sixth leading cause and accounted for 2.7 percent of deaths.

Diseases of the Airways

This category of diseases accounted for about 52,402 deaths in 1978, representing about 22 percent of the deaths due to lung diseases of all types (figure 2). As shown by adding the data from the first three disease categories in table 5, COPD* was the underlying cause of approximately 49,000 deaths in 1978 but was also a contributory cause for approximately 70,000 other deaths. As an underlying cause, COPD* resulted in approximately 59,000 deaths in 1981 and ranked as the fifth leading cause of death (table 6). If current trends continue, it may become the nation's fourth or even third leading cause of death by the year 2000. The airway diseases were responsible for about 1.2 million hospital discharges in 1979, representing an estimated 8.5 million days of hospital care (table 7), or 40 percent of the days due to the major lung diseases. In 1979, the airway diseases were also responsible for about 19 million visits to physicians' offices (table 8).

Chronic bronchitis affects persons of all ages. As of 1979, an estimated 7.5 million persons suffered from chronic bronchitis. Of these, 381,000 persons, or 5.1 percent, were limited in activity (table 9). In 1979, there were about 88 million days of restricted activity, 28.5 million bed days, and 7.2 million days of work-loss due to chronic bronchitis (table 10), which was responsible for 115,000 hospital discharges and 1.048 million hospital days (table 7) and 981,000 visits to physicians' offices (table 8).

An estimated 2.1 million persons had emphysema as of 1979. Of these, 1.1 million, or 52.3 percent, were limited in activity (table 9) and 93 percent were 45 years of age or older. The disease caused about 144.9 million days of restricted activity, 57.1 million bed days, and 314,000 work-loss days (table 10). The last number reflects the fact that only a few elderly people are employed. Emphysema was responsible for 57,000 hospital discharges and 556,000 hospital days (table 7). An estimated

*ICD-8 codes 490-492, 519.3, ICD-9 codes 490-496.

Table 4. Number of Deaths From Selected Lung Diseases
United States, 1978

Cause of Death	Number of Deaths	Subtotals
Diseases of the Airways		52,402
COLD	28,613	
Emphysema	15,627	
Chronic bronchitis	4,376	
Asthma	1,872	
Cystic fibrosis	505	
Bronchiectasis	635	
Acute bronchitis and bronchiolitis	756	
Pneumonias		58,566
Pneumonias with organism unspecified or manifestations of other infectious diseases	46,092	
Bacterial pneumonia	6,909	
Mycoplasma pneumonia	71	
Mycotic pneumonia	247	
Viral pneumonia (includes influenza pneumonia)	5,247	
Neonatal Pulmonary Disorders		12,656
RDS (including hyaline membrane disease)	6,012	
Immaturity, unqualified	3,679	
Asphyxia of the newborn	2,965	
Disorders of the Pulmonary Circulation		12,591
Cor pulmonale	1,412	
Pulmonary edema*	238	
Pulmonary embolism	10,941	

*Excludes pulmonary edema related to heart failure.

Table 4. Number of Deaths From Selected Lung Diseases
United States, 1978 (concluded)

Cause of Death	Number of Deaths	Subtotals
Interstitial Lung Disorders (by etiology)		7,436
Chronic interstitial pneumonia	3,146	
Granulomatous diseases including sarcoidosis	364	
Occupational lung diseases*	1,422	
Tuberculosis	2,504	
Lung Cancer		
Bronchus and lung	94,929	94,929
		TOTAL 238,580

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

Source: National Center for Health Statistics.

Table 5. Number of Deaths for Which Selected Lung Diseases Represent Underlying or Contributing Cause of Death United States, 1978

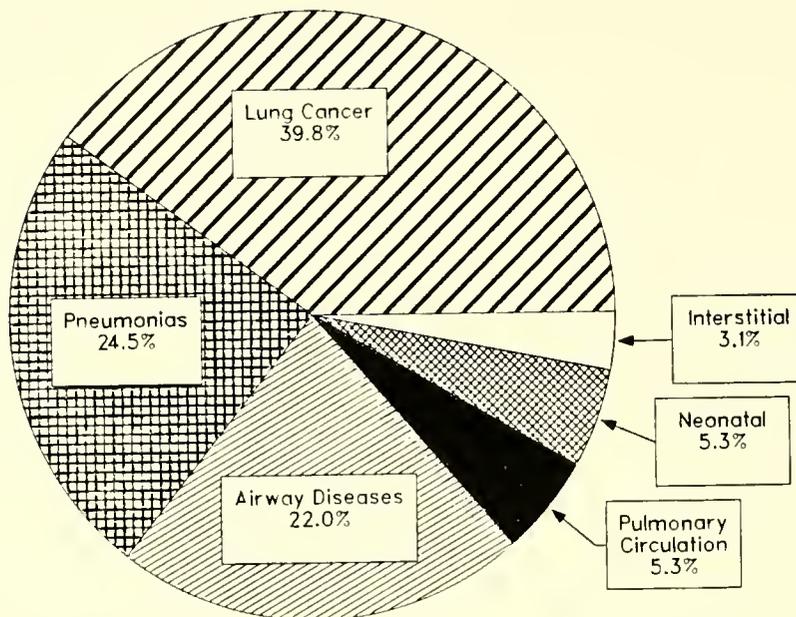
Disease	Number of Times Reported as	
	Underlying Cause*	Contributing Cause*
Bronchitis, chronic and unspecified	4,376	6,047
Emphysema	15,627	26,721
Asthma	1,872	4,401
Chronic obstructive lung disease	28,613	36,857
Pneumonia and influenza	58,566	128,363
Cancer of bronchus and lung	94,929	8,274

*The underlying cause of death is the disease or injury that initiated the course of events leading directly to death. Contributory causes of death are all other diseases or injuries listed on the death certificate.
Source: National Center for Health Statistics.

Table 6. Mortality From the 10 Leading Causes of Death United States, 1981*

Cause of Death	Number	Rate per 100,000 Population	Percent
Total	1,965,900	866.4	100.0
1. Diseases of the heart	747,710	329.5	38.0
2. Malignant neoplasms	418,200	184.3	21.3
3. Cerebrovascular diseases	161,580	71.2	8.2
4. Accidents	99,110	43.7	5.1
5. COPD and allied conditions	59,140	26.1	3.0
6. Influenza and pneumonia	53,720	23.7	2.7
7. Diabetes	34,230	15.1	1.7
8. Chronic liver diseases and cirrhosis	29,100	12.8	1.5
9. Arteriosclerosis, not elsewhere classified	28,410	12.5	1.5
10. Suicide	26,010	11.5	1.3
All other causes	308,690	136.0	15.7

*Provisional statistics.
Source: National Center for Health Statistics.



Source: National Center for Health Statistics.

Figure 2. Percent Distribution of Deaths From Lung Diseases, 1978

707,000 visits to physicians' offices in 1979 were due to the disease (table 8).

A high proportion of asthma patients are young; 35 percent are under 17 years of age, 34 percent are 17 to 44; 23 percent are 45 to 64; and 8 percent are 65 and over. As of 1979, an estimated 6.4 million persons suffered from asthma. Of these, 1.3 million or 19.9 percent, were limited in activity (table 9). It caused approximately 109.7 million days of restricted activity, 35.3 million bed days, and 6.9 million days of work-loss (table 10). There were also an estimated 339,000 discharges from hospitals, accounting for 2.1 million days of care (table 7). Asthma was also responsible for about 6.8 million visits to physicians' offices (table 8).

Bronchiectasis is primarily a disease of the middle to late years with a reported prevalence of 2 per 1,000 persons between 45 to 64 years of age and of 2.3 per 1,000 persons 65 and over. It affected an estimated 208,000 persons in 1979. Of these, 42,000,

Table 7. Number of Short-Stay Hospital Discharges* and Hospital Days for Selected Lung Diseases United States, 1979

Broad Diagnostic Group	Diagnosis (ICD-9-CM Code)	First-Listed Discharges (number in thousands)	Hospital Days	Average Length of Stay in Days	
Diseases of Airways	Cystic fibrosis (277.0)	11	164	14.9	
	Bronchitis, not specified as acute or chronic (490)	112	560	5.0	
	Chronic bronchitis (491)	115	1,048	9.1	
	Emphysema (492)	57	556	9.8	
	Asthma (493)	339	2,059	6.1	
	Bronchiectasis (494)	11	105	9.5	
	Chronic airway obstruction, not elsewhere classified (496)	238	2,467	10.4	
	Acute bronchitis and bronchiolitis (466)	236	1,369	5.8	
	Acute epiglottitis (464.3)	3	18	6.0	
	Group (464.4)	45	140	3.1	
		TOTAL:	1,167	8,486	7.3
	Pneumonias	Viral pneumonia (480)	36	246	6.8
		Other bacterial pneumonia (482)	23	246	10.7
Pneumonia due to other specified organisms (481, 483-486)		697	5,580	8.0	
	TOTAL:	756	6,072	8.0	
Neonatal Pulmonary Disorders	Disorders relating to short gestation and unspec. low birth wt. (765)	13	229	17.6	
	Intrauterine hypoxia and birth asphyxia (768)	1	22	22.0	
	Respiratory distress syndrome (769)	2	32	16.0	
	Bronchopulmonary dysplasia (770.7)	1	10	10.0	
	Other respiratory conditions of fetus and newborn (770.0-.6, .8, .9)	17	149	8.8	
		34	442	13.0	
		TOTAL:			

*Hospital stays of 30 days or less.

Table 7. Number of Short-Stay Hospital Discharges* and Hospital Days for Selected Lung Diseases United States, 1979 (concluded)

Broad Diagnostic Group	Diagnosis (ICD-9-CM Code)	First-Listed Discharges (number in thousands)	Hospital Days	Average Length of Stay in Days
Disorders of Pulmonary Circulation	Acute pulmonary heart disease (415)	72	1,019	14.2
	Chronic pulmonary heart disease (416)	8	98	12.2
	Other diseases of pulmonary circulation (417)	0	3	**
	Acute edema of the lung, unspecified (518.4)	25	264	10.6
	TOTAL:	105	1,384	13.2
Interstitial Lung Disorders	Sarcoidosis (135)	10	104	10.4
	Pneumonitis due to solids and liquids (507)	14	184	13.1
	Respiratory conditions due to other and unspecified external agents (508)	1	10	10.0
	Postinflammatory pulmonary fibrosis (515)	20	244	12.2
	Pulmonary insufficiency following trauma and surgery (518.5)	5	67	13.4
	Collagen vascular disease (517)	**	**	**
	Occupational lung diseases (495, 500-506)	7	57	8.1
	Tuberculosis (011)	23	441	19.2
	Influenza (487)	67	332	5.0
		TOTAL:	147	1,439
Cancer of Bronchus and Lung	Cancer of bronchus and lung (162.2-162.9)	264	3,354	12.7
	TOTAL:	264	3,354	12.7
Total for all selected lung diseases		2,483	21,177	8.5

*Hospital stays of 30 days or less.

**Too few in the sample for a reliable estimate.

Source: National Center for Health Statistics; Hospital Discharge Survey.

Table 8. Number of Physician Office Visits for Selected Lung Diseases
United States, 1979

Broad Diagnostic Group	Diagnosis (ICD-9-CM Code)	Number of Visits (in thousands)
Diseases of the Airways	Cystic fibrosis (277.0)	61
	Bronchitis, not specified as acute or chronic (490)	5,319
	Chronic bronchitis (491)	981
	Emphysema (492)	707
	Asthma (493)	6,786
	Bronchiectasis (494)	179
	Chronic airway obstruction, not elsewhere classified (496)	1,985
	Acute bronchitis and bronchiolitis (466)	2,948
	Acute epiglottitis (464.3)	*
	Group (464.4)	*
TOTAL:	18,966	
Pneumonias	Viral pneumonia (480)	127
	Other bacterial pneumonia (482)	36
	Pneumonia due to other specified organisms (483)	12
TOTAL:	175	
Neonatal Pulmonary Disorders	Disorders relating to short gestation and unspec. low birth wt. (765)	36
	Intrauterine hypoxia and birth asphyxia (768)	23
	Respiratory distress syndrome (769)	*
	Bronchopulmonary dysplasia (770.7)	*
	Other respiratory conditions of fetus and newborn (770.0-.6, .8, .9)	27
	TOTAL:	86

*Too few in the sample for a reasonable estimate.

Table 8. Number of Physician Office Visits for Selected Lung Diseases
United States, 1979 (concluded)

Broad Diagnostic Group	Diagnosis (ICD-9-CM Code)	Number of Visits (in thousands)
Disorders of the Pulmonary Circulation	Acute pulmonary heart disease (415)	118
	Chronic pulmonary heart disease (416)	28
	Other diseases of pulmonary circulation (417)	*
	Acute edema of the lung, unspecified (518.4)	8
	TOTAL:	<u>154</u>
Interstitial Lung Disorders	Sarcoidosis (135)	56
	Pneumonitis due to solids and liquids (507)	*
	Respiratory conditions due to other and unspecified external agents (508)	*
	Postinflammatory pulmonary fibrosis (515)	73
	Pulmonary insufficiency following trauma and surgery (518.5)	8
	Collagen vascular disease (517)	2,273
	Occupational Lung Diseases (495, 500-506)	44
	Tuberculosis (011)	200
	Influenza (487)	<u>2,544</u>
		TOTAL:
Cancer of Bronchus and Lung	Cancer of bronchus and lung (162.2-162.9)	
		TOTAL:
	TOTAL:	<u>25,031</u>

*Too few in the sample for a reasonable estimate.

Source: National Center for Health Statistics; Ambulatory Medical Care Survey.

Table 9. Prevalence and Prevalence Rates for Selected Chronic Lung Conditions:
Total and for Persons Limited in Activity
United States, 1979

Selected Chronic Conditions	Total Prevalence (no. of persons in thousands)	Limited in Activity (thousands)	Percent Limited in Activity	Total Prevalence (rate per 1,000 persons)	Limited in Activity* (rate per 1,000 persons)
Chronic bronchitis	7,474	381	5.1	34.6	1.8
Emphysema	2,137	1,118	52.3	9.9	5.2
Asthma	6,402	1,274	19.9	29.7	5.9
Pneumoconiosis	302	143	47.4	1.4	0.7
Other chronic interstitial pneumonia	189	22	11.6	0.9	0.1
Bronchiectasis	207	42	20.2	1.0	0.2
Active tuberculosis	165	41	24.8	0.8	0.2
Cystic fibrosis	89	11	12.4	0.4	----**

*Percent limited in activity times total prevalence rate.

**Too few in the sample for a reasonable estimate.

Note on Standard Errors: An estimate below 215,000 and a rate based on that estimate are statistically unreliable, i.e., a relative standard error in excess of 30 percent.

Source: National Center for Health Statistics; Health Interview Survey (unpublished data).

Table 10. Disability Days for Selected Chronic Lung Conditions
United States, 1979

Selected Chronic Lung Conditions	Restricted Activity Days (number of days in thousands)	Bed Days	Work-Loss Days	Restricted Activity Days (days per condition per year)	Bed Days	Work-Loss Days
Chronic bronchitis	88,165	28,519	7,246	11.8	3.8	1.0
Emphysema	144,927	57,137	314	67.8	26.7	0.1
Asthma	109,660	35,275	6,903	17.1	5.5	1.1
Pneumoconiosis	13,169	7,901	*	43.6	26.2	*
Other chronic interstitial pneumonia	4,555	3,981	*	24.1	21.1	*
Active tuberculosis	3,730	2,665	*	22.6	16.2	*

*Too few in the sample for a reasonable estimate.

Note on Standard Errors: An estimate of restricted activity days or of bed days below 34 million and of work-loss days below 22 million and corresponding estimates of days per condition are statistically unreliable.

Source: National Center for Health Statistics; Health Interview Survey (unpublished data).

or 20.2 percent, were limited in activity (table 9). Bronchiectasis was responsible for approximately 11,000 discharges from hospitals and 105,000 hospital days (table 7). It was also responsible for about 179,000 visits to physicians' offices (table 8).

Cystic fibrosis, the most common, lethal, inherited disease among Caucasians, creates severe respiratory problems for many children. Improved health care has allowed more children to survive adolescence, and as a result, there is a growing number of young adults with this disease. Approximately 89,000 persons in the United States have the disease. In 1979, 11,000 discharges from hospitals and 164,000 hospital days were attributed to this condition (table 7), and it accounted for 61,000 visits to physicians' offices (table 8).

Pneumonias

Pneumonias of various kinds resulted in 756,000 discharges from hospitals and 6.1 million inpatient days of care in 1979, and about 175,000 visits to physicians' offices (tables 7 and 8). It accounted for about 29 percent of days of hospital care for lung diseases.

Neonatal Pulmonary Disorders

Many of the neonatal pulmonary disorders are associated with prematurity. In 1978, neonatal pulmonary disorders were cited as the underlying cause of death for 12,656 cases, about 50 percent of which represented respiratory distress syndrome and 29 percent immaturity (unqualified). Asphyxia of the newborn accounted for the remainder (table 4). The decline in the birth rate together with technological advances in management of newborns at high risk has reduced the number of deaths due to this cause, but in 1979 neonatal pulmonary disorders accounted for about 34,000 hospital stays, 442,000 inpatient days, and 86,000 physician visits (tables 7 and 8).

Disorders of the Pulmonary Circulation

In 1979, pulmonary circulation disorders were identified as the reason for 105,000 hospitalizations, representing 1.4 million inpatient days (table 7). These disorders were also estimated to account for 154,000 visits to physicians' offices (table 8).

The difficulties in making a diagnosis of pulmonary embolism causes problems in making an accurate determination of the magnitude of this health problem. In 1978, there were 12,591 deaths

attributed to pulmonary embolism and infarction in the United States. Most deaths in which pulmonary embolism is the immediate cause, however, are attributed to another underlying etiology. It is therefore widely suspected that pulmonary embolism may account for at least 50,000 deaths in hospitals each year. If less than 1 embolic event in 10 is fatal, there are approximately 500,000 episodes of pulmonary embolism each year in hospitalized patients in the United States.

Disorders of the pulmonary circulation such as pulmonary hypertension and cor pulmonale frequently occur as complications of other respiratory diseases, and their presence is usually a poor prognostic sign. However, since they are rarely listed as the cause of morbidity or mortality, these disorders are under-represented in this report.

Interstitial Lung Disorders

Interstitial lung disorders account for relatively few deaths, but they are responsible for substantial morbidity and disability. Because interstitial lung diseases represent a manifestation of a variety of diseases, morbidity and disability data are likely to be understated. In 1979, the category of interstitial lung disorders accounted for 147,000 hospital stays and 1.4 million inpatient days, representing 6.5 percent of the total days of care for all selected lung diseases (table 7). Further, 5.2 million physician office visits were attributed to interstitial lung disorders (table 8). The increase in prevalence of these disorders correlates with increase in age.

As of 1979, an estimated 302,000 persons had pneumoconiosis, of whom almost 50 percent were limited in activity (table 9). A person with this disease spends an average of about 44 days out of the year in restricted activity, 26 of which are actually spent in bed (table 10). These data yield 13 million days of restricted activity and 8 million days in bed during 1979. In addition, occupational lung diseases were the cause of an estimated 44,000 visits to physicians' offices in 1979 (table 8).

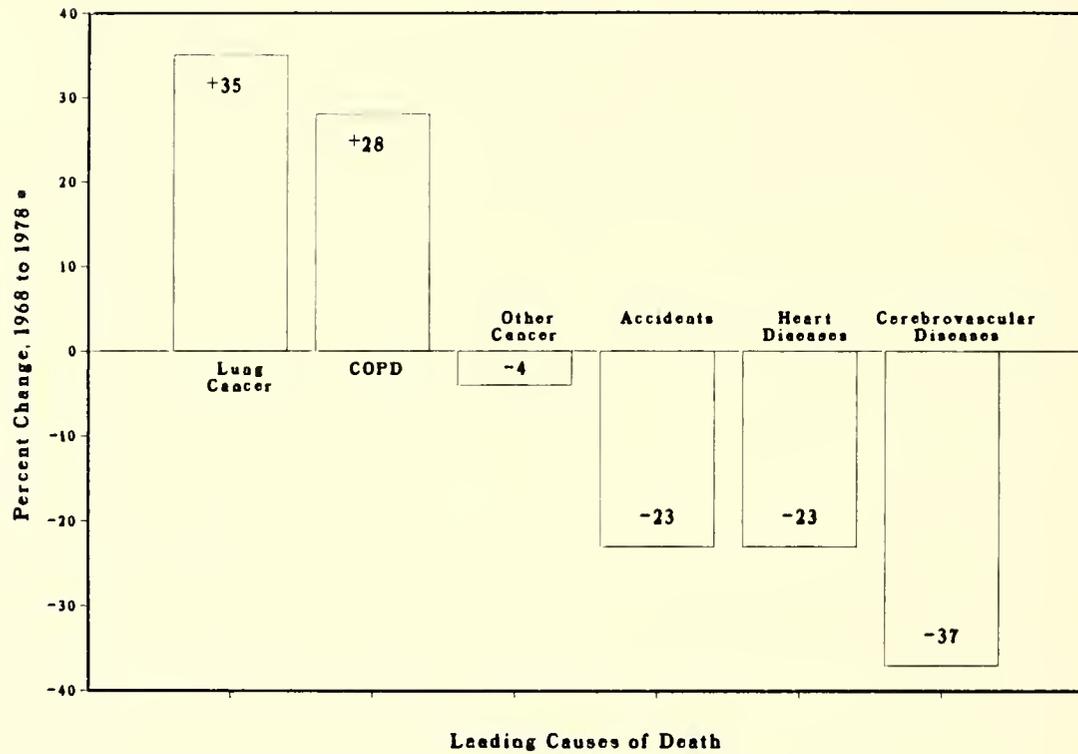
Lung Cancer

It is estimated that in 1981 there were 129,000 new cases of lung cancer. Lung cancer patients accounted for approximately 264,000 hospital discharges and 3.4 million days of hospital care in 1979. They made about 450,000 visits to physicians in that year (table 8).

Trends in Morbidity and Mortality

Trends in death rates for the leading causes of death have been downwards over the last 10 years or more (figure 3). Only 3 of the 10 leading causes of death exhibited increased rates from 1968 to 1978, namely malignant neoplasms, COPD, and suicide. The increase in the malignant neoplasms category is a result of a 60 percent increase in deaths caused by lung cancer between 1968 and 1978. During that same period, the age-adjusted death rate increased 35 percent for lung cancer and 28 percent for COPD; and the death rate for influenza/pneumonia, for pulmonary embolism, and for asthma declined 43 percent, 10 percent, and 42 percent respectively. Over the longer term, lung cancer and COPD mortality rose substantially, but the rate of increase has been slower in recent years, especially for COPD. Of concern is that the 28 percent increase for COPD between 1968 and 1978, although less steep than in earlier years, contains a near doubling of the death rate for white females and a 56 percent increase for nonwhite females (figure 4). Previously, rates were very low among women. The increase for lung cancer in recent years has also been much greater for women than for men, but with smaller increases in the 1970's than in the 1960's. By contrast, infant death rates for lung diseases declined rapidly over the same 10-year period.

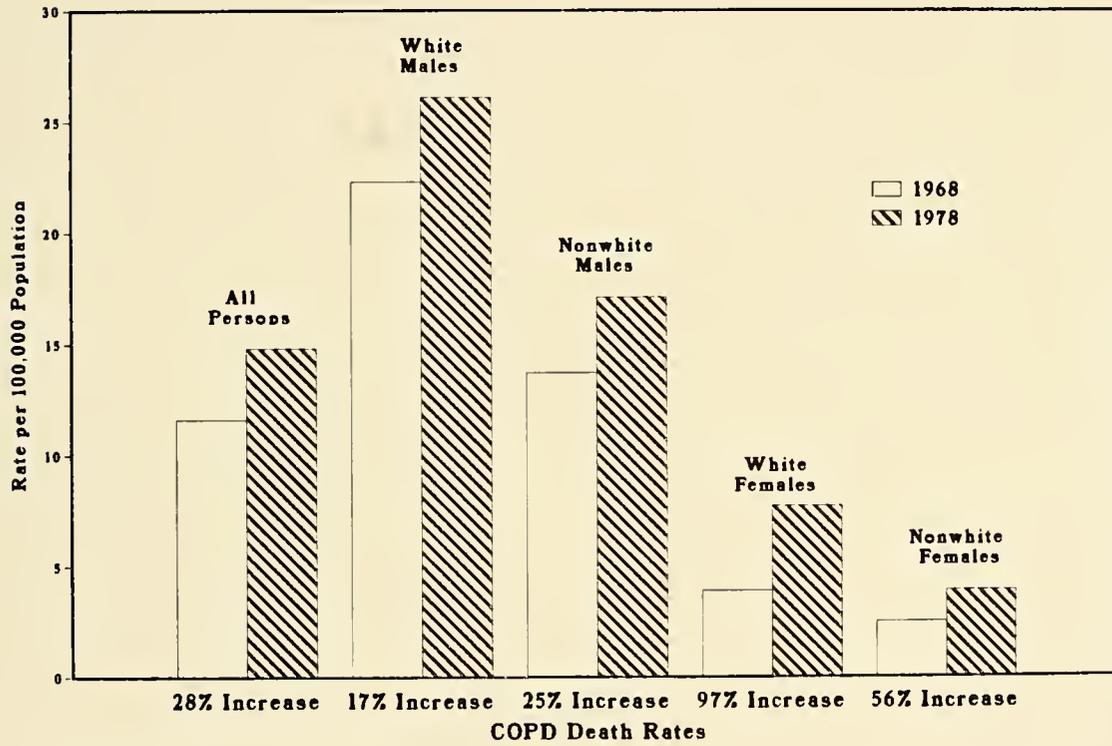
It is not known whether the trends in morbidity from lung diseases are in the same direction as those in mortality. Even for the very common diseases, estimation of morbidity trends is tenuous primarily because measurements through the years may not be comparable. Also, trends in the frequency of common acute lung diseases such as acute bronchitis, influenza, and pneumonia fluctuate in cycles of epidemics. The one trend that stands out is the large increase in the prevalence of emphysema, as shown by the Health Interview Survey of the National Center for Health Statistics. An estimated 1.3 million persons had emphysema in 1970, and by 1978 the estimate was 2.1 million persons. It is possible, however, that an increase even this large has resulted from problems of comparability of data. The same survey suggested that there was no change in the prevalence of chronic bronchitis and asthma. No other morbidity trends appear firm enough to characterize at this time.



* Age-adjusted to the 1940 U.S. population.

Source: National Center for Health Statistics.

Figure 3. Percent Change in Death Rates* for the Leading Causes of Death United States, 1968 to 1978



Source: National Center for Health Statistics.

Figure 4. Changes in Age-Adjusted Death Rates for COPD for 1968 to 1978

Contributors

PULMONARY DISEASES ADVISORY COMMITTEE MEMBER

Alfred P. Fishman, M.D.
William Maul Measey Professor
of Medicine
Director, Cardiovascular Pulmonary
Disease Division
University of Pennsylvania
School of Medicine
Philadelphia, Pennsylvania

DIVISION STAFF

Dorothy Gail, Ph.D.
Structure and Function Branch
Division of Lung Diseases
National Heart, Lung, and
Blood Institute

Hannah Peavy, M.D.
Airways Diseases Branch
Division of Lung Diseases
National Heart, Lung, and
Blood Institute

Thomas J. Thom
Biometrics Research Branch
Division of Heart and
Vascular Diseases
National Heart, Lung, and
Blood Institute

3. Structure and Function of the Lung

Contents

STRUCTURE AND FUNCTION OF THE LUNG.	31
PHYSIOLOGY.	33
RESPIRATORY MECHANICS.	33
State of Knowledge in 1972.	33
Program Goal Through 1982	36
Accomplishments Through 1982.	36
State of Knowledge in 1982.	41
Program Goals 1982 to 1987.	41
Research Activities 1982 to 1987.	42
CONTROL OF BREATHING	43
State of Knowledge in 1972.	43
Program Goal Through 1982	46
Accomplishments Through 1982.	46
State of Knowledge in 1982.	55
Program Goals 1982 to 1987.	56
Research Activities 1982 to 1987.	56
GAS EXCHANGE	57
State of Knowledge in 1972.	57
Program Goal Through 1982	58
Accomplishments Through 1982.	58
State of Knowledge in 1982.	61
Program Goals 1982 to 1987.	62
Research Activities 1982 to 1987.	62
NONVENTILATORY FUNCTIONS OF THE RESPIRATORY SYSTEM.	63
PULMONARY SURFACTANT	63
State of Knowledge in 1972.	64
Program Goal Through 1982	64
Accomplishments Through 1982.	65
State of Knowledge in 1982.	67
Program Goals 1982 to 1987.	68
Research Activities 1982 to 1987.	68
LUNG CELL BIOLOGY.	69
State of Knowledge in 1972.	69
Program Goals Through 1982.	69
Accomplishments Through 1982.	69
State of Knowledge in 1982.	74
Program Goals 1982 to 1987.	76
Research Activities 1982 to 1987.	76
LUNG INJURY AND REPAIR.	77
State of Knowledge in 1972.	78
Program Goal Through 1982	78
Accomplishments Through 1982.	78
State of Knowledge in 1982.	82
Program Goal 1982 to 1987	83
Research Activities 1982 to 1987.	83
LUNG GROWTH AND DEVELOPMENT	84
State of Knowledge in 1972.	85
Program Goal Through 1982	85
Accomplishments Through 1982.	86
State of Knowledge in 1982.	88
Program Goals 1982 to 1987.	89
Research Activities 1982 to 1987.	89
CONTRIBUTORS.	91

3. Structure and Function of the Lung

Remarkable progress has been made during the past decade in understanding the complex functions of the various organs involved in respiration and also the interactions between them that are necessary for the integrated function of the respiratory system. This progress in large part represents advances made possible by combining traditional approaches of physiology with new technologies and with a broad range of scientific disciplines that had previously contributed little to biomedical research. It has been known for some time, for example, that the elastic properties of the lungs are altered in disease states in association with changes in connective tissues and lung structure; the field of continuum mechanics, however, is now providing new tools with which to link various separate observations into coherent bases for understanding altered organic function.

During the past decade, major new insights have been gained into the nature of the complicated interactions between the heart, lung, and thorax, and there is promise of revolutionary changes in clinical approaches in support of these vital organs.

Advances in both the theory of airflow limitation and the technology of various measurements have enabled more precise interpretation of expiratory flow data readily obtainable during screening tests. The advances clearly have the promise of leading to the detection of the subtle impairments in lung function that antedate by many years the occurrence of clinically significant obstruction of airways.

Disorders of ventilatory control are viewed in a perspective that is totally different from the perspective 10 years ago. Formerly thought to be fascinating but rare manifestations of abnormalities in poorly understood respiratory control centers, these disorders are now known to be quite common and to play important roles in such diverse conditions as sleep apnea in children and episodes of decompensation in elderly people with chronic respiratory impairments. Awareness of these problems has resulted from advances in several areas including basic muscle physiology, knowledge of the nature and function of chemoreceptor cells that detect changes in the gas tensions in the blood, and particularly research on the integrated control of respiration. Heredity is now known to be a factor in control of ventilation. As scientists have examined the responsiveness of ventilation to

stimulation, it has become clear that familial aggregations of healthy individuals with reduced responsiveness are quite common, especially among families of patients demonstrating deficient ventilatory responses.

Studies of gas exchange in the lungs and in other tissues are important in several respects. They provide the information for understanding normal lung function and the alterations created by lung disease. New technologies have permitted more detailed analysis of gas exchange, particularly with the use of multiple gas tracers. Such studies are defining the abnormalities of gas exchange that occur in many lung diseases. Further, they will provide information that is critically needed for developing support systems for use in hostile environments such as the deep sea or outer space.

The science of lung cell biology came of age during the last decade, and exciting advances have been made in the basic understanding of lung function in many disease processes. In neonatal respiratory distress syndrome (RDS), for example, basic science information concerning the function, metabolism, chemistry, and hormonal control of surfactant (a surface tension lowering substance) has provided the clinician with the means to predict, prevent, and manage this serious neonatal disease. The result of such a coordinated research effort has culminated in a dramatic decrease in the number of infants dying from RDS.

Basic laboratory techniques of maintaining isolated lung cells in culture have resulted in significant new information. The metabolic function of pulmonary endothelial cells, for instance, is now known to have a very important role in the regulation of many potent mediators and hormones. These cells come in contact with the entire cardiac output, and an appreciation is developing of how they exert regulatory influences on other organs and their physiologic functions. In the 1980's, the roles of potential mediators and hormones in either the causation or prevention of various lung diseases will be further elucidated.

During the last decade, a more thorough knowledge has been acquired of the normal regulation of water movement, mucus secretion, and ciliary motion. All of these fundamental processes of epithelial cells and glands involving the control of mucus secretion and movement will provide important information for elucidating the basic defects in the lungs of patients with cystic fibrosis.

Another important area that has been studied during the past 10 years and is of continuing interest is the lung's defense mechanism, especially the role of the alveolar macrophage.

Alveolar macrophages can scavenge inhaled infectious organisms and harmful particles, participate in diseases such as tuberculosis and cell-mediated lung diseases, and recognize and destroy cancer cells.

Great strides have also been made in understanding normal lung development. Techniques to measure lung function in adults have been adapted for the pediatric patient, and new techniques specifically designed for the young child have been developed. During the next 5 years, correlative structural-functional studies should attempt to determine how an aberration in normal lung maturation may be related to the development of chronic obstructive lung diseases in adulthood. Nonrespiratory functions need to be explored, such as lung defense mechanisms. In addition, possible disordered lung function as a consequence of treatment with modalities such as mechanical ventilation and high oxygen levels is an area that needs careful evaluation.

The 1970's will probably be remembered as the decade in which basic knowledge was acquired of the structure and function of the normal and diseased lung and of many of the mechanisms involved in these processes. Much of this knowledge has already been transferred into better diagnostic tools, preventive interventions, and management of patients with respiratory diseases.

Physiology

RESPIRATORY MECHANICS

The area of physiology concerned with how the mechanical properties of the lungs and thorax influence the volume and flow of blood and gas in the blood vessels and airways is called respiratory mechanics.

State of Knowledge in 1972

The techniques of measuring pressure, flow, and volume in isolated organs, in animal preparations, and in normal and ill human subjects were highly developed. From such measurements, much had already been learned about the mechanical properties of the respiratory system and the importance of the role of altered mechanics in respiratory disease.

Static Pressure-Volume Relations

Respiratory disease was, and to a large extent still is, divided into two distinct categories: restrictive, where the volume of gas within the lungs is small, and obstructive, where the flow of gas within the airways is reduced. It was known that the volume of gas within the lungs depended on the elastic properties of the lung tissue and on the surface tension of the fluid between the alveolar surface and the air within the alveoli. It was also known that the lungs could become less compliant, or stiffer, when the properties of either the lung tissue or the surface tension are altered. Alterations in lung tissue were known to be responsible for the restrictive component of fibrotic lung disease, and alterations in surfactant, at least in part, for the restrictive component of respiratory distress syndrome in both the newborn and the adult. A change in the mechanical properties of the thorax, either structurally as in kyphoscoliosis or obesity, or from weakness of respiratory muscle, as in myasthenia gravis, could also lead to small, stiff lungs.

It was recognized that the major feature and cause of obstruction in emphysema is an alteration in lung tissue that causes the lungs to be more flabby or compliant and leads to an increase in lung volume. It was also known that lungs can become more compliant with aging.

The complexity of interactions of the thorax and lungs that determine the shape of the lungs and the distribution of stress on lung surfaces was recognized. This interdependence, which is influenced by gravity, leads to a greater distention of the upper lungs and less distention in the lower lungs. The greater distention in the upper portions causes these regions to be stiffer, and the stiffening leads to decreases in ventilation when compared to regions of the lower portions. It was known that the interaction of lungs and thorax depends on how the tidal volume is partitioned by descent of the diaphragm and expansion of the rib cage. In fact, there was evidence to suggest that the descent of the diaphragm itself is a significant causal factor in the expansion of the thorax. Methods had been developed that allowed for study of the interaction of diaphragm and rib cage, but there was minimal application of them to the study of the mechanism by which the respiratory muscles produce inflation through enlargement of the thorax.

Pulmonary interdependence was known--that is, inflation of one portion of the lungs has a profound influence on adjacent portions of the lungs. In general, the parts of the lungs that are inflated tend to cause expansion of uninflated adjacent parts so that lung inflation is stabilized. This stabilization is comparable to the stabilization caused by surfactant.

It was also known that there is a profound interdependence of pulmonary vessels and airways. The small pulmonary vessels (alveolar vessels) that are exposed to alveolar pressure (such as septal vessels) are compressed during lung inflation, whether spontaneously or artificially, because of the rise in alveolar pressure relative to the pleural pressure. At the same time, the vessels within the lung interstitium, which are the extra-alveolar vessels, are expanded during lung inflation in an activity that is comparable to that of pulmonary interdependence. Appreciation of this interdependence was considered important in understanding the effect of gravity on the regional distribution of blood flow.

Dynamic Pressure-Flow and Volume-Flow Relations

Perhaps the major achievement prior to 1972 was the demonstration that the limitation of airflow determines the maximum rate of expiratory flow. By 1972, it had been shown that beyond a specific level of expiratory effort, expiratory flow is independent of any increase in effort. It was also known that the level of flow depends on lung volume, lung compliance or elastic recoil, tone of airway smooth muscle, resistance of small airways, and the cross-sectional area of the large airways. While the general significance of airflow limitation was appreciated in 1972, the mechanism, especially in relation to specific disease states, was not understood at a fundamental level.

One of the great contributions to pulmonary mechanics prior to 1972 was the demonstration that the major resistance to airflow in normal subjects is in large airways and that the small airways contribute very little to the total resistance. Since it had become apparent that an increase in the resistance of small airways is a major cause of limitation of airflow in chronic respiratory disease, it was assumed that there would have to be a major involvement of small airways before a significant degree of limitation can be detected. In 1972, it was accepted that there must be a long transition between the beginning of disease of the small airways and the development of significant limitation. In order to understand the natural history of the transitional process and perhaps prevent the development of the limitation, it was realized that new approaches to the detection of small airway dysfunction were required, and it was in this area that one of the most important contributions was made.

By 1972, the general features of reflex bronchoconstriction were known. Inhalation of irritant gases, such as sulfur dioxide and chemically inert dust aerosols, were known to cause bronchoconstriction, which depends on intact motor parasympathetic pathways. The rapid response and reversal of the constriction suggested that changes in smooth muscle tone are the cause of the bronchoconstriction. It was known that the asthmatic subject

shows a markedly increased response to nearly any bronchoconstrictive agent and that this airway hyperreactivity is the one characteristic always present in asthma. It was suggested, but not known, that asthma was a disease characterized by an increased responsiveness of the afferent or efferent limb of the reflex pathway or an increase in responsiveness of the smooth muscle. There was little general knowledge about the contraction of smooth muscle, and even less about bronchial smooth muscle. In addition to reflex bronchoconstriction, the role of mediators, such as histamine, that are released from lung tissue in allergic reactions was also being considered.

Program Goal Through 1982

- Elucidate respiratory mechanics in normal breathing and in physiologic adjustments to exercise, altered environments, and disease states.

Accomplishments Through 1982

Static Pressure-Volume Relations

While the general role of the elastic properties of lung tissue and surface tension in determining the static pressure-volume characteristics of the lungs has been upheld, investigators now realize that the process is more complicated than was originally thought. The compliance of the lungs has been shown to depend on the geometric arrangement of the tissue and the distensibility of the tissue. The magnitude of surface tension has been found to affect the geometric arrangement of the tissue components, so that change in surface tension can produce a change in the elastic properties of the components. One of the newest exciting areas of research is the correlation of descriptions of the chemical structure of the tissue with the sophisticated mathematics of lung elasticity that is being developed by engineers through the use of continuum mechanics. Knowledge of the stresses and strains that exist in three dimensions in the respiratory system can now be provided by implanting small metal markers in the lungs of experimental animals and reconstructing three-dimensional patterns of deformation through computerized roentgenographic techniques.

Interactions Between Lungs and Thorax

There has been an explosion of information about the role of the respiratory muscles in controlling the volume of the thorax. By application of methods that partition the tidal volume between descent of the diaphragm and expansion of the rib cage, coupled with measurements of diaphragmatic tension (transdiaphragmatic pressure) and of electrical activity of the respiratory muscles (from the electromyogram), it has been learned that inspiration involves a comprehensive integration of all of the muscles of respiration: when the muscle function is coordinated, the diaphragm increases lung volume not only by its descent, but also by enlarging the rib cage. Optimal diaphragmatic function requires coordinated function of the intercostal and accessory muscles that stabilize the rib cage. Lack of such stabilization has been found to be a principal cause of the ventilatory insufficiency that may accompany high transection of the spinal cord. It has also been suggested as a significant cause of ventilatory dysfunction during sleep, especially in infants. During rapid eye movement (REM) sleep, a lack of coordination between the diaphragm and intercostal muscles can result in a descent of the diaphragm that causes the rib cage to move paradoxically.

New studies of respiratory muscle function have shown that muscle fatigue can contribute markedly to the ventilatory failure that accompanies respiratory disease and can be a major factor in keeping a patient on artificial ventilatory support. In fact, death from apnea can result from fatigue. Recent work also shows that respiratory muscle fatigue can be the primary cause of death in circulatory failure. When the cardiac output is markedly impaired, the respiratory muscles can fail to respond to neural stimulation even when the circulation is still sufficient to maintain adequate function of the brain, heart, and other vital organs. It is just now being recognized that apnea plays a major role in the cause of death, even when, with the exception of the development of muscle fatigue, the respiratory system is functioning normally.

Respiratory and Circulatory Interdependence

The most exciting and important development in this area is a new understanding of the interaction of the lungs and thorax with the heart. It was known that the changes in pleural pressure that accompany respiration play an important role in affecting venous return through changes in right atrial pressure. It was also known that spontaneous inspiration causes an increase in the output of the right heart from the increase in venous return. Nevertheless, left ventricular output always decreases with spontaneous inspiration. It had been assumed that the decrease in left ventricular output was due to a decrease in the filling of

the left heart, either from pooling of blood within pulmonary vessels or from compression of the left ventricle caused by enlargement of the right ventricle. Recent studies suggest that the primary mechanism of the reduction of left ventricular output is the reduction of pressure, caused by the fall in pleural pressure, on the surface of the left heart. The decrease in left ventricular output that accompanies spontaneous inspiration has been found to be exaggerated in conditions where the fall in pleural pressure is increased, as in acute asthmatic attacks.

Perhaps the most striking effect of pleural pressure and lung inflation on cardiac function has been revealed through studies of the mechanism of the maintenance, by chest compression, of blood flow in the nonbeating heart during cardiopulmonary resuscitation (CPR). Until recently it was assumed that chest compression caused blood flow by the direct compression of the heart, but recent compelling evidence shows that systemic blood flow is the result of the increase in intrathoracic pressure that causes movement of blood from the lungs and the heart. Accordingly, general principles of pulmonary mechanics are now being applied in therapeutic methods that were not even under consideration a few years ago. Rather than cause local depression of the sternum, emphasis is now placed on increasing pleural pressure.

Flow Limitation

The mechanism of flow limitation in the airways and indeed in elastic tubes in general is now understood at a much more fundamental level. Since 1972, the importance of the wave speed mechanism has been established in experimental studies of animals in vivo and of excised human lungs. The events of flow limitation can now be analyzed mathematically, and a mathematical model has been developed that allows precise understanding of how lung elasticity, bronchial tree mechanics, and gas density affect maximal flow. The change in forced expiratory flows that occurs when gases of different density are breathed, particularly oxygen and 80 percent helium in comparison to room air, is now understood at a much more fundamental level. The study of the effect of density on maximal flow has permitted an evaluation of the relative effect of large and small airways on maximal flow in both health and disease. Much work has been done in establishing the normal range of flow maxima. It is now appreciated that much of the normal variability reflects individual differences in terms of the relative size of the airways and lungs, as well as the relative size of large and small airways. The term "dysanaptic growth" was coined to identify this important concept.

Compelling new evidence shows that the earliest manifestation of obstructive lung disease begins with significant impairment of only a few regions of the lungs, either small airways or

parenchyma, and that as the disease progresses the number of regions involved increases. Tests that are capable of detecting regional inhomogeneities are much more sensitive for detecting abnormalities of the earliest stages of obstructive disease than tests that evaluate overall lung function when only a few regions are involved. The flow-volume curve and spirogram, which are the simplest and most commonly used methods for evaluating pulmonary function, had been assumed to measure only overall function and therefore would be insensitive to the earliest changes of obstructive disease. It now seems likely that careful analysis of the flow-volume curve in terms of shape, and of the spirogram in terms of time are as sensitive as any of the more complicated tests of pulmonary function that measure directly the extent of regional inhomogeneity. If these methods are validated, simple techniques will be available that will allow the detection of obstructive disease at a very early stage, and population studies can be undertaken to determine the effectiveness of such early detection in the prevention of disease.

The exploration of the mechanism of flow limitation has refocused attention on the mechanism of the cough. Experimental models have shown that as flow limitation develops, there are vibrations (waves) in the wall of the airways that can dislodge mucus and assist in the defense of the lungs. Nevertheless, recent work has shown that repetitive coughing in experimental animals can lead to dysfunction of mucociliary clearance. This dysfunction can lead to an increased deposition of irritant or carcinogenic materials. A clinically intriguing finding is that the choke point of flow limitation, where the vibrations in the wall of the airways are at their greatest level, and the squamous cell carcinoma have a common site.

Tests for Early Detection of Chronic Respiratory Disease

The assumption has been confirmed that there can be extensive impairment of small airway function without significant overall impairment of pulmonary function. A major challenge was met during the past decade to develop tests of pulmonary function that could detect impairment of pulmonary function at an early stage of disease and were simple enough to apply to population studies. Since there were no adequate experimental models, it was difficult to develop a specific test capable of detecting the early changes, and it was difficult to compare the effectiveness of such tests. One of the great achievements of this past decade was an interdisciplinary approach to the challenge that pooled the efforts of pulmonary physiologists and epidemiologists. Their approach was to compare tests in populations that were presumed to be at high risk for the development of disease such as cigarette smokers, special occupational groups, and individuals who were presumed to come from populations with a familial or genetic susceptibility to

chronic respiratory disease. When large numbers of subjects from such populations were compared to presumably nonsusceptible populations, small but statistically significant differences in the pulmonary function were presumed to reflect the earliest functional impairment of the disease. Studies were made at a number of institutions. Much more has been learned from them about the risk factors for the development of chronic disease, and the effectiveness has been established of a number of simple tests that are capable of detecting disease at early stages.

Airway Smooth Muscle

It has been learned that the smooth muscle of the airways has many features in common with smooth muscle from other locations, and with striated muscle as well. Ultrastructural examination of tracheal and bronchial smooth muscle has demonstrated certain differences in muscle cell connections and innervation. Human airway smooth muscle shows many cell-to-cell junctions of the gap-junction type. This finding indicates that the smooth muscle can function as a single unit or syncytium. More knowledge about the electrical activity in the airway smooth muscle may help increase the understanding of hyperreactive airways in asthma and other lung diseases.

The neural control of airway smooth muscle, which 10 years ago was thought to be a simplified scheme of excitatory cholinergic and inhibitory adrenergic nerves, largely determined by morphology, is now known to be a very complex system with three basic neural pathways and numerous interactions and controls between the different pathways.

Airway smooth muscle contains numerous receptors for a variety of chemicals. Of recent interest are the effects of prostaglandins on the airway smooth muscle and their possible function in disease. Extensive work has recently demonstrated that the leukotrienes C_4 and D_4 , which are thought to be the slow reacting substance of anaphylaxis (SRS-A), are active on human airway muscle and may play a role in allergic diseases. In the past few years, the presence has been demonstrated of numerous peptides in nerves and ganglia of the airways. Of particular interest was the suggestion that vasoactive intestinal peptide (VIP) may be the chemical mediator of the nonadrenergic inhibitory system. Of the many new drugs that have been developed, disodium cromoglycate, salbutamol, and the atropine-like compounds seem to act as bronchial smooth muscle relaxants.

Another area of interest has involved the relationship between the neuroendocrine cells in the airway epithelium and the possible function that the contents of these cells may have in the control of airway smooth muscle. Numerous peptides and biogenic

amines have been demonstrated in these cells, and the distribution of the cells in the human health and disease states has been studied.

State of Knowledge in 1982

Studies of the effect in lung disease of the alterations in lung tissue components on lung compliance have just begun: Are the increased compliance of emphysema and the decreased compliance of fibrosis due to a change in the nature and amount of collagen and elastin or to the altered geometry? What components of the tissue are responsible for the elastic properties? Until recently, it was assumed that these properties were largely dependent on collagen and elastin. It has been shown, however, that actin and myosin, which are the major contractile components of muscle, are ubiquitous in lung tissue and that they might be responsible for the altered properties of lung tissue in disease. It has been demonstrated, for example, that lung tissue from experimental models of pulmonary fibrosis not containing smooth muscle shows an increased response to smooth muscle agonists, presumably through their effect on nonmuscle actin and myosin. This increased responsiveness may have a significant function in the stiffness of the lung tissue.

New approaches to understanding respiratory and circulatory interdependence have suggested avenues of investigation with direct application to cardiopulmonary resuscitation. Recent knowledge about airway smooth muscle is likely to increase the understanding of the mechanical properties of the respiratory system.

Program Goals 1982 to 1987

- Develop better understanding of micromechanics of the respiratory system and its correlation with connective tissue biochemistry.
- Understand respiratory muscle fatigue in health and disease.
- Understand the mechanics of circulatory and respiratory interdependence in various disease states.
- Evaluate the relationships between pulmonary mechanics and improved circulation during cardiopulmonary resuscitation.

- Attempt to correlate mechanical dysfunction in early disease states with morphologic and biochemical changes.

Research Activities 1982 to 1987

The following activities are given as examples:

- Understand the roles of collagen, elastin, and parenchymal contractile components in affecting pressure-volume relationships of the lung in human health and disease states and in animal models of disease.
- Determine the role of localized alterations in alveolar connective tissue and contractile components in affecting regional and global pulmonary ventilation and perfusion.
- Evaluate the interaction between endothelial, interstitial, and vascular smooth muscle tissue components in control of regional and global pulmonary blood flow.
- Understand the mechanisms of respiratory muscle fatigue and correlate these with changes in circulation, blood gases, nutrition, and other factors.
- Develop methods of detecting muscle fatigue.
- Utilize knowledge about muscle fatigue to design methods of prevention and treatment.
- Evaluate the effects of direct mechanical interdependence of the normal lungs and the heart as well as during states of altered lung, thoracic, and pericardial mechanics and altered myocardial function.
- Delineate in humans the role of alterations in lung volume, pleural pressure, and right ventricular volume on cardiac output and pulmonary vascular congestion.
- Devise methods of alleviating the deleterious effects of altered respiratory mechanics on circulation, and manipulate respiratory mechanics to support the failing circulation.
- Conduct hemodynamic measurements in human subjects with cardiac arrest to test a variety of manipulations of intrathoracic pressure.

- Establish animal models for the study of specific aspects of resuscitation research.
- Expand research on theoretical models and validation of these models to answer questions relative to distribution of systemic blood flow and cerebral and pulmonary circulation.
- Develop methods to assess blood flow and metabolism and the state of microcirculation during severely depressed flow conditions.
- Define thoracoabdominal mechanics and elucidate pressure-volume and stress-strain characteristics of displacement within the thoracoabdominal area.

CONTROL OF BREATHING

Breathing is a complex motor act in which respiratory muscles rhythmically contract and relax. This vital process is subject to volition; the respiratory muscles and lungs are used in executing other functions, such as speaking, adjusting posture, and swallowing. The control of breathing, therefore, serves two ends: to meet primal needs for a supply of oxygen and the elimination of carbon dioxide, and to participate in nonrespiratory behavioral activity. The overriding priority attaches to the first, and to this end, breathing is automatically controlled by the brain.

The brain, the respiratory muscles, and the lungs, which comprise a person's respiratory control system(s), work together harmoniously and unconsciously to achieve the exact appropriate amount of breathing while the person is resting, talking, exercising, sleeping, and even while lightly anesthetized. Important respiratory variables, such as amounts of carbon dioxide (CO_2) and oxygen (O_2), are measured by specialized sensors, which, in turn, influence the respiratory control centers of the brain and control the flow of gas into and out of the lungs so that the CO_2 and O_2 of blood are held constant.

State of Knowledge in 1972

In 1972, the knowledge of the control of breathing, to a large extent, was phenomenological. Physiologists appreciated two types of negative feedback, chemical and mechanical. The former derives from specialized chemosensors that detect the pressures of oxygen and carbon dioxide in arterial blood. These pressures reflect the performance of the lung. Physiologists realized that

chemical feedback constitutes a principal source of excitation of the respiratory centers. Nonetheless, available knowledge in 1972 indicated that such chemosensory activity alone would not result in adequate performance of the respiratory control systems. In order to be effective in producing the to-and-fro motion of the chest, the brain has to produce rhythmic bursts of neural activity. While scientists had long appreciated that areas of the brain, referred to as respiratory centers, possess an inherent neuronal rhythmicity, they partially understood the importance of mechanically operated feedback to achieve effective breathing. In this feedback, neural information derived from specialized sensors "measuring" lung volume provides feedback to the respiratory centers that promote the rhythmic activity.

Chemosensors

Two types of chemosensors were known in 1972. One, the peripheral chemosensor, lies in the wall of a major artery. The other, the central chemosensor, lies somewhere in the brain. Scientists realized that the peripheral chemosensor provides the sole source of warning for low blood oxygen. How the sensor detects a decrease in the pressure of oxygen was not understood. In fact, there was no knowledge of which cellular elements respond to a change in oxygen pressure or of the molecular or cellular basis for this response. A truly remarkable feature was appreciated; the receptor responds to changes in O_2 tension at levels well above those known to exert any metabolic effect. The cellular and biochemical mechanism of response to low blood oxygen, therefore, represented an intriguing mystery. The response of the sensor to changes in CO_2 tension was better understood; CO_2 excites the receptor by causing changes in the concentration of hydrogen ions. The cellular and biochemical mechanisms responsible for this response remained obscure. Scientists appreciated that the sensor is particularly sensitive to simultaneous alterations in both CO_2 and O_2 .

In 1972, virtually all aspects of the central chemosensor, including its identity, were uncertain. A general consensus based on inferential evidence held that the unknown receptor cells probably respond to changes in hydrogen ion concentration in their immediate environment. This belief rested on the finding that breathing is influenced by changes in the acidity of extracellular brain fluid at a constant arterial CO_2 pressure. While it was well established that such changes are important in certain situations, such as adaptation to high altitude or to an acid-base imbalance in the blood, scientists had no understanding of how these readjustments are accomplished.

Mechanosensors

In 1972, mechanosensors were recognized to exist in two locations in the respiratory system: in the lung and in the respiratory muscles. Scientists had identified three types of lung mechanoreceptors: pulmonary stretch receptors, "irritant" receptors, and J receptors (so named because they were presumed to have "juxta"-pulmonary capillary location). The first two possess large fibers that travel in the vagus nerve to the brain, and the last is supplied by so-called unmyelinated small axons. About all that was established in 1972 was that the stretch receptors effectively monitor the volume of the lungs, that the irritant receptors respond in an irregular pattern in response to noxious gases, and that the J receptors respond to congestion of the pulmonary vasculature as would occur in heart failure.

In 1972, scientists appreciated that, while many respiratory muscles are richly endowed with mechanosensors called muscle spindles, the diaphragm, which is the primary muscle of breathing, lacks such sense organs. The function of these receptors and their local effects in the spinal cord were known to be comparable to that of other muscles. They provide automatic adjustment in muscle performance to meet the local demands to accomplish the desired movements. Intriguing evidence, however, indicated that these muscle spindles may also exert their effects higher in the nervous system.

Respiratory Control Centers

With the advent of microelectrode recording techniques, physiologists were able to monitor the behavior of individual neurons in the base of the brain (pons and medulla) that are concerned with the control of breathing. In 1972, respiratory neurons could be classified as inspiratory and expiratory, but almost nothing was known of the function of individual neurons, their exact location, or their connection with other parts of the brain or the respiratory sensors. Finally, the neuronal basis of the genesis of the respiratory rhythm, long a challenging mystery to neuroscientists, remained as enigmatic as ever. By 1972, physiologists had described the relationship between global activity of the respiratory centers, pulmonary ventilation, and chemical feedback. However, they lacked insight into the nature of the activity leaving the respiratory control centers. A conceptual framework had been developed in which the centers transmitted a "drive" to the respiratory muscles, as shown in figure 5. This concept, however, lacked concrete definition and experimental support. Finally, the control centers were thought to be influenced by changes in the higher nervous system, but again, specific evidence supporting this notion was meager.

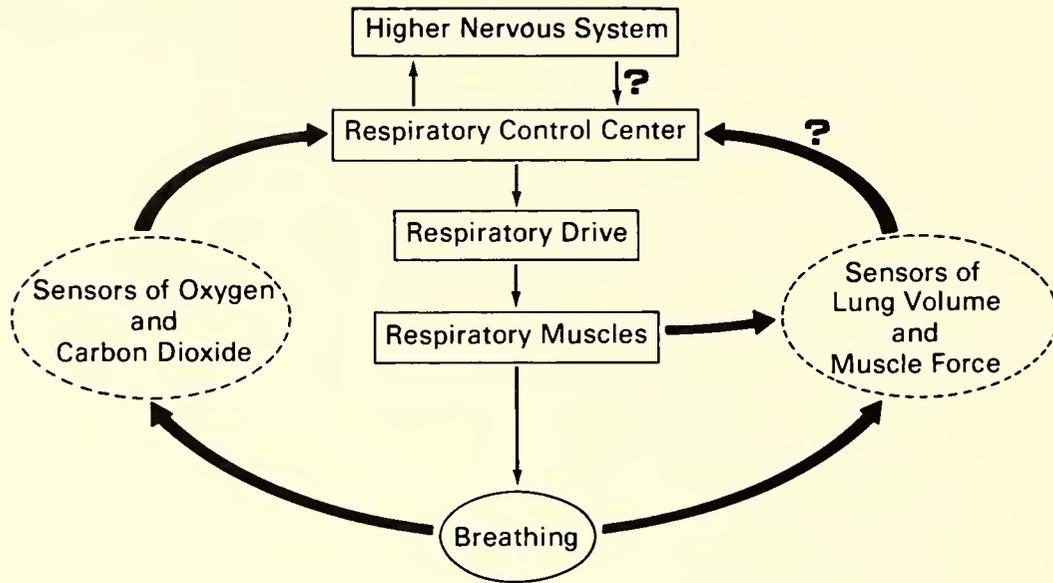


Figure 5. Concepts of Control of Respiration in 1972

Program Goal Through 1982

- Increase knowledge of the roles of chemical, mechanical, and neural factors in the control of ventilation, in the course of adjustments to exercise, sojourn at high altitude, in sleep, and in various pulmonary disease states.

Accomplishments Through 1982

Major advances have occurred in research on each of the components of the control system(s): chemical feedback, mechanical feedback, respiratory control centers and muscles, the higher nervous system, and human ventilatory control.

Chemical Feedback

Using the carotid body (a small mass of tissue situated at the large arteries on each side of the neck) as a prototype of the peripheral chemosensor, investigators combined a variety of approaches to investigate the cellular and biochemical mechanisms by which this receptor senses hydrogen ions and low oxygen. One

particular focus of investigation has been the glomus cell, the most numerous cell of the carotid body. Investigations have shown that nearly all the nerve endings of the carotid body terminate on glomus cells. Whether the nerve endings themselves sense chemical changes or whether the glomus cell is the sensitive element has not been resolved. Investigations have established that the glomus cell contains a variety of neurotransmitters. This finding has led to the tentative conclusion that whatever the sensitive element is, the interaction of glomus cells and nerve endings has an important function in chemoreception by the carotid body. In other words, glomus cells probably communicate with the sensory nerve terminals through release of neurotransmitters such as dopamine, norepinephrine, serotonin, and acetylcholine. Moreover, the enkephalins, the endogenous "morphine" of the nervous system, appears to be released by the glomus cells. Investigations during the past 10 years have established that a mechanism exists in which the peripheral chemoreceptor can be triggered at different levels ("reset"). This triggering is accomplished by the transmission of neural impulses from the brain to the carotid body where they exert an inhibitory action. A reasonable conclusion is that this action is exerted through the release of the neurotransmitters. Finally, important research has shown that the peripheral chemoreceptor responds rapidly to hydrogen ions and to low-oxygen stimuli, with the result that information transmitted to the nervous system reflects not only the average level of these important variables but their oscillations and rhythmic fluctuations, which are caused by the periodic nature of breathing.

Considerable progress has been made in locating the central chemosensor. A variety of evidence suggests that the receptor cells lie just below the ventral surface of the medulla. Evidence indicates that the concentration of hydrogen ions of extracellular brain fluid is actively regulated so as to maintain a constant acid-base balance. Once again, the body appears to be able to "reset" the chemoreceptor, this time in an attempt to protect the brain from disorders of acid-base balance. The means by which this adjustment is accomplished was debated throughout the past decade, but recent evidence has conclusively shown that active transport mechanisms similar to those operating in the kidney to excrete acid are active at the interface between the blood and the extracellular brain fluid. These energy-consuming transport mechanisms regulate the concentration of hydrogen ions in the extracellular brain fluid. This regulation sets the response level of the central chemosensor to arterial CO_2 tension.

Several investigators have provided suggestive evidence that the lung contains receptors sensitive to CO_2 . While this is true of the avian lung, the presence of such receptors in the mammal has been debated. The function of such receptors would presumably

be to sense the changes occurring during muscular exercise wherein metabolically produced CO_2 is carried to the lung by the circulation. If lung CO_2 receptors exist, they would sense the increase in CO_2 arrival during muscular exercise and stimulate an increase in pulmonary ventilation response. The most convincing evidence at the present time does not favor the existence of a chemosensor lying within the lung; the regulation of CO_2 and O_2 in the blood appears to be mediated by CO_2 and O_2 in systemic arterial blood.

Mechanical Feedback

Perhaps the most impressive growth of knowledge about the control of breathing in the past 10 years has come in understanding factors that influence breathing in humans and animals. According to recent research findings, the pattern of breathing, the muscles that are used, and the duration and size of each breath are principally governed by mechanical feedback. Figure 6 shows the steps in translating the activity of the respiratory control centers into breathing. The first step involves the partitioning of neural excitability into bursts of inspiratory and expiratory activity. The duration of these bursts is determined through mechanical feedback. Researchers have localized lung stretch sensors within the tracheal bronchial tree, and they have shown that the sensors lie in the wall of the large airways and that they are activated not only by increases in lung volume, but also by constriction of airway smooth muscle. In both animals and humans, these sensors have been shown to have a crucial function in determining the size of each breath, the duration of inhalation and exhalation, and the volume of the resting lung. The respiratory muscle sensors, which have a similar function, were found to compare the desired respiratory movement with actual movement. Their signals to the nervous system influence the timing of the events of the respiratory cycle as well as the final neural activity at the spinal level. Neural activity from both lung and muscle sensors may have a function in sensations of shortness of breath in lung disease.

Respiratory Control Centers and Respiratory Drive

There has been progress in identifying the neurons of the brain that generate the respiratory rhythm and in understanding their interaction with other parts of the nervous system. Specifically, three areas of concentration of respiratory neurons have been located, two in the medulla and one in the pons. These neurons have been identified with regard to their functional types and their importance in processing afferent information and

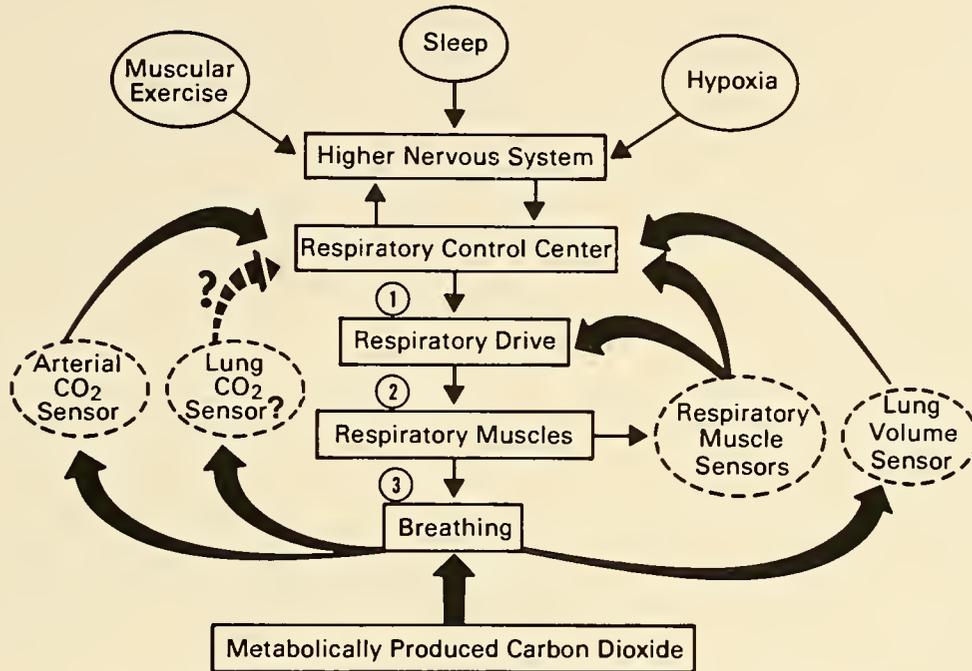


Figure 6. Concepts of Control of Respiration in 1981

generating the respiratory drive. Perhaps the most fundamental advance has derived from microelectrode recordings made inside these cells. The recordings have allowed an examination of the means by which the cells generate their spontaneous rhythmic firings. These investigations failed to reveal intrinsic spontaneous activation analogous to that seen in pacemaker cells of the heart. Evidently, the rhythm generated by these respiratory centers probably arises through the interconnections of the various inspiratory and expiratory neurons. Exactly how these interconnections generate the respiratory rhythm has not yet been shown, but the overall concept seems to have been established. Research has shown that, once initiated, inspiratory neural activity builds up along a predetermined path until inhibitory processes, derived either from mechanical feedback or from other parts of the brain, activate a specialized group of neurons that suppress this activity and cause a switch to expiratory phase. Respiratory "drive," therefore, can be equated with the rate of rise of inspiratory neural activity.

A series of important studies has shown the characteristics of the mechanisms by which respiratory drive results in activation of the respiratory muscles and by which the contraction of the respiratory muscle results in breathing. This understanding has allowed an appreciation of the remarkable performance of the various respiratory muscles functioning in coordination with ribcage, abdominal, and laryngeal muscles, and particularly of how the muscles achieve the required ventilation despite mechanical loads such as presented in diseases. This new information has allowed the development of comprehensive theoretical analyses by which the transformation of neural activity into volume excursion by the lungs can be accurately predicted, and the contribution of mechanical abnormalities of the respiratory system can be precisely quantified.

In another series of studies, it has been demonstrated that the neuronal networks of the control system(s) have a "memory"--that is, the effect of a stimulus, whether excitatory or inhibitory to respiration, can last for some minutes even though the stimulus has ended. Undoubtedly, this important mechanism dampens the fluctuations of respiration that would otherwise occur. Paradoxically, the deleterious prolonged cessation of respiration that occurs in newborns following laryngeal stimulation may also be due to the "memory."

As in other areas of neurobiology, an interest has recently developed in the effects of various neurochemicals, produced by the brain itself, on the function of neurons involved in respiration and on ways by which these neurotransmitters and neuro-modulators affect the level of breathing. Dopamine, serotonin, norepinephrine, and some of the amino acids are clearly involved, although precise mechanisms and loci of action have not yet been determined. A number of neuropeptides also affect respiration. Endorphin, which is the brain's natural opiate-like substance that may have a continuously inhibitory modulating effect on respiration, has been studied the most. It seems likely that several of these substances are involved in setting the level of breathing in both normal and abnormal states. An understanding of their function may lead to better explanations for abnormalities of breathing and to better treatment of disease.

Higher Nervous System

How and under what circumstances the neural structures above the pons and medulla influence breathing has been a subject of considerable research since 1972. The investigations have predominantly been related to muscular exercise, sleep, and brain hypoxia.

An intriguing and important mystery is the way the control system(s) produce the large and precisely controlled increase in breathing during muscular exercise. While progress over the past decade has been substantial, the mystery is still not completely solved. Certain speculations, such as resetting of the peripheral chemoreceptors, have been abandoned. Other speculations, such as the postulated lung CO₂ receptor, have been thoroughly explored and are possible but somewhat tenuous explanations. Factors of the central nervous system within the brain itself seem likely. The higher nervous system contains areas referred to as "locomotion centers." When the areas are stimulated in experimental animals, quasi-normal locomotion results. If the animal has been paralyzed before the locomotion centers are stimulated, the nervous system engages in the same motor processes, but no overt muscular activity occurs. Observations of breathing in this situation have shown that neural respiration is stimulated during these periods of "fictive locomotion." This finding indicates that neither CO₂ production nor sensory activity related to muscular exercise is crucial to breathing, but that the essential mechanism lies within the nervous system itself. Overall, substantial progress has been made in understanding one of the most fundamental properties of the respiratory control system in the mammalian organism, the ventilatory adjustment to muscular exercise. This advance has provided a basis for understanding failure of respiratory control during exercise in disease states.

Considerable advances have recently been made in understanding the mechanisms of hyperpnea from exercise in normal humans, and the understanding is now beginning to be used in treating patients with pulmonary disease. It is now clear that there are two discernible phases of the ventilatory response to exercise. The first is relatively rapid in onset and continues until O₂ and CO₂ concentration in the blood begin to change. The first phase is abrupt in a change from rest to work, whereas the response between different rates of work is slower. Investigators have attributed the first phase of hyperpnea to neurogenic mechanisms originating in the exercising limbs and to "cardio-dynamic" mechanisms; the hyperpnea is somehow linked to the increase in cardiac output and delivery of CO₂ to the lungs. The second, and slower, phase occurs only during the period in which levels of O₂ and CO₂ change. These responses have been found to be extremely slow in subjects without functioning carotid bodies and fast when carotid response is increased by low O₂ or metabolic acidosis.

Another fundamental change occurs in the mammalian central nervous system during sleep, and much has been learned during the past decade about the changes in the control of breathing that

occur during sleep and how the changes are mediated. Sleep consists of two states, quiet sleep and active sleep. During quiet sleep, the brain is quiescent, whereas during active sleep, the brain is highly active, but its overt manifestations are inhibited by neuronal activity in the spinal cord. Investigations have shown that during quiet sleep, the respiratory control system(s) operate on "automatic pilot." The various negative feedback loops exert tight control on the CO_2 and O_2 concentration in blood. During active sleep, however, neural components of behavior, such as might be associated with dreaming, disrupt the respiratory rhythm, and the effectiveness of nearly all the negative feedback control systems is compromised. Nearly all the respiratory muscles, with the exception of the diaphragm, become quiescent. This circumstance has important consequences for the airways at the level of the larynx and above, where maintaining the patency of the airways often depends upon activation of various upper airway respiratory muscles. The diffuse loss of activity of these and other respiratory muscles means that the respiratory control system(s) is highly susceptible to blockage of the respiratory airways during these periods of active sleep. These advances have led to important understandings of the pathophysiology of the sudden infant death syndrome and of sleep apnea in the adult. In addition, new therapeutic approaches to treatment of sleep apnea has been derived directly from this new knowledge. Some apneas appear to be attributable to the development, in the upper airways, of an obstruction that seems to be a consequence of loss of tone in muscles that normally act to keep the upper airways open. Recent studies have indicated that the activity of these muscles, which are located in the upper neck and throat area, is activated by the same factors that drive the classical muscles of breathing, such as high CO_2 and low O_2 , and are in fact controlled by the same "drive" that controls breathing itself. Deficiencies in this drive, therefore, may be responsible not only for inadequate volume of breathing, but also for the occurrence of obstruction of the upper airways in sleep. When the dysfunction is mild, snoring results, but in the extreme cases the upper airways can be completely blocked during inspiration. Increasingly exaggerated inspiratory effort that is entirely without movement of air results.

Animal experiments have greatly increased the understanding of the direct effects of hypoxia on the respiratory control system(s). A previous concept--that a low level of oxygen in that brain exerts only a depressant effect on breathing--omitted a very important and complex effect of low oxygen. A moderately low level of brain oxygen has been found actually to exert the opposite effect--namely, it stimulates breathing. This activity may be partly related to the development of an acidic state within the brain that stimulates central chemoreceptors, but it may also be related to increased activity of neural transmitters within the brain that influence breathing. Advances in understanding the

effects of brain hypoxia are leading to an understanding of how breathing is affected by chronic hypoxia, which occurs during acclimatization to high altitude, chronic lung disease, and cerebral vascular disease.

Ventilatory Control in Humans

In recent years, considerable useful information about breathing has been derived from the measurement of responses to various kinds of respiratory stimuli in humans. Comparison of these responses to those which result from respiratory stimulation or stresses during exercise and disease have yielded clues to the causes of deficient breathing. The responses most commonly tested are those evoked by oxygen deficiency (hypoxia) or carbon dioxide excess (hypercapnia) and by the application of mechanical devices, such as resistors, which make it more difficult to breathe.

One of the earliest examples of the value of this kind of information in understanding how normal respiratory adjustment may fail to occur has come from studies of long-term residents of high altitude. Some individuals show an excess of oxygen deficiency for their altitude of residence, a syndrome often called chronic mountain sickness. It soon became clear that these individuals breathe less efficiently than others at the same altitude. This finding led to a laboratory study of the breathing response evoked by an acute lowering of oxygen. Results showed that these individuals were deficient in the normal response, in which there is an impressive increase in breathing as oxygen concentration is reduced.

It has long been known that the extent to which patients with severe chronic obstructive pulmonary diseases maintain normal breathing varies considerably. Patients who work very hard to keep their breathing at normal levels have been called "fighters" or "pink puffers." (The latter term refers to the rosy color that patients maintain because they are not oxygen deficient.) In contrast, there are patients with equally severe lung disease who do not maintain normal breathing and appear to make little effort to do so. They are called "nonfighters" or "blue bloaters." (Their blue color develops with oxygen deficiency, and the bloated or edematous manifestation develops with fluid retention due to impending heart failure.) While it had long been suspected that the distinction between these two groups might relate to differences in respiratory drive, it had not been possible to distinguish between an inadequate response to mechanical limitation of breathing and a deficient response that was known to reflect a deficient drive. During the last decade, an ingenious and simple noninvasive test was developed that measures breathing not only in terms of the amount of air that is moved but also in terms of the attempt that is made to move it. During inspiration, the pressure

generated against a briefly occluded portion of the airways is measured. A convenient index of breathing effort that is relatively uninfluenced by mechanical derangements of the lung itself results. This and other techniques have confirmed the earlier suspicion that in contrast to "fighters" and "pink puffers," "nonfighters" and "blue bloaters" have a clearly deficient response to the classical breathing stimuli of increased CO_2 or decreased O_2 concentrations. Furthermore, indices of respiratory effort, such as the inspiratory occlusion pressure technique, allow investigators to measure the response of breathing effort to added respiratory loads, such as increased inspiratory resistance. With the use of these tests, the "blue bloater" has once again been found to be a "nonfighter" with a deficient increase in respiratory effort in response to factors that physically impede breathing. There is also some evidence that this condition may be related to a lesser ability of such individuals to perceive added respiratory loads. Because a decreased response of breathing effort to an added respiratory load is a classical effect of narcotic drugs such as morphine, the question has arisen as to whether deficient responses in patients can be attributed to the operation of the so-called endogenous opiate system. In fact, administration of naloxone, which blocks the action of opiate drugs, has seemed to improve the response in some affected patients who have chronic obstructive pulmonary disease.

The realization that there is considerable variation in ventilatory drives within any group of normal individuals has led to interesting findings. It has become apparent that the variation is not random between individuals but that there are well-defined familial clusters of high and low responses. Ventilatory drives have been found to be considerably more similar in identical twins than in nonidentical twins. These findings suggest that the variation in the general population may have a genetic base.

This information is important in understanding breathing in disease. Normal family members of "blue bloaters," for instance, have breathing drives that are considerably lower than those of "pink puffers." Similarly, evidence of familial factors has been found for control of breathing in connection with the sudden infant death syndrome (SIDS). In some studies of breathing, healthy parents of SIDS victims have shown deficient responses to increased CO_2 , to decreased oxygenation, and to added respiratory load. Finally, low ventilatory drives have been frequently found in successful endurance athletes and have been associated with an equally frequent occurrence of low drives in nonathletic members of their immediate family. Such findings again suggest the operation of familial or genetic factors in the determination of breathing drives. How decreased breathing drives are related to successful endurance in athletic performance is unclear, but the

evidence suggests a potentially exciting area for future investigation.

Thus, in both wakefulness and sleep, ventilatory drive seems to be important in determining whether patients maintain breathing in a disease state. To a great extent, the status of such drives may be determined by genetic factors. This realization not only enables a better understanding of why breathing is sometimes inadequate but also an ability to predict its occurrence and ultimately develop better forms of treatment.

New Approaches to Ventilatory Control

Until recently, the study of control of breathing was limited to measurements of pulmonary ventilation and its two classic components, the tidal volume and respiratory frequency. Simple as they look, the movements of breathing are the results of complex processes: nerves stimulate muscles, muscles move the chest wall, the chest wall moves the lungs, and lungs move gas. To some extent, these complex processes can be understood by new analyses and methods.

Investigators have begun to use dynamic forcing regimens and rapidly responding sensors coupled with digital computers to characterize the respiratory control system(s) in its transient response behavior. These approaches to the study of ventilatory control have provided a better understanding of the complex steps involved in the transformation of the activity sent by the "respiratory centers" into ventilation under both normal and pathological conditions.

State of Knowledge in 1982

Scientists currently understand the control of breathing in terms of a control system or systems, but concepts have been greatly expanded since 1972, as can be seen by comparing figure 6 with figure 5. While the general outlines remain the same, the understanding of how the various components contribute and how the overall system(s) behaves has been vastly expanded. The existence of newly found feedback loops and knowledge of their effective operation are appreciated. Of equal importance is the fact that the behavior of the system(s) is known in a variety of states, such as muscular exercise, sleep, respiratory loading, chronic hypoxia, and to some extent, during changes in such states. Neurohumoral transmitters in the sensors and in the brain are considered likely to exert a dominant influence in health and in disease. Partial understanding has been gained of how the respiratory control centers operate, how chemoreceptors and other

parts of the neuronal system impinge on it, and how the system communicates with and controls other respiratory neurons in the brain.

Certain deficiencies and gaps in knowledge were not remedied during the past 10 years. With regard to the chemosensors, the cellular and biochemical mechanisms of the sensitivity to CO₂ and O₂ remain unknown, and how they feed into the respiratory control centers to stimulate breathing is obscure. With regard to mechanosensors, little information exists about the stimulation of and the effect of J receptors. This is a particularly important gap, inasmuch as these receptors probably have key functions in many heart and lung diseases. Present understanding of the respiratory control centers is primitive. Knowledge in this area is fundamental to the detection and treatment of various forms of apnea in children and adults.

Program Goals 1982 to 1987

- Understand how breathing is controlled in selected states and situations.
- Gain understanding of the role of putative neurotransmitters and neural peptides in control of breathing.
- Improve understanding of sensory activity in the control of breathing and conscious perceptions.
- Identify the neuronal basis for respiratory rhythmogenesis.

Research Activities 1982 to 1987

The following activities are given as examples:

- Elucidate the change in control of breathing in muscular exercise, sleep, chronic hypoxia, chronic exposure to elevated carbon dioxide, and chronic acid-base imbalance.
- Document what putative neurotransmitters and neural peptides influence breathing, and elucidate how these effects are exerted.
- Identify and characterize poorly understood afferent activity important in determining pattern of breathing and respiratory sensations, such as unmyelinated afferents from the lung, and respiratory muscle afferents.

- Establish the neuronal basis for respiratory rhythmogenesis to examine the characteristics of response of the central chemoreceptors and to elucidate how the chemoreceptors impinge on respiratory "center" neurons.

GAS EXCHANGE

The history of the knowledge of respiratory physiology and gas exchange can be divided into three periods. The first includes pioneering work done by Haldane, Barcroft, and the Kroghs. These investigators were responsible for codifying much of the information developed by Lavoisier, Priestley, and others. With the exception of a few pieces of equipment such as the Van Slyke blood gas apparatus or the Haldane gas analyzer, the instrumentation during the first period was primitive, and in many cases, the approach tended to be qualitative rather than quantitative. The second period covers the era from World War II to the end of the 1950's. Spurred by national needs and in many cases helped by the advent of new technologies, several laboratories in the United States studied with a renewed vigor problems of respiratory gas exchange. New theories were proposed, concepts were tested, and a broad picture of the subject emerged. A new era began in the 1960's. Ideas were refined, and correlations of anatomic and physiologic findings were being started.

There has been recent steady growth in knowledge of many aspects of gas exchange. The areas discussed below are of particular interest. They are ones in which new developments have provided answers to questions that have been asked for a long time.

State of Knowledge in 1972

The basic principle for the determination of gases, often dating back to the pre-World War II era, was adapted to new methods, which required less manual dexterity and much smaller samples than had been needed previously. In addition, methods borrowed from other fields led to the development of new instruments. Polarography, for instance, was adapted to measurements of oxygen pressure in blood, spectrometry served to determine oxygen concentration, and gas chromatography was used to measure either respiratory or nonrespiratory gases. By 1972, most analyses could be done accurately and routinely in laboratories of small or medium size. There is little doubt that much of the subsequent progress can be attributed to the ability of such laboratories to generate vast amounts of data.

Although many of the fundamental relationships had to some extent been foreseen and explored earlier, the advent and popularization of equations that describe exchange of O_2 and CO_2 in the alveoli and represent the exchange graphically were responsible for imbuing researchers with the need for quantitative analysis. The progressive transition from slide rule, to desk calculator, to computer allowed one to extract more information out of available data. By 1972, the oxygen and carbon dioxide transport in blood as well as the interrelationship of oxygen and carbon dioxide had been well described. The great advance of the 1950's was probably the advent of kinetic methods that allowed for measurement of the time required for different reactions.

Scientists studying gas diffusion across the alveolar membrane continued to use carbon monoxide, but in a more sophisticated fashion, and they described the relationship of diffusion capacity to ventilation and to blood flow. The relationship between the two transport mechanisms (ventilation and pulmonary blood flow) had been well established, and a model had been described that allowed one to quantify the way in which uneven distribution of ventilation and perfusion affects gas exchange.

Program Goal Through 1982

- Increase knowledge of the roles of chemical, mechanical, and neural factors in control of ventilation, in the course of adjustments to exercise, sojourn at high altitude, in sleep, and in various pulmonary disease states.

Accomplishments Through 1982

Gas Phase Diffusion

Ten years ago, the view held by almost everyone was that diffusion of gases in the terminal airways occurs so fast that the inspired gas mixes with the alveolar gas practically instantaneously. Such a view implies that gas phase diffusion presents no measurable resistance. Evidence to the contrary has now been obtained. More specifically, when a subject inspires a test breath of a gas mixture containing two poorly soluble tracers of different molecular weights, the heavier of the two gases has a relatively higher concentration in the early part of the subsequent expiration, and a lower concentration in the later part of that expiration. Although it is tempting to attribute this event to a layering of the inspired gas--hence the term "stratified

inhomogeneity"--other interesting views have emerged. One of them is that there may be an intraregional difference in distribution of ventilation, with some parts of the lung inflating before others. At the end of the inspiration, gases move by diffusion between adjacent parts of the lung, and the tracer gases are separated. The churning action of the heartbeat in enhancing this mixing has now been well established. Regardless of the nature of this diffusive inhomogeneity, it now appears that it may have some practical importance, since up to one-third of the diffusive resistance to transport of oxygen from the inspire to blood may reside in the gas phase at rest. There is little doubt that in exercise, when the respiratory rate increases, and in hyperbaric conditions, when the diffusivity of gases drops, the effects may be more pronounced.

There have been significant applications of this knowledge. The avian embryo, which can exchange gas only by diffusion across the eggshell, has become a popular experimental model. In addition to supplying basic information on gas transfer by diffusion, avian experiments have provided phylogenetic data on adaptations to altitude. The second application is the development of ventilation by high frequency oscillations. This technique takes advantage of the diffusive mixing of gases in the airways and enhances the mixing by increasing the ventilatory frequency. It is now possible to obtain adequate alveolar ventilation at tidal volumes lower than dead space volumes. The information on normal gas exchange that this technique supplies is substantial, and the potential of the method, which will allow one to maintain oxygenation of patients without the need for high intrapulmonary pressures or large expansion of the chest wall, is enormous.

Blood Gas Transport

The presence in the lung of reasonably high levels of carbonic anhydrase, which is an enzyme that catalyzes the reaction between CO_2 and water, has long presented a puzzling question. Substantial progress has been made in defining its location and function. The enzyme is present in the pulmonary endothelium, where it can be a factor in facilitating the elimination of CO_2 .

The ancient question of whether oxygen is transported actively across the alveolar membrane is being asked again. A theory has emerged that cytochrome P450 can facilitate O_2 movement. The enzyme would also enhance CO_2 transport. There are interesting implications in terms of saturation of this transport and of the competition of CO_2 and O_2 it presumes. The importance of cytochrome P450 as an oxygen carrier is debated strongly, and regardless of the resolution, the attention paid to this subject may result in new valuable data on oxygen transfer.

Alveolar Gas Exchange

Maldistribution of ventilation-perfusion ratios has traditionally been assessed on the basis of the disequilibrium of O_2 in alveolar gas and arterial blood. In a radical departure from conventional approaches, it was proposed in the late 1960's that the use of gases that do not combine chemically with blood constituents can provide more information. That approach was validated in experiments in which three such "inert" gases of different solubility were used. In the last decade, the technique has been extended and refined considerably, mainly along the following lines:

- The number of tracer gases has been extended to six, covering the range from extremely soluble gases (acetone) to practically insoluble (sulfur hexafluoride), evenly spread across the scale of solubility.
- The gas chromatography technique has been improved.
- A new mathematical approach allows a description of the lung in terms of an equivalent model in which each of 50 compartments have a different ventilation-perfusion ratio.

Although there are severe limitations to the amount of information that the technique can provide, the approach has been used to describe the pattern of ventilation-perfusion distribution in a variety of situations.

Inert gases have also long been used to calculate pulmonary blood flow. Here again, the techniques have been refined and expanded. They provide more accurate information and data on different aspects of lung function. A 15-second rebreathing maneuver from a bag containing trace amounts of helium, acetylene, and carbon monoxide, for example, can now be used to determine functional residual capacity, lung tissue volume, diffusing capacity, distribution of alveolar ventilation, and pulmonary blood flow.

Tissue Gas Exchange

It is axiomatic that in order to ensure gas exchange, there must be sufficient blood flow to body tissues as well as adequate diffusion of gases into or out of the tissues. The question of whether perfusion or diffusion limits gas exchange remains unresolved, but the classical Krogh cylinder analysis has indicated that areas can have insufficient partial pressure of O_2 even if the blood at the venous end of the catheter is not hypoxic. Recent progress in investigating this problem can be

attributed, to a large extent, to a classic theoretical paper that reinforced the view that the pressure of O_2 in the smallest blood vessels is an excellent predictor of O_2 concentration in tissue.

It had long been known that when humans and experimental animals are suddenly exposed to a decrease in ambient pressure, tissue and blood gas bubbles can be formed by the inert gas previously dissolved, as seen in divers who emerge too quickly to the surface. The formation of skin bubbles was observed in a subject under hyperbaric conditions after the inert gas component of the breathing mixture was changed while the chamber pressure remained the same. It was thought that the bubbles formed because the increase of the pressure of the new gas in the tissues was greater than the decrease of the pressure of the resident gas. This theory, known as "counter-current diffusion," has been validated in a number of animal models. It is expected to lead to a better understanding and improved prevention of decompression sickness. This condition is responsible for several deaths every year in both recreational and commercial diving.

A study of intake and elimination of inert gases has also shed light on the basic behavior of cellular membranes. It has long been known that most gases have some anesthetic effect at high pressures, the effect being directly related to the fat solubility of the species. Several theories have been proposed to explain that effect, but none have been verified experimentally. During the last 10 years, a new entity was described, the high pressure nervous syndrome, which is a condition of hyperexcitability observed in animals and in humans breathing helium-oxygen mixtures at high pressures. Since the syndrome also occurs under hydrostatic compression alone, the increase in inert gas pressure cannot be responsible for the condition. It now appears that the high pressure nervous syndrome is caused by compression of the membrane and decrease of its thickness whereas the anesthetic effects of gases result from their solution in the membrane and its subsequent swelling.

State of Knowledge in 1982

Studies of gas phase diffusion, with perhaps some emphasis on high frequency oscillations and on the basic laws of diffusion, and studies of peripheral gas exchange and of carbonic anhydrase appear to be particularly promising. If progress is to be made in understanding the importance of gas phase transport, more information on the basic laws of gas diffusion is needed. Most of the available data deal with mixtures of only two gas species, whereas O_2 , CO_2 , N_2 , and H_2O normally coexist in lung spaces.

Recent theoretical and experimental work has shown that multi-component gas mixtures may behave quite differently from binary mixtures.

Program Goals 1982 to 1987

- Attempt to resolve the questions of whether diffusion in the peripheral air spaces play an important role in gas exchange or not, whether carbon dioxide in the alveolar gas can indeed exceed that in the arterial blood, and whether oxygen is actively transported by carrier.
- Describe peripheral gas exchange under a variety of experimental conditions as well as in disease.
- Investigate the possible influence of oxygen availability on oxygen consumption in peripheral tissues.

Research Activities 1982 to 1987

The following activities are given as examples:

- Investigate utilization of O_2 at the cellular level and develop noninvasive (or minimally invasive) methods for monitoring intracellular events during hypoxia and acid-base disturbances.
- Explore the mechanism of gas exchange in the peripheral circulation to yield information on the interplay between metabolism, blood flow, and diffusion across the tissues.
- Explore the effects of abnormal gas tensions on gas delivery. These include the study of the arrangements and homostatic mechanisms during hypercapnia, and hypoxia and hyperoxia.
- Elucidate the adaptive mechanism that allows peripheral tissue to function in disease when their gaseous environment is altered for long periods of time.

Nonventilatory Functions of the Respiratory System

The 1970's were preceded by two decades of descriptive studies defining how the lung appears under certain circumstances and how the lung mechanically does its job, but there had been no attempts to define how the lung is able to effect such a wide and diverse spectrum of functions. Respiratory physiology of the lung had attracted a great deal of attention, and major accomplishments had been made in the 1950's and 1960's. The advent of the electron microscope during this same period settled the 100-year-old argument of whether the terminal air sacs, the alveoli, have an epithelial lining. Structural studies of the lung were published in great quantity during the 1960's, but there were few attempts to define correlative cellular biochemical aberrations. A concept envisioned by only a few investigators was that the lung is an endocrine organ that can secrete or release a variety of different humoral substances that produce various endocrine syndromes and even influence the function of other organs. In the early 1970's, when immunology as a discipline entered into its period of phenomenal growth, the lung was one of the organs that did not receive any immunologic emphasis or study. These directions of interest are somewhat surprising in view of the unique position of the lung for exposure to both blood-borne and air-borne foreign substances.

The fact that the lung possesses an effective defense mechanism by which the peripheral lung tissue is invariably kept sterile was appreciated by scientists, although the mechanisms of the cellular membrane hair-like processes, the cilia, which function to clear mucous secretions that can contain infectious organisms and noxious particles, were not yet well characterized. In addition, there were no metabolic studies of the lung before 1973. In advances of the past 10 years, however, nonventilatory functions of the respiratory system have been clearly identified as an area of research from which answers to a variety of questions relative to all aspects of lung diseases should be forthcoming.

PULMONARY SURFACTANT

Alveolar interfacial tension is controlled by a special substance synthesized and released by alveolar epithelial cells. This lipid-rich material, which is called pulmonary surfactant, contains a high concentration of a phospholipid that is capable of lowering the alveolar interfacial tension. The elaboration of surfactant requires the sophisticated metabolic machinery involved in the synthesis and active secretion of a complex lipoprotein. Factors that are commonly found in many pulmonary diseases, such

as pulmonary edema, may interfere with the function of surfactant. Premature birth before the prenatal surfactant system has fully matured often results in a life-threatening neonatal respiratory insufficiency. It is evident, therefore, that understanding the function, metabolism, physical chemistry, and hormonal control of surfactant is important for the prediction, prevention, and management of certain pulmonary diseases. Perhaps the most compelling feature of research on pulmonary surfactant in the last decade is that much of it has been conducted in a collaborative effort of physiologists, biochemists, obstetricians, anesthesiologists, and pediatricians. The result has been a markedly improved understanding of the composition and function of surfactant, with a concomitant, dramatic decrease in the number of premature infants dying of respiratory failure. (This subject is fully discussed in section 5 of this report.)

State of Knowledge in 1972

In 1929, the physiologist K. von Neergaard recognized the importance of alveolar surface tension and conducted important experiments on its effects on respiratory mechanics, but interest in the subject became dormant until the 1950's. Between 1955 and 1970, studies were made of the physiological function of surfactant and its importance in pulmonary disease. It was known by 1972, for instance, that surfactant can reduce alveolar surface tension to values lower than that possible with any other biological material, and that the substitution of natural surfactant with other surface active materials that have higher surface tensions results in widespread alveolar atelectasis. Chemical analyses showed that the effects of surface tension manifested by surfactant are due to the large amount of dipalmitoyl phosphatidylcholine in the substance. The effects of surfactant on respiratory mechanics were described in terms of physicochemical properties. Initial experiments drawing together composition, physicochemical properties, and physiological function had been completed. An important finding in 1959 had showed that the surface tension of lung extracted from infants dying of respiratory distress syndrome is significantly higher than that of infants dying of other causes. This work provided a credible hypothesis for the etiology of this disease.

Program Goal Through 1982

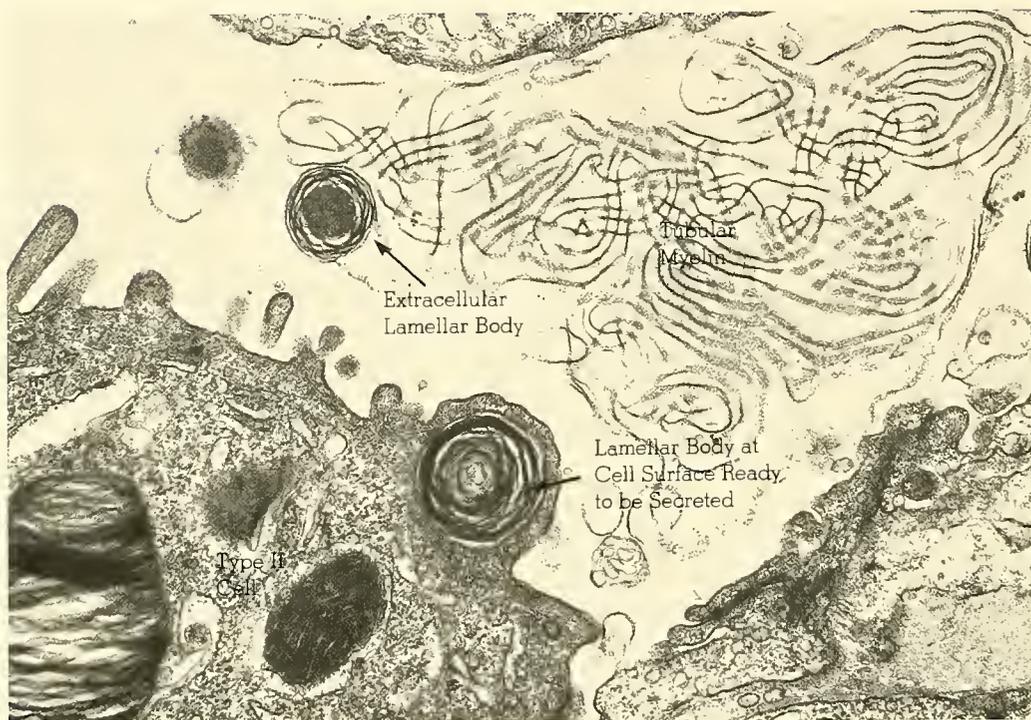
- Improve the understanding of the synthesis, secretion, and degradation of pulmonary surface active material and of the effects of endogenous and exogenous factors.

Accomplishments Through 1982

Advances during the last decade include a better understanding of the biochemical mechanisms associated with fetal development, examinations of the pathways and regulation of the metabolism of surfactant, and a better appreciation of physiological functions of this material. Improved methods were developed for the isolation of pulmonary surfactant, and its composition in several species was described. The results of these studies confirmed the high content of dipalmitoyl phosphatidylcholine found in earlier experiments and also described other unsaturated phosphatidylcholines and phospholipids in the surfactant complex. An intriguing finding was the presence of about 10 percent phosphatidylglycerol. This lipid is usually in low concentration in other mammalian tissues. Experiments attempting to relate the composition of surfactant to its function led to an appreciation of the need for this complex composition. Surfactant appears to have a balance of unsaturated and saturated phosphatidylcholines, other phospholipids, and proteins in order to fulfill all of its physicochemical functions, including transport (adsorption) to the alveolar interface, spreading at the interface, reduction of interfacial tension, and maintenance of a surface film that shows relatively slow collapse. No single constituent of surfactant has all of these requisite properties, and surfactant must be a delicately balanced mixture of several constituents to function.

Several proteins have been found in the surfactant purified from alveolar fluid. One protein was shown to be specifically associated with surfactant, and its composition, cellular localization, and metabolism have been studied. Other proteins in this complex are suspected to be metabolic products of this protein or to be associated with other materials that are also released into the alveolar milieu. The function of the major protein, which interacts readily with lipids and might be required for the proper interfacial adsorption of surfactant, is not known. The formation of an extracellular form of surfactant, which is called tubular myelin, may also be dependent upon this protein, but the importance of this structure for the physiologic function of surfactant is also not known. Considerably more effort will be required before these findings can be fully appreciated (figure 7).

The metabolism of surfactant in the fetal and adult lung has been actively explored. Studies indicate that this material is replaced in about 6 to 8 hours in small animals and that pathophysiological conditions that might interfere with such processes probably lead to a rapid depletion of the stores of surfactant. The rate of metabolism appears to be under neurogenic control in both the adult and the fetal animal. Some progress has been made in identifying enzymatic pathways for the synthesis of the



Within the cytoplasm of the type II cell, several lamellar inclusion bodies are seen. One is ready to be secreted to the alveolar space. Tubular myelin, an aggregated form of surfactant, is also seen within the alveolar space.

*Courtesy of Dr. Mary Williams, University of California, San Francisco.

Figure 7.* Electron Micrograph Showing the Aggregated Surfactant and the Type II Cell

saturated phosphatidylcholine, and there is now considerable evidence that remodeling reactions partially regulate the fatty acid composition of the phosphatidylcholine.

There has been progress in understanding the relationship between patterns of breathing or ventilation and the physical state of the lung surfactant. Recent studies demonstrate, for example, that different patterns of ventilation or increases in temperature can influence the amount of surfactant, which assumes an aggregated form of tubular myelin. In contrast to less aggregated surfactant, this form has a diminished ability to lower surface tension rapidly. Other studies have shown that there is an increased amount of aggregated surfactant in anesthetized

animals and in animals with elevated temperatures. These studies suggest that changes in the physical state of surfactant (that is, the amount in the aggregated form) can cause impairment of function, which can lead to alveolar instability and occasionally to respiratory distress. The data suggest that this situation may occur clinically during anesthesia and high fever. These studies may also explain why ventilation in or below the resting tidal volume range without an occasional deep breath leads, in both animals and humans, to a fall in pulmonary compliance, to the development of areas of alveolar collapse (atelectasis), and low levels of oxygen in the blood (hypoxemia). These findings may be relevant to abnormalities in the surfactant system in adults with respiratory distress syndrome.

Developmental endocrinologists have continued to investigate the hormones involved in fetal lung development. Some epidemiological data suggest that male infants are at greater risk of dying from RDS than are females, and investigators are beginning to examine the role of male and female sex hormones on fetal development.

State of Knowledge in 1982

Microtechniques have made it possible to measure surface tension of surfactant directly on the alveolar surface while the lung is ventilated, and new knowledge of the composition and physical properties of pulmonary surfactant has made it possible to consider synthesizing surfactant for instilling into the lungs of premature babies whose natural surfactant is deficient. Such experiments are just beginning, but preliminary findings are encouraging.

The molecular basis for hormone stimulation of surfactant synthesis is becoming better understood. The rate-limiting activities have been shown to be stimulated by corticosteroids, and one enzyme is apparently modulated by phosphatidylglycerol. The importance of exogenously administered corticosteroids has been confirmed, and the use of them in clinical situations has been cautiously explored. Newer findings suggest that other hormones, including small peptides synthesized and released by cells along the tracheobronchial tree, may be involved in lung maturation. The overall picture appears to be far more complicated than was imagined in 1972, and development of the fetal lung may involve several hormones and the interchange of substances through cell-to-cell interactions within the lung itself.

Program Goals 1982 to 1987

Type II cells produce surfactant in response to peptides and other components yet to be defined that are elaborated by other lung cells, such as fibroblasts. The major goals in the studies of the control of surfactant synthesis and secretion are:

- Describe the pathways and means of regulation of the synthesis, secretion, and clearance of pulmonary surfactant in the neonate and adult, and define relevant metabolic pools that may contain transitional forms of the surfactant complex.
- Describe the endocrine systems in relation to surfactant that may affect fetal lung development.
- Determine how the structure of pulmonary surfactant is formed and maintained, describe its physicochemical properties, and determine its physiologic importance.

Research Activities 1982 to 1987

The following activities are given as examples:

- Describe the effects of alveolar-vascular interaction at different gestational ages, and explore the role of the pulmonary circulation in the development of the surfactant system.
- Determine whether surfactant replacement can be successfully applied therapeutically in premature infants.
- Establish specific types of lung cells that respond to changes in hormonal levels by elucidating specific factors that stimulate surfactant synthesis.
- Establish the exact nature of "factors" that stimulate surfactant secretion.
- Establish the general conditions that lead to inhibition of surfactant synthesis.
- Elucidate the relationship between physicochemical alterations in surfactant and adult respiratory disorders.

LUNG CELL BIOLOGY

The histologic appearance of the cells that fascinated lung biologists during this last decade had been described fully by early cytologists. In the 1970's, cytology grew significantly. Principles of cell physiology were introduced, and lung cell biology became a discrete area of study.

State of Knowledge in 1972

During the 1960's, there was a substantial increase in the literature on normal appearances of various lung cells and their structural alterations after various cellular insults. The information was of a descriptive nature and was correlated with physiologic derangements of organs. In a prime example of this type of study, alveolar type II epithelial cell lesions were described and correlated with physiologic studies that indicated altered surfactant properties. Overall, the development of cell biology as a discipline had matured, and many cell biologists became interested in pulmonary research. The need to explore the biology of lung cells and connective tissues was clearly indicated for the 1970's. Cell biologists brought their expertise and investigative tools to the lung, and studies of the biochemical and structural features of the cells and connective tissues were begun.

Program Goals Through 1982

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

Accomplishments Through 1982

The lung contains cells of many origins--17 distinctly different types of epithelial cells, 12 types of connective tissue cells, several types of blood and lymphatic vessel vascular cells, smooth muscle and visceral mesothelial cells, and 4 or 5 different species of nerve cells. During the last 10 years, various types of these cells have been isolated, maintained in tissue culture,

and characterized. Of particular interest has been the isolation and characterization of the type II epithelial cell. It was appreciated that this cell has a secretory function, and it was suspected that surfactant is the product, the presence of which greatly reduces the work of breathing and assures adequate gas exchange.

The isolation of the type II cell was a major advance. Biochemical observations could now be attributed directly to isolated type II cells rather than to the whole lung. Studies performed on isolated alveolar type II cells showed that they contain the two major classes of phospholipids found in purified surface active material, phosphatidylcholine and phosphatidylglycerol. The isolated type II cells synthesized these lipids as shown by studies in which precursors (acetate and glycerol) were incorporated into phospholipids. In other experiments in which cells were treated with radiolabeled choline and then incubated in the presence of a compound causing surfactant release, type II cells were shown to secrete phosphatidylcholine. In addition to these two functions, synthesis and secretion of surfactant, the type II cell was also shown to be responsible for the repair of the alveolar surface after injury, such as exposure to oxidant gases or other irritants. In response to injury, type II cells proliferate and repair the lining epithelium and then reestablish a normal lining by differentiating into alveolar type I cells, which are very thin and allow for rapid gas exchange.

Although isolated cells have been useful in the elucidation of surfactant synthesis and secretion, they have been of lesser value for the study of hormonal control of differentiation of the type II cell. It has been shown that some thyroid and corticosteroid hormones can influence fetal lung development and surfactant production. These findings have great clinical relevance to the prevention of neonatal RDS.

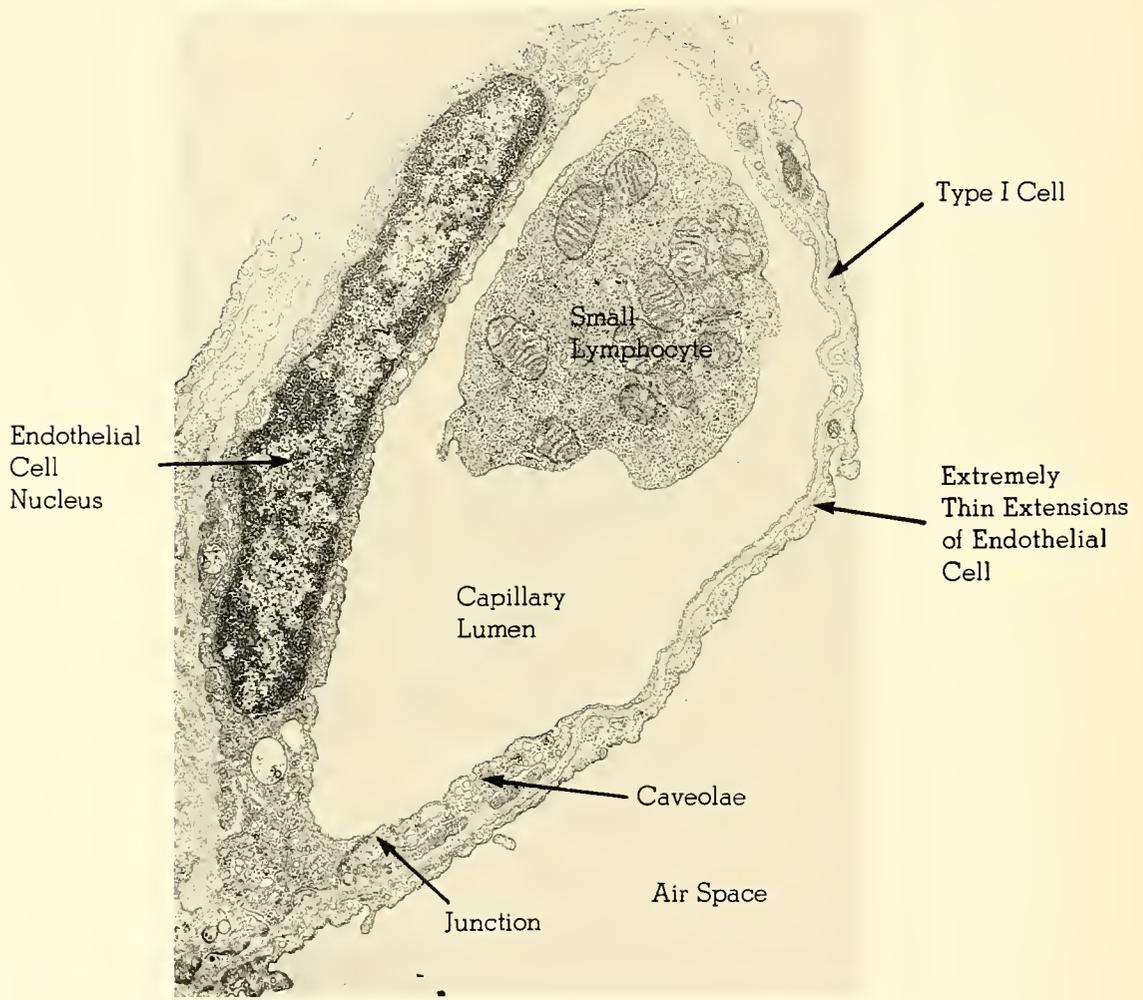
Since lower concentrations of cortisol have been observed in cord blood of infants with RDS, the importance of corticosteroids to lung development has needed study. Mixed lung cell cultures were therefore developed to determine the cellular action of hormones and other compounds known to accelerate fetal development. In such studies, treatment of cultures from mid-gestation fetuses with cortisol showed only enhancement. In cultures established from rabbit fetuses in late gestation, however, cortisol administration slowed growth while promoting differentiation of type II cells, as shown by increased incorporation of choline into disaturated phosphatidylcholine. By comparing choline incorporation in isolated type II cells with that in mixed cell cultures, investigators have concluded that fibroblasts produce a soluble fibroblast-pneumocyte factor in response to cortisol that is capable of stimulating increased surfactant synthesis in type II cells. Such studies have indicated a need to

develop mixed cell cultures and organotypic cultures in which important neurohumoral and cell-to-cell interactions are maintained.

The pulmonary capillary bed has a surface area of 90 square meters and would extend for about 2,400 kilometers. Another recent breakthrough in lung cell research has been the successful isolation of endothelial cells from pulmonary artery and pulmonary vein. Because of the strategic position of the pulmonary vascular bed, studies of the metabolic functions of such cells have a major importance. The cells are bathed with the entire cardiac output and may exert a regulatory influence on the physiologic functions of other organs. Endothelial cells have proved to be capable of processing a host of hormones and other excitatory substances, including biogenic amines, adenine nucleotides, and polypeptides. They can selectively process different hormones or prohormones that arrive through the circulation. Bradykinin and serotonin, for example, are inactivated whereas angiotensin I is activated into angiotensin II, and other endogenous substances are allowed to pass through unaltered (figure 8).

Angiotensin converting enzyme, which is located on the endothelial cell membrane, is present in all species studied thus far, and it activates 60 to 70 percent of angiotensin I in a single passage through the lung. The same enzyme has been shown to inactivate bradykinin, which is a potent vasodilator. Pulmonary endothelial cells, therefore, can affect systemic blood pressure. Recent studies suggest that the hypotension often accompanying neonatal respiratory distress syndrome may be due to hypoxic inhibition of angiotensin converting enzyme. In these immature infants, the nervous system has not developed sufficiently to serve as the major regulator of blood pressure, as in older infants and adults. Consequently, the neonate depends mainly on the vasoactive peptides for circulatory control. This control is impaired when the action of angiotensin converting enzyme is inhibited by low oxygen levels. In adults with impaired oxygenation, inhibition of the converting enzyme might lead to hemodynamic derangements, as has been suggested by study of this enzyme system in an emphysematous dog model.

Endothelial cells also contain on their surface an enzyme called lipoprotein lipase, which participates in the metabolism of triglyceride-rich lipoprotein. This enzyme, which acts at the endothelial surface of blood vessels, is instrumental both in clearing lipid from the circulation as well as in supplying fatty acids for lung metabolism. Its activity may be associated with prevention of atherosclerosis. Endothelial cells are likely to have an active function in clearing emboli and thrombi. Thromboplastin and factor VIII antigen, which are important coagulation components, have been identified in endothelial cells.



This illustration shows the thin endothelial and epithelial linings. The thin walls of the endothelial lining have a large surface area and are responsible for the processing of a number of vasoactive substances. Note the large number of vesicles (caveolae) thought to be important in transport processes across the endothelium.

* Courtesy of Dr. Una Ryan, University of Miami, Coral Gables, Florida.

Figure 8.* Electron Micrograph of the Air-Blood Barrier of the Lung

An important clinical setting in which defective function of endothelial cells can be seen is oxidant injury, such as oxygen toxicity. This endothelial dysfunction frequently results in pulmonary edema, which is almost always a characteristic of patients with acute respiratory failure.

Another very important cell in the respiratory tract is the mucous cell, which is located in glands situated beneath the airways and in the surface epithelium of the airways. In cystic fibrosis, which is a genetically determined disease characterized by alteration in glandular secretion, serious mucous abnormality results in airway obstruction, which is the usual cause of death in cystic fibrosis. (This subject is discussed in detail in section 5 of this report.) Mucus secreted from glands and surface cells combine with water to form the respiratory tract secretions. The secretions are moved up the airways to the mouth by the sweeping action of the cilia. Determining the abnormalities in cystic fibrosis requires a knowledge of the normal regulation of water movement, synthesis and secretion of mucus, and ciliary motion. A decade ago, little was known about these subjects, but major advances have resulted from recent multidisciplinary approaches and technical breakthroughs.

Since water makes up most of the airway secretions, its regulation is of utmost importance. Techniques used in other epithelia, such as gut and kidney, have recently been applied to the airways. These studies show that the movement of water in airways is controlled by a "pump" that actively moves ions across the airway surface. Water follows passively. The mechanisms that control the pumps have been explored, and drugs have been shown to modify the movement. Circulating factors may prevent normal ion pumps from operating, or the cells themselves may lack normal pumps. The use of drugs might conceivably correct such deficiencies. Methods have been developed to measure even the minute volumes of water that are secreted, and studies have been initiated that use these techniques in diseased tissue to explore underlying abnormalities.

Biochemists, pharmacologists, physiologists, cell biologists, anatomists, and immunologists have joined in a multidisciplinary approach to research on the submucosal glands, from which most secretions of mucus are believed to be derived. From these studies, investigators have learned that the gland secretions are regulated by nerves, humoral mediators, and by drugs. Recent studies suggest that the function of two types of cells (serous and mucous) involved in production of mucus are controlled separately. This observation suggests that more or less viscous secretions can be mobilized, depending on the stimulus. Because selective stimulation of viscous secretions may cause impaired clearance, such abnormalities may be amenable to drug therapy. The biochemistry of mucus is very complex, but there has been

major progress in determining its physicochemical nature and relevance to disease states.

It has been shown that in the absence of mucus or in the presence of its altered properties, cilia cannot function properly. Cilia must beat in a specific, coordinated fashion in order to move a stream of liquid and to clear mucus. The ultra-microscopic structure of cilia shows a characteristic pattern of filaments. It has recently been shown that cilia are powered by their own supply of energy. The biochemical nature of the process and the mechanical details of the movement of cilia are now fairly well understood, although to a lesser extent in the respiratory tract than in other organs.

Along with the interest in the basic mechanisms of ciliary action has been the discovery of diseases associated with paralyzed cilia or cilia that move asynchronously. Similarly, some studies suggest that biological "factors" that seem to exist in cystic fibrosis may impair the function of cilia.

Another cell that has excited pulmonary researchers during the past decade is the mast cell. The normal function of mast cells is still a matter of debate. Investigators have focused on the release of mediators of inflammation from these cells. It is now clear that not only immunologic stimuli but also pharmacologic stimuli (such as calcium ionophore, concanavalin A, and compound 48/80) and air pollutants (such as ozone and ammonium ion) can cause secretion of potent mediators from these cells. These agents can produce a direct action on target cells such as secretory glands, mucous cells, and airway smooth muscle cells; can stimulate sensory nerve endings; and can alter the permeability of respiratory epithelium and endothelium.

An exciting alternate hypothesis is that mast cells function as a microchromatographic column for adsorption of toxic chemicals on the highly charged proteoglycans (where they are stored for months and perhaps years) and for release of modified, detoxified products into extracellular fluid. According to this concept, the secretion associated with IgE-mediated reactions is really an abnormal aspect of function of these cells.

State of Knowledge in 1982

Techniques for successfully maintaining and characterizing a number of pulmonary cells are constantly being refined. Since smooth muscle cells have important functions in the airways and in the vasculature, studies are in progress to identify their unique endothelial and neural interactions. A line of murine pleural

epithelial cells has become available that will allow investigators to determine the characteristics of the cell and its importance to fluid and solute exchange in the pleural space. Although the pleura has been neglected in pulmonary research, it has become important because of the increased incidence of asbestosis and associated problems of pleural and lung malignancies.

A cell type that remains elusive to all cell separation techniques at present is the Clara cell. This nonciliated cell within the bronchiole is characterized by organelles that strongly support a secretory function. Although investigators have been unable to define the secretory process and products of the Clara cell, its many pathologic responses have been described. The secretory granules of the Clara cell have been shown to undergo marked ultrastructural changes in animals with experimentally induced diabetes. The lesion can be reversed by insulin. In addition, the Clara cell has been shown to exhibit marked changes after 48 hours of exposure to 100 percent oxygen. Inhaled toxic gases such as nitrogen dioxide have also been shown to induce bronchiolar cell injury. In isolated perfused murine lungs, beta-adrenergic agents appear to stimulate the release of secretory granules in Clara cells. The secretion can be blocked by parasympathomimetic agents. Finally, Clara cells appear to be important for lung metabolism of drugs and other exogenous compounds. Isolation of the Clara cell should allow for definitive biochemical studies.

A variety of mast cells, including those of human origin, are available for experimental study. Successful short-term tissue culture of human cells and primate cells has been achieved, but long-term tissue culture has been achieved only in the murine and rat basophil leukemia cell. There are major differences among species in structure and function of these cells, and the most appropriate model for experimental study remains to be determined. An interesting area to pursue in embryology is the relationship of mast cells to the autonomic nervous system. Developmental studies show that the mast cell originates from the neural crest, accumulates at the site of nerve degeneration, and is found commonly in association with parasympathetic ganglia. These observations suggest a functional relationship that has yet to be defined.

Although the endocrinologic function of the lung has been recognized for many years, there is heightened interest in the system of diffuse endocrine or endocrine-like cells that are scattered throughout the epithelium of the lung. These cells have been well characterized in the gut and brain and have been shown to be responsible for the production and storage of many different types of polypeptides and hormones. Their abundance in fetal lungs is well documented, but their precise functions have not been well-defined in either the fetal or adult lung. When these

cell types are grouped into clusters, they are called neuroepithelial bodies. Such bodies are found in airway epithelium, and the capillaries that supply blood to them have fenestrated, or open, endothelium. These findings suggest that neuroepithelial bodies have an endocrine function. Some scientists believe that because they contain abundant nerve endings, neuroepithelial bodies may be sensory receptors, or they may act as chemoreceptors and mediate states of hypoxic vasoconstriction in the lung.

Program Goals 1982 to 1987

- Further characterize the structural and functional features of various types of lung cells, interrelationships among the different cell types, and the cellular modifications associated with lung injury and disease.
- Better understand neural and humoral regulation of airway secretion, the nature of secretions, and solute movement across the airway epithelium.

Research Activities 1982 to 1987

The following activities are given as examples:

- Separate, maintain, and characterize the Clara cell of bronchiolar epithelium, and elucidate its interrelationship with other lung cells.
- Elucidate the structural-functional characteristics of the endocrine-like cells of the tracheobronchial tree.
- Determine the *in vitro* behavior and characteristics of normal pleural cells and their reaction to various types of injury.
- Determine the characteristics of the smooth muscle cell in health and disease, and define its relationship to endothelium and to other actin-containing interstitial cells.
- Find new and better techniques for selective culturing of fetal lung cells and sensitive means of studying their biochemical properties.
- Characterize the nature of cell-cell recognition.
- Develop new approaches and techniques to study lung cell populations and metabolic functions of the lung.

- Characterize the mast cell (tissue basophils), and determine its functions alone or in combination with neutrophils, platelets, and macrophages.
- Attempt to understand the mechanisms of ion, water, and macromolecular transport in airway epithelia at various levels of the respiratory tract in normal as well as in disease states.
- Determine how changes in ion transport and water flow affect the physiologic and biochemical properties of mucus and the efficiency of cough and mucociliary clearance in health and disease.
- Develop micromethods for the detailed biochemical characterization of samples from discrete structures, such as glands.
- Characterize the neurohumoral regulation of gland cells, and establish the role of possible feedback systems through ganglia and intracellular mediators such as calcium, calmodulin, and cyclic AMP.

Lung Injury and Repair

The lung often undergoes injury and requires repair, and scientists have recently begun to explore the organ as living tissue, cells, and subcellular particles. The complexity of the reactions of pulmonary tissue to injury are well known to clinicians. Pneumococcal bacteria, for example, cause an intense acute inflammatory reaction that can be repaired completely; tubercle bacilli, in contrast, cause a chronic reaction upon repair (fibrosis and calcification). Other stimuli can lead to destruction of lung tissue with the subsequent repair being accompanied by overgrowth of fibrous connective tissue, as in pulmonary fibrosis, or by no overgrowth, as in emphysema. Although some insight has been attained concerning the reparative response that follows diffuse alveolar damage, ignorance of the basic processes involved in most types of lung injury and repair far exceeds the knowledge. Major breakthroughs, however, have occurred in understanding the general biology of inflammatory processes, and some of these insights are applicable to the lungs. Scientists know that lung injury frequently blocks or damages normal methods of defense in the host lung, and extensive study has been devoted to characterizing these important mechanisms.

State of Knowledge in 1972

The importance of an intact and functional mucociliary apparatus as a clearance mechanism for harmful agents inhaled by the lung was widely appreciated in 1972. Specific information on ciliary ultrastructure and biochemistry, however, was not known. The biochemical characterization of respiratory mucins, though under active investigation, had not yet been accomplished. Phagocytosis of microbiologic agents by alveolar macrophages and polymorphonuclear leukocytes was being studied in many laboratories, and the ability to recover large numbers of phagocytes for study by lung lavage was an important achievement. In regard to the immunologic features of the lungs, the limited information available was related to the cell-mediated diseases of tuberculosis and sarcoidosis. The defense of the lung against exogenous and endogenous insults was to become an area of intense study.

Program Goal Through 1982

- Elucidate the roles of lung cells, enzymes, and hormones in the metabolic activities of the lung against exogenous and endogenous insults and disease.

Accomplishments Through 1982

The lung serves as a biologic barrier between man and his environment and protects the host against such potentially injurious materials as microorganisms, irritant dusts, and gases. The maintenance of the lung in a sterile state is dependent upon many features of the lung defense system. The conducting airways, which begin in the nose and extend to the respiratory bronchioles, the extensive branching of the respiratory tree, entrapment of mucus and ciliary clearance, the cough response, bronchoconstriction, and local mucosally derived proteins such as secretory immunoglobulin, all act to exclude potentially injurious materials or clear them from the lung (see table 11).

The mucociliary clearance mechanism has long been appreciated as an important defense mechanism. Mucus acts as a barrier and protects underlying epithelial cells from harmful inhaled agents, and it also contributes to the mechanism by which particulates and cellular material from more distal parts of the lung are cleared. Mucus contains antibodies or nonspecific microbicidal factors and thus elicits antimicrobial properties. In addition, immunoglobulins, especially IgA, are found in mucus and contribute to local immune responses. The understanding of these various lung

Table 11. Lung Host Defenses to Airway Challenges

Surveillance Mechanisms

Mechanical barriers and airway angulation
Lymphoid tissue
Mucociliary clearance
Cough
Local immunoglobulin coating-secretory IgA
Other immunoglobulin classes (IgG, IgE)
Fe-transporting proteins (transferrin)
Alternate complement pathway activation
Surfactant
Alveolar macrophages

Augmenting Mechanisms

Initiation of immune responses (humoral antibody and cellular)
Generation of an inflammatory response (influx of polymorpho-
nuclear granulocytes, eosinophils, and possibly lymphocytes
and edema fluid)

components is of utmost importance because of the frequent clinical problems of pulmonary infections.

During the last decade, scientists have studied various aspects of airway inflammation. Chronic bronchitis, a disease of large airways, has undergone careful scrutiny, and the role of smoking in inducing these changes in large airways has been established. More recently, interest has focused on so-called small airway disease, again a disease associated frequently with smoking and with inflammatory changes of small diameter airways. Airway inflammation that is seen in bronchial asthma has also been studied, and the inflammatory response and mediators elicited by the allergic reaction is now much better understood. (This subject is fully discussed in section 4 of this report.)

Another important defense mechanism is the cough, which has two main functions: it protects the lung against aspiration of foreign objects, and it propels secretions and other material from

the airways. It is a normal physiologic mechanism that rarely occurs in healthy subjects, and its frequent presence in a patient usually denotes disease. It has been shown that the cough is much more effective in increasing the clearance of plugs of mucus in chronic bronchitis than either exercise or postural drainage. During the past 10 years, the functions of the cough, the stimuli that cause it, and its mechanism have been studied and characterized. It is now appreciated that various factors, such as smoking, sleep, weather, gender, physical activity, and multiple disease states, can determine the severity or frequency of the cough.

Cells of great importance for lung defense that have undergone extensive study within the last 10 years are the alveolar macrophages. The recovery of pulmonary macrophages from lung washings was introduced as a method in experimental animals during the 1960's. During the 1970's, extensive use of the fiberoptic bronchoscope with associated pulmonary lavage technique in humans has allowed routine recovery of alveolar macrophages in normal and diseased lungs. It is now recognized that the alveolar macrophages are not just simple scavengers. They are involved in cell-mediated immunity, allograft rejection, delayed hypersensitivity reactions, and perhaps in the pathogenesis of autoimmune diseases. Studies have indicated that alveolar macrophages can recognize and destroy neoplastic cells. It has become evident within the last few years that in addition to these diverse functions, the macrophage is also a secretory cell, and knowledge of its products has expanded phenomenally. It has been shown, for instance, that macrophages can both enhance and impede inflammation. They have also been shown to be able to secrete enzymes capable of degrading connective tissue. Collagenase and elastase activities can be detected in fluids from macrophage cultures in many species. Because unrestrained breakdown of protein (proteolysis) can lead to the clinically important lung disease emphysema, the exact function of alveolar macrophage in breakdown of connective tissue requires clarification.

Important questions concerning the origin and turnover of pulmonary macrophages have been approached and partly answered within the last 10 years. Alveolar macrophages are derived from cells in the bone marrow. There appears to be a resident macrophage population within the interstitium of the lung that can proliferate to help maintain renewing numbers of macrophages. A mechanism that supplies macrophages from the interstitium rather than the blood stream appears to operate in normal animals. Under severe stress, however, the number of macrophages can be increased by an increased flux of monocytes directly from the blood into the lung.

The respiratory system reacts to injury also with immunologic mediators of lung defense. The function of cell-mediated immune

reactions in the lung has received some study, and there is evidence that the lymphoid cells of the lung can produce a variety of mediators, including macrophage migration inhibition factor (MIF), a macrophage aggregating factor (MAF), and monocyte chemotactic factor (MCF). Lymphocytes also show an adaptive response to inhaled cigarette smoke, and the induction of aryl hydrocarbon hydroxylase reportedly increases in the lymphocytes of lung cancer patients as compared to those of controls.

The importance of proteases in the etiology and pathogenesis of acute lung injury has been studied intensively during the past decade. Some of the proteases found in the human neutrophil have been of particular interest to researchers. They are known to digest collagen and elastic fibers, which are important components of connective tissue of the lung. The significance of proteases has been well described in the pathogenesis of pulmonary emphysema. An important additional role of these substances is their ability to interact with complement, a family of protein molecules such as C3 and C5, which can serve as leukotactic factors that can further destroy lung tissue.

Major research efforts have determined that the lung is a primary site for synthesis, degradation, conversion, and intake of an array of humoral mediators. Some mediators regulate smooth muscle tone in the airways and pulmonary vasculature, others have a function in lung growth and development, and still others exert metabolic effects in the normal and diseased lung. Prostaglandins have been extensively researched in the last few years. Although much is known about many of their functions and actions in the lung, the exact mechanisms and pathogenesis by which they are involved in various disease states are poorly defined. They have been implicated in such responses as bronchial airway narrowing and pulmonary vascular constriction, and possibly even in causing increased pulmonary vascular leaking. They are, therefore, related to pulmonary disorders such as pulmonary hypertension, pulmonary edema, respiratory distress syndrome, pulmonary thrombosis, and asthma.

Prostaglandins continue to interest researchers because of their diverse effects. The lung can inactivate, synthesize, and release these compounds. With the availability of radioimmunoassays and other sensitive techniques for measuring different prostaglandins, investigators are studying the mechanisms by which prostaglandins are produced by lung cells, and how they vary with gestational age and in experimental conditions, such as hemorrhagic shock and anaphylaxis.

Two major diseases in infants and adults are the respiratory distress syndrome of the newborn and the adult respiratory distress syndrome, and they share a possible common complication of their treatment, oxygen toxicity. The mechanisms involved in

the toxicity that results from high levels of oxygen and other oxidants, such as paraquat, ozone, and peroxides, continue to be of great interest to clinicians. Among enzyme systems that have a protective function in the lung against such agents are the antioxidants, of which superoxide dismutase has been the most extensively investigated. Antioxidants protect lung cells against the toxic effects of exposure to high levels of oxidants, which are assumed to form highly reactive intermediates that damage the cells. The antioxidant enzymes diminish the toxic effects by converting free radicals into harmless products.

When exposed continuously to almost pure oxygen, neonatal, but not adult, animals show increases in activity of superoxide dismutase and other antioxidant enzymes. This finding is consistent with the observation that immature animals are more resistant than adults to oxygen toxicity, and indicates the protective function of antioxidant enzyme systems. A technical advance that should facilitate basic studies of oxidase-induced lung injury is a noninvasive optical method for detection of chemoluminescent compounds. The method is based on the premise that oxidants are responsible for the formation of free radicals of oxygen, of hydrogen peroxide, and of lipid peroxides that emit optically measurable light.

Immunocytochemical techniques have been used to localize superoxide dismutases in lung tissue and to quantify changes resulting from exposure to oxygen. It has been found that a single intraperitoneal dose of superoxide dismutase prior to exposure to high oxygen protects against the hyperoxic depression of serotonin that is considered an early indicator of lung injury. Another observation, and one of potential therapeutic value, is that a single dose of endotoxin protects animals from lethal hyperoxic lung damage. After a month of recovery period following O₂ exposure, there is only slight diffuse lung damage in endotoxin-treated animals, whereas those not treated with endotoxin show marked pulmonary fibrosis. It is believed that endotoxin activates the lung antioxidant system. This supposition is based on the fact that the activity of superoxide dismutase and other antioxidant enzymes increases after exposure to endotoxin.

State of Knowledge in 1982

Inaccessibility of tissue and the smallness of the structures involved have made it difficult to study mucociliary clearance in humans. New techniques now enable investigators to sample fluid from the airways and to study its contents. The main clinical advance has been the development of methods for the study of the process by which mucus is moved up the airway "escalator" and is cleared. Much headway has been made in understanding the

deformation of airways during the cough, but this information needs to be applied to studies of the efficacy of the cough in health and disease.

Although some insights into the importance of pulmonary macrophages and pulmonary immunologic mechanisms have been gained, this subject continues to warrant extensive study. No overall pattern of control is understood. Many lung diseases, such as hypersensitivity pneumonitis and interstitial pneumonia, are no doubt caused by aberrations in the immune response of the lung, and researchers must close the gaps of knowledge in this important subject.

Basic scientists will continue to focus upon the identification of the factors such as the complement, coagulation, and fibrinolytic cascade interactions and their importance to the normal and diseased lung. Extensive studies of many of the plasma-derived mediators are continuing. The effect of oxygen-enriched mixtures known to affect the lung in high concentrations is being carefully studied. Special attention is being focused on the function of free radicals and antioxidants in oxygen toxicity.

Program Goal 1982 to 1987

Lung injury and repair are relevant to a variety of lung disorders. Because the lung has a rather limited way of reacting to exogenous insults and endogenous abnormalities, common pathways may be involved in many of the reactions observed after different types of injury.

- Define the morphologic, biochemical, and physiologic reactions that occur in the respiratory system at the cellular and subcellular level in response to a variety of insults.

Research Activities 1982 to 1987

The following activities are given as examples:

- Elucidate the interaction between the alveolar macrophages and the fluid of the alveolar lining.
- Determine surfactant degradation and turnover in lung injury and repair and the role of alveolar macrophages in these processes.

- Define better the interactions between pulmonary macrophages and bronchoalveolar lymphocytes.
- Explore further the origin and turnover of alveolar macrophages in both fetal and adult lung.
- Determine the importance of bronchopulmonary lymphocyte subpopulations in the local immune response of the lung.
- Investigate the mechanism(s) of acute lung injury at the tracheal, bronchiolar, and alveolar level in the lung.
- Characterize further oxidant-induced and free radical-induced injury and repair and mechanisms of protection at the cellular and subcellular level.
- Elucidate the interactions between cells and connective tissue matrix in the normal repair process.
- Determine the interaction of formed blood components with lung parenchymal cells (such as endothelium, smooth muscle cells, epithelium, secretory cells, and mast cells).
- Elucidate further the role of prostaglandins and other mediators in injury and repair processes of the normal and diseased lung.
- Study the interactions of the complement, coagulation, and fibrinolytic cascades and their potential role in lung injury and repair.
- Determine the role of neural and humoral influences on pulmonary endothelium and other parenchymal lung cells.
- Assess the efficacy of the cough in health and disease.

Lung Growth and Development

The effects of disease, environmental hazards, and aspiration of foreign materials can divert the developing lung from a course of normal growth and impair its functions. Central to advances in the prevention and treatment of lung disorders in infants and children--and ultimately in adults--is an understanding of the normal development of lung structure and function.

In the past 10 years, there has been a significant increase in knowledge of normal lung development and an appreciation of the processes involved in lung maturation and adaptation to

extrauterine life. Careful analysis of the importance of surfactant deficiency in the pathogenesis of RDS, for instance, has clearly illustrated the principle that identification of normal patterns of lung maturation, growth, and functional development are critical for determining appropriate therapy for such conditions as neonatal respiratory distress syndrome and other forms of acute and chronic respiratory failure in childhood.

State of Knowledge in 1972

It was known that children's lungs differ significantly in structure and function from adult lungs. The lungs at birth, for instance, have the same number of airways as adult lungs, but they have markedly reduced numbers of alveoli. This finding translates into decreased neonatal elastic recoil pressure, which predisposes the infant lung to premature closure of airways during expiration.

In addition, a close relationship was appreciated between recurrent aspiration of foodstuffs, either during swallowing or following regurgitation of stomach contents, and persistent pulmonary symptoms with an abnormal chest roentgenogram among infants and children with neuromotor impairments or tracheoesophageal fistulae. Considerable debate, however, existed concerning the function of gastroesophageal reflux in otherwise normal children in such conditions as asthma, atelectasis, and recurrent lung infections.

Of the several obstacles to expanding the knowledge of normal respiratory physiology in infants and children, probably the single most important one was the technical problems of measuring lung function in neonates and young children. Many of the techniques developed in adults were invasive or difficult to adapt to pediatric subjects. Other techniques required a level of cooperation that is unattainable in pediatric subjects.

Program Goal Through 1982

- Increase knowledge of structural and functional changes during prenatal and postnatal growth and development of the respiratory system and of the effects of endogenous and exogenous factors.

Accomplishments Through 1982

Over the last 10 years, new techniques have been developed to measure respiratory function in small children, and adult techniques have been adapted to young children. A better understanding of how respiratory function changes with growth has clearly resulted. These techniques include a method for measuring resistance and other mechanical parameters of the respiratory system that do not require the cooperation of the subject. In addition, methods for measuring lung capacities have been adapted for use in small children, and data have been obtained in small groups of subjects. Prediction equations for children are now available that cover the pediatric age group, and more recently, prediction equations have been developed for nonwhite populations. Longitudinal lung function data in children are currently being collected at a number of centers. The geometry of the large airways can now be measured by a simple and safe technique that is based on the use of oscillating airwaves introduced at the mouth. This technique requires minimal cooperation from the child and can be repeated frequently.

Many questions concerning the morphological maturation and development of the lung have been answered over the last 10 years. Progress has been made in the descriptive histology of fetal, neonatal, and infantile lungs. Many morphologic differences between adult and infant lungs have been described. Some of them have been correlated with certain types of lung disease in which such structural differences may provide their pathophysiological basis. Structural differences between the lungs of boys and girls, for instance, have been described, and these differences are being proposed as factors in rates of prevalence and severity of symptoms between boys and girls in childhood asthma and respiratory infections. In addition, airway size and the distribution of airway resistance are believed to be factors that contribute to the higher prevalence and greater severity of asthma in children. Similarly, the possibility has been raised that abnormal lung growth may be a risk factor for the development of chronic airflow obstruction in adulthood.

A number of factors have been identified that can modify the pattern of morphologic and functional development of the lung during fetal life. These include naturally occurring hormones such as adrenocorticotrophic hormone (ACTH), corticosteroids, thyroid hormones, prolactin, and insulin, as well as pharmacologic agents such as heroin, beta-mimetics, phosphodiesterase inhibitors, and vitamins. Interest has recently been focused on the role of epidermal growth factor (EGF) in lung development after it was initially observed that EGF infusion into fetal rabbits accelerates their lung maturation, both morphologically and functionally, and that EGF infusion into fetal lambs prevents an otherwise irreversible fatal respiratory distress in these

animals, with the characteristic pathological changes in the lungs. Vitamin A influences the orderly growth and differentiation of epithelial cells, including pulmonary epithelium. In deficient animals and humans, the epithelium of conducting airways undergoes squamous metaplasia, in which the normal epithelium is replaced by squamous epithelium topped with keratinized surface cells. Similar cell changes can occur under a number of adverse circumstances, such as after exposure to carcinogens and to chronic cigarette smoke, and in bronchiectasis. Interestingly, squamous metaplasia has been observed in the epithelium of the conducting airways of infants dying from bronchopulmonary dysplasia, and it has been found to be the predominant alteration of the epithelial cells of the tracheobronchial tree of fetal and newborn animals that have been exposed to EGF. Vitamin A deficiency, therefore, strikingly resembles the effects of EGF on epithelial tissues, and it is currently hypothesized that this deficiency allows growth-promoting processes to proceed uninhibited. It is currently not known whether there is an interaction between vitamin A and EGF, nor is it known whether the premature lung has deficient vitamin A stores, but such questions are currently under investigation.

Despite marked progress in understanding the roles of neural and chemical factors in control of ventilation in adults, information about the perinatal and postnatal periods is still limited. In utero, human fetal movements that resemble breathing have been observed, and it is believed that they may be a clue to the well-being of the fetus. Noninvasive Doppler systems to assess fetal breathing have been developed, and they are being evaluated for their reliability in providing information for use in prenatal and perinatal care in high-risk pregnancies. It has been observed that neonates tend to regulate gas exchange to maintain levels of arterial carbon dioxide lower than levels found in adults, that under hypoxic conditions they also maintain ventilation more poorly than adults do, and that they have a tendency toward irregular breathing.

Studies in the late 1970's established an increased incidence of gastroesophageal reflux among children with recurrent wheezing, hyperinflation, cough, and pulmonary infiltrates. Because surgical correction of the gastrointestinal abnormality has not led to resolution of the lung disorder in all cases, it remains unclear whether the two problems are causally related. It also remains unknown whether gastroesophageal reflux is a manifestation of altered lung function or vice versa. Many of these pediatric lung problems have been found to have other causes, such as immune defects. To date, no reliable way of detecting gastric contents in the respiratory tract has been found, and progress in management is hampered by lack of knowledge concerning the reflexes that control breathing and swallowing in the pediatric group.

Researchers have begun to examine the metabolic and defense functions of the developing lung, especially the importance of alveolar macrophages, angiotensin-converting and antioxidant enzymes, and prostaglandin synthesis and degradation. Changes found in the first postnatal week of a term neonate include a dramatic increase in the number of alveolar macrophages, a considerable increase in activity of the antioxidant enzyme superoxide dismutase, and a threefold increase in angiotensin-converting enzyme activity. The microbicidal activity of the alveolar macrophage appears not to develop until after the first postnatal week. Of particular interest is recent evidence that surfactant probably has a function in the increase of the number of macrophages and that the macrophages have a role in scavenging inactive or excess surfactant. The content of surfactant lipids in the alveolar macrophage is particularly prominent in the early postnatal period, and both lamellar and tubular myelin have been found in cytoplasmic inclusion bodies of the macrophage of the developing as well as adult lung.

Angiotensin-converting enzyme activity, which is at very low levels at the beginning of the last trimester of pregnancy, has recently been found to be present as early as the second trimester. The low activity during the last trimester is attributed to the limited surface area of the vascular bed in the fetal lung. This notion is supported by the finding that extensive capillary development, without appreciable increase in lung weight, coincides with the greatest increase in activity of the enzyme. The presence of angiotensin converting enzyme in the placenta as early as the second trimester suggests that the placenta may be a major site of the enzyme in utero, and that a prematurely delivered infant would be severely handicapped at times of hypotensive stress because it would lack the capacity to generate angiotensin II and inactivate bradykinin, both of which depend on activity of angiotensin converting enzyme.

State of Knowledge in 1982

Although much has been learned in the past decade about the regulation and maturation of the pathways involved in the production of surface-active materials by the fetus and neonate, the case has been otherwise with other nonrespiratory lung functions. It seems highly probable that studies of these subjects will enhance the ability to control a variety of neonatal and pediatric lung conditions such as bronchopulmonary dysplasia, cystic fibrosis, lung infections, and multiple interstitial lung processes in much the same way that knowledge of the control of surfactant synthesis has created the opportunity to prevent and treat surfactant deficiency.

Knowledge of normal patterns of lung growth in humans should help to improve the diagnosing and reporting of many neonatal and childhood lung disorders. Because of technical difficulties, lack of appropriately trained individuals, and ethical constraints, functional and structural correlations of the kinds that have been made over the past 10 years for adult lung disease are still lacking for most pediatric conditions. Animals delivered prematurely with immature lungs should be studied to learn about lung disease associated with prematurity and its sequelae. Advances in this area also require appropriate pathologic samples in infants and children.

Program Goals 1982 to 1987

- Evaluate prospectively the structure-function relationship during development of the respiratory system in normal as well as in disease states.
- Understand the development of the nonventilatory functions of the lung, their relationships to lung diseases, and their alterations by the environment.

Research Activities 1982 to 1987

The following activities are given as examples:

- Develop appropriate standards of lung structure, function, and growth in normal infants and children so that the influence of gender and ethnic origins as well as other factors such as nutrition, prematurity, and therapeutic intervention can be properly evaluated.
- Develop appropriate age-related pathophysiological correlates of the relationship between structure and function in the developing lung during various lung disorders.
- Understand the role and control of fetal breathing movements and the development of control of breathing in health and disease.
- Understand the physiological principles of laryngeal-esophageal reflexes and upper airway protective mechanisms.

- Further develop noninvasive techniques to assess respiratory function and how it changes with age in healthy and diseased lungs.
- Develop methods to assess function of respiratory muscles so that the pattern of their maturation and differentiation can be determined.
- Develop noninvasive or minimally invasive methods of assessing intracellular oxygenation in infants and children during hypoxia.
- Elucidate factors that stimulate or inhibit structural and functional growth of the lung.
- Understand the functional development of defense systems in the lung during its maturation.
- Determine the structural and functional development of the innervation of the respiratory system.
- Sustain suitable animals with immature lungs in which the effects of lung injury on growth can be studied in the intact animal as well as at the cellular and subcellular levels.

Contributors

PULMONARY DISEASES ADVISORY COMMITTEE MEMBERS

Jacqueline J. Coalson, Ph.D., Chairman
Professor of Pathology
Pulmonary Pathology Department
University of Texas Health
Science Center at San Antonio
San Antonio, Texas

Margit Hamosh, Ph.D.
Associate Professor of
Pediatrics
Georgetown University
School of Medicine
Washington, D.C.

Roger Menendez, M.D.
Assistant Professor
of Pediatrics
University of New Mexico
School of Medicine
Albuquerque, New Mexico

Jay A. Nadel, M.D.
Professor of Medicine, Physiology
and Radiology
Chief, Section of Pulmonary
Diseases
Cardiovascular Research Institute
University of California,
San Francisco
School of Medicine
San Francisco, California

Solbert Permutt, M.D.
Professor of Medicine
The Johns Hopkins University
Baltimore City Hospitals
Baltimore, Maryland

CONSULTANTS

Frederic L. Eldridge, M.D.
Professor, Department of
Physiology
University of North Carolina
School of Medicine
Chapel Hill, North Carolina

Robert E. Hyatt, M.D.
Professor of Physiology
and Internal Medicine
Mayo Graduate School of
Medicine
Rochester, Minnesota

Leon E. Farhi, M.D.
Department of Physiology
State University of New York
at Buffalo
Buffalo, New York

Waldemar G. Johanson, Jr., M.D.
Professor of Medicine
Department of Medicine
University of Texas Health
Science Center at San Antonio
San Antonio, Texas

CONSULTANTS (continued)

Richard King, Ph.D.
Professor of Physiology
University of Texas Health
Science Center at
San Antonio
San Antonio, Texas

Joseph Milic-Emili, M.D.
Director, Meakins-Christie
Laboratories
Department of Medicine
McGill University
Montreal, Quebec
Canada H3A 2B4

John E. Remmers, M.D.
Professor of Medicine and
Physiology
University of Texas
Medical School at Galveston
Galveston, Texas

John B. Richardson, M.D., Ph.D.
Professor of Pathology
and Pharmacology
McGill University
Montreal, Quebec
Canada H3A 2B4

Suzan A. Ward, D. Phil.
Assistant Professor of
Anesthesiology
University of California,
Los Angeles
School of Medicine
Los Angeles, California

John V. Weil, M.D.
Associate Professor of Medicine
University of Colorado Medical
Center
Denver, Colorado

Brian J. Whipp, Ph.D.
Professor of Physiology and
Medicine
Harbor-UCLA Medical Center
Torrance, California 90509

DIVISION STAFF

Bitten Stripp, Ph.D.
Chief, Structure and Function Branch
Division of Lung Diseases
National Heart, Lung, and Blood Institute

Dorothy Gail, Ph.D.
Structure and Function Branch
Division of Lung Diseases
National Heart, Lung, and Blood Institute

Everett Sinnett, Ph.D.
Structure and Function Branch
Division of Lung Diseases
National Heart, Lung, and Blood Institute

4. Chronic Obstructive Pulmonary Disease

Contents

CHRONIC OBSTRUCTIVE PULMONARY DISEASE.	93
State of Knowledge in 1972.	93
Epidemiology and Pathogenesis.	94
Treatment and Prevention	97
Program Goals Through 1982.	98
Accomplishments Through 1982.	98
Epidemiology	99
Factors Associated with COPD	99
Pathogenesis	101
Progression of Disease	104
Basic Advances in Pulmonary Function Testing . .	104
Advances in Treatment and Management	107
Advances in Prevention	111
State of Knowledge in 1982.	111
Program Goals 1982 to 1987.	112
Epidemiology and Pathogenesis.	112
Pathophysiology.	113
Diagnosis, Management, and Prevention.	113
Research Activities 1982 to 1987.	114
ASTHMA	115
State of Knowledge in 1972.	116
Program Goals Through 1982.	118
Accomplishments Through 1982.	118
State of Knowledge in 1982.	124
Program Goals 1982 to 1987.	125
Epidemiology	125
Pathogenesis	125
Pathology.	126
Clinical Studies	126
Prevention and Self Management	126
Research Activities 1982 to 1987.	127
CONTRIBUTORS	128

4. Chronic Obstructive Pulmonary Disease

Chronic obstructive pulmonary disease is a frequent health problem with a mortality rate that in the last several years has been increasing steadily. It attacks people at the height of their productive years. It disables them with unremitting shortness of breath, destroys their ability to earn a living, causes frequent use of the health care system, and disrupts the lives of the victims' family members for one to two decades before death occurs. In 1970, chronic obstructive pulmonary disease was the tenth most common cause of death in the United States; and in 1980, it ranked as the fifth, after heart disease, cancer, stroke, and accidents. Such a marked increase makes this the fastest rising cause of death in the country.

The term chronic obstructive pulmonary disease is often used to encompass both chronic bronchitis and emphysema. Historically, the two terms have somewhat loosely referred to progressive respiratory impairment and to varying degrees of coughing, expectoration, and right-sided heart failure. Chronic bronchitis, which is customarily defined in terms of clinical manifestations, is characterized by cough and expectoration that occur daily for at least 3 months of each year for more than 2 successive years. In contrast, emphysema, which is defined on the basis of pathological changes, is manifested by dilatation of terminal air spaces of the lung with destruction of alveolar septae. More often than not, the two conditions coexist in the same individual although the contribution of each condition to the obstruction of airflow varies from individual to individual. Because of difficulties and inadequacies of definitions of both states, the noncommittal and nonspecific term, chronic obstructive pulmonary disease, has been established. As used in this report, COPD includes both chronic bronchitis and emphysema except where a distinction is necessary.

State of Knowledge in 1972

Mortality from COPD has been increasing since 1949. It follows a seasonal pattern with increased numbers of deaths occurring in the winter, due in part to influenza and pneumonia, to which persons with COPD have increased susceptibility. In 1967, the death rate from emphysema was reported to be 10.6 per 100,000, and from chronic bronchitis 3 to 4 per 100,000. In 1970,

there were an estimated 1.54 million newly diagnosed cases of COPD in the United States, with an overall prevalence of 38 per 1,000 population. Approximately 6.5 million persons were reported to have chronic bronchitis and 1.3 million to have emphysema. Since patients with COPD frequently die of pneumonia (death rate of 28 per 100,000 in 1967), the actual number of deaths related to these diseases is probably much higher than is reported. Although mortality rates were lower for women than for men in the 1960's and 1970's, the rates for women were clearly increasing. Also, death rates for COPD were more than 20 times higher among smokers than nonsmokers.

There are striking differences in mortality rates reported from various countries. It has been thought that these differences partly reflect nonstandardized usages of diagnostic terms or underreporting of cases. Marked regional differences, however, have been observed in reported death rates from COPD within the United States; Vermont, New Hampshire, the Rocky Mountain States, and Arizona are especially high. Some of these regional variations can be explained by the differences in the ages of the population and by the migration of persons with respiratory diseases.

The economic impact of COPD is difficult to assess. A survey in 1970 showed that of the 1.3 million persons estimated to have emphysema, 97 percent had consulted a doctor and 45 percent were limited in their activity. In the same survey, of the 6.5 million persons estimated to have chronic bronchitis, 94 percent had consulted a doctor and only 4 percent were limited in their activity. In 1972, estimated direct costs in terms of hospital care, physician visits, and drugs for COPD were \$803 million. Indirect costs in terms of lost earnings due to disability were estimated at \$3 billion, and lost earnings due to mortality at \$645 million.

Epidemiology and Pathogenesis

Cigarette Smoking and Air Pollution

By 1972, numerous exogenous and endogenous factors had been implicated in the etiology of COPD. Cigarette smoking was clearly recognized as the most important exogenous factor. A dose-response relationship was suggested between the amount smoked, the severity of the disease, and the risk of dying from it. Studies from many countries had indicated that smokers have a higher prevalence of clinically diagnosed chronic pulmonary disease, manifested by wheezing and shortness of breath, impairment of lung function, and recurrent chest infections. Patients with chronic bronchitis who were heavy cigarette smokers were known to exhibit

an excessive production of bronchial mucus caused by enlargement of mucous glands within the airways.

While it was clear that almost all patients with severe COPD are smokers, only 10 to 15 percent of smokers develop severe pulmonary dysfunction. Therefore, other factors were also important in the etiology. Females were less likely to develop irreversible airway obstruction than males, but the reason for this sex difference in susceptibility was unknown. The role of previous airway diseases, such as bronchiolitis in childhood and repeated viral or bacterial respiratory tract infections, still required definition.

Occupations associated with dusts were believed to result in increased incidence of chronic bronchitis, but evidence for this was not conclusive. Because photochemical oxidants, sulfur dioxide, and particulate pollutants had been shown to be associated with losses of respiratory function in acute exposures, air pollution in the locale was also considered a risk factor for COPD. It was not clear, however, whether the losses in respiratory function that occurred in individuals after acute exposures were permanent. Furthermore, it remained to be established whether long-term exposures to lower levels of the pollutants frequently encountered in large cities lead to an accelerated decline in lung function.

The Protease-Inhibitor Hypothesis

In the early 1960's, it was found that individuals who have low blood concentrations of alpha-1-antitrypsin (AAT), which is a serum protein that inhibits many proteolytic enzymes, usually develop emphysema, and that instillation of a protease into the lungs of experimental animals results in the development of lung abnormalities that resemble emphysema in humans. Because of these two observations, it was hypothesized that emphysema is caused by an imbalance between the protease, elastase, and AAT. The imbalance results in an excess of elastase that allows uninhibited digestion of lung proteins. These critically important observations led to much of the basic research on emphysema in the decade between 1972 and 1982, and they will clearly provide the focus for many investigations in the 1980's.

Clinical Studies of AAT Deficiency

In 1972, investigators were able to measure total trypsin inhibiting activity, to assess AAT concentration, and to determine phenotype. Between 1963, when the association was made between emphysema and low blood concentrations of AAT, and 1972, many variants of the protein were discovered, and the frequency of the

PiZ phenotype (homozygous AAT deficiency) was determined in large population studies in several countries. It was suggested that the mode of inheritance for AAT deficiency is autosomal recessive, with an expected incidence of about 1 per 5,000 in the United States. Although it was recognized that this genetic abnormality can account for only a small fraction of cases of emphysema, it offered potential clues that could possibly lead to an understanding of the biochemical defect that underlies the pathogenesis of emphysema. In order to establish whether other genetic factors might also be important, studies of identical twins and of relatives of patients with COPD were planned.

The pathologic abnormalities of established emphysema were well described in 1972, although the earliest lesions were poorly understood. The lesions of chronic bronchitis were less well described, although mucous gland hyperplasia and goblet cell metaplasia appeared to be the characteristic abnormalities.

Progression of Disease and Testing

In 1972, it was recognized that patients with COPD who present with breathlessness or other symptoms are already at a comparatively advanced stage of their disease. There was no evidence that any therapeutic measures (including cessation of smoking) would delay deterioration of ventilatory impairment and development of respiratory failure, cor pulmonale (right-sided heart failure secondary to lung disease), or death. Since tests of lung function that could serve as sensitive indicators of mild abnormalities were just being developed, very little was known about the earlier stages of these diseases.

By 1972, physiologic abnormalities characteristic of the advanced stages of both chronic bronchitis and emphysema could be detected by tests designed to measure lung mechanics, ventilation distribution, gas exchange, diffusion, and pulmonary circulation. The forced vital capacity (FVC) (a measure that indicates the amount of air that can be forced from the lung) and the forced expiratory volume in 1 second (FEV_1) (a derivative of FVC) were widely used to follow the course of COPD. These spirometric tests provided useful data on airflow abnormalities associated with advanced disease. They were relatively simple to conduct and could be easily performed on large numbers of subjects. In contrast, many other tests of lung function could be performed and interpreted only in the laboratories of the most skilled investigators. Tests to measure small airway function had just been developed, but little was known about them at this time.

Treatment and Prevention

In 1972, treatment for patients with COPD consisted mainly of helping the patient to keep symptoms under control. Patients were advised to stop smoking, to avoid occupational exposures such as dusts, and to curtail physical activities during air pollution alerts. Vaccinations for influenza were often advocated for this high-risk group. Good hydration was recommended to help keep secretions loose, and a high protein diet, taken in many small feedings, was considered helpful. General exercise programs and relaxation techniques were taught. The major medications were bronchodilators, including drugs from two main categories, sympathomimetics and methylxanthines. Antibiotics were given at the first sign of respiratory infection, and corticosteroids were recommended if wheezing could not be kept under control with bronchodilators. Inhalation of aerosols from intermittent positive pressure breathing (IPPB) machines was extremely popular as a method for mobilizing and removing secretions from the respiratory tract. Chest percussion, postural drainage, and controlled coughing techniques were also used.

Inhalation of oxygen at home for end-stage COPD was being prescribed for hypoxemic patients with cor pulmonale because it had been shown that continuous low-flow oxygen produced a significant drop in pulmonary vascular resistance and a gradual fall in pulmonary artery pressure. Another benefit of oxygen therapy was that, by producing a fall in hematocrit, it eliminated the need for phlebotomy. Oxygen toxicity did not seem to be a problem in these patients.

Although exercise programs resulted in limited improvements in endurance, maximum work levels, and sense of well-being, performance in pulmonary function tests did not seem to improve in these patients. Pursed-lip breathing (a respiratory pattern that some COPD patients used spontaneously) provided partial symptomatic relief from dyspnea, decreased the respiratory rate, increased the tidal volume, and led to a small improvement in arterial blood gas tension. The technique was believed to aid the escape of air from the lungs by preventing the collapse of large airways.

Comprehensive rehabilitation programs, which included outpatient and home visits, vigorous bronchial hygiene, retraining of breathing, and physical exercise (mostly walking), were believed to be effective in producing some interrelated physical and psychological effects. While there was agreement that rehabilitation programs seemed to provide some benefit to these patients, concrete physiologic and psychosocial data were not available to evaluate long-term benefits.

Because cigarette smoking was well recognized as the major risk factor for COPD, efforts were already under way in 1972 to educate the public about the risks of smoking and to encourage the establishment and evaluation of programs to stop smoking.

Program Goals Through 1982

Among the goals proposed for this period were the following:

- Develop methods for early detection and diagnosis.
- Identify etiologic and risk factors through prospective epidemiological studies.
- Evaluate treatment modalities and rehabilitative techniques and programs.
- Measure, in controlled longitudinal evaluations, the extent of reversibility in patients under treatment and in those who quit smoking or move to less polluted locales.
- Elucidate the pathogenesis of chronic bronchitis and emphysema through studies of animal models and humans.
- Develop mechanical, physiological, and mathematical models of the lung to further understand the pathophysiology of emphysema.
- Identify and characterize the nature and interactions of proteolytic and antiproteolytic substances having access to the lung.

Accomplishments Through 1982

Since 1972, a large portion of the research effort on COPD has been focused on understanding its pathogenesis, natural history, and epidemiology. Many major advances have been made in these areas. Of particular significance is the information that has emerged from research on the protease-antiprotease hypothesis of emphysema. Investigators have postulated a chemical link between the cause of emphysema in AAT-deficient individuals and the cause in smokers, and they have identified some of the chemical mechanisms involved in the toxicity of smoke to the lungs. Advances in airflow theory and the evaluation of sophisticated tests of pulmonary function have led to the concept of small airway dysfunction as an early indicator of the lung damage in smokers that may be linked to later development of COPD.

Structure-function correlations have added to the understanding of the natural history of the disease process. Lesions in airways that may predate clinical COPD have been described in smokers. These observations provide the first insights into the early evaluation of COPD.

Advances such as these hold promise for improvement in therapy. A clinical trial of oxygen therapy has demonstrated for the first time that the life of patients with COPD can be prolonged. Primary prevention through reduction in smoking and air pollution remain the optimal means of protecting individuals from COPD because, at present, once the disease is established, there is no therapy that will arrest its progress. A long-range program is under way to use advances in the protease-antiprotease mechanism of disease production to develop new therapeutic approaches in the future.

Epidemiology

The development of a uniform questionnaire and of standardized guidelines for pulmonary function testing and chest radiography were important advances that helped make COPD epidemiologic data from different sources more comparable. Under the auspices of the American Thoracic Society (ATS), minimum standards for spirometers have been established. These efforts have helped to increase the quality of pulmonary function testing throughout the country.

A number of epidemiological studies to investigate the endogenous and exogenous risk factors for COPD have yielded important information. Chronic coughing and reduced levels of lung function were frequently found to cluster in family members. One study indicated that airway hyperreactivity might be another familial factor that can increase a person's risk of developing COPD. In this study, it was found that the sons of COPD patients, in contrast to those of normal individuals, had hyperreactive airways as indicated by methacholine challenge tests. When the subjects were reexamined 4.5 years later, the group with hyperreactive airways had lost six times as much lung function as those with normal responses.

Factors Associated With COPD

AAT Deficiency

The strikingly unique factor that has been associated with COPD is a genetic deficiency of AAT that can lead to emphysema. It has been postulated that multiple alleles are found for the AAT

gene. A large number of allelic types have been identified (such as PiM, PiZ, PiSZ, PiMZ). PiM is the most prevalent in the general population. Among the heterozygotes for the Pi locus, PiSZ individuals are known to have very low concentrations of serum AAT, which clearly correlates with high risk for COPD. Whether PiMZ individuals who have intermediate serum-AAT concentrations are also predisposed to emphysema is an important question. Approximately 2 to 3 percent of the United States population has the PiMZ phenotype as compared to the 0.02 percent who are PiZ. Several well-designed studies, including a multi-institution study that examined this question in 143 PiMZ subjects and matched PiM controls, have concluded that the PiMZ phenotype carries no greater risk of developing lung disease than the PiM phenotype.

Investigations have confirmed that not all individuals with severe genetic deficiency of AAT associated with PiZ phenotype develop emphysema. While many of these persons develop emphysema by age 44, up to 40 percent may have no obvious disease even at age 50. These data suggest that other factors probably contribute to the development of disease. Cigarette smoking decreases the mean age at onset of dyspnea in AAT-deficient emphysema patients from 44 to 35. Similarly, abnormalities of pulmonary function and roentgenographic changes suggestive of emphysema are more pronounced and occur earlier in AAT-deficient smokers. The natural history of PiZ-emphysema is not known, since only a small number of patients have been available for study at any one location. This information is vital to any attempt to treat these genetically deficient individuals with replacement therapy. A group of investigators in the United States has therefore recently pooled longitudinal retrospective data on 293 severely AAT-deficient individuals and compared them with similar data from Sweden. Preliminary analysis of both sets of data indicate that for this group of PiZ individuals with documented airway obstruction, the mean annual decline in FEV₁ was considerably greater than has been observed in other groups of COPD patients.

Cigarette Smoking and Environmental Agents

Cigarette smoking has been identified repeatedly as the most important of the exogenous risk factors for developing COPD. It has been found to interact additively, and sometimes synergistically, with exposure to occupational risk factors and local air pollution.

Since 1972, the influence of environmental agents in the development of COPD has been better clarified. Determination of lung function has allowed the assessment of the effects of exposure to various pollutants. Such studies have shown small but measurable abnormalities in lung function resulting from long-term

exposure to photochemical oxidants, nitrogen dioxide, and sulfates. Epidemiologic data on children suggested that indoor pollution from gas stoves and parental smoking may also adversely affect lung function.

It has become evident that occupational exposures are a greater respiratory hazard than general air pollution in a locale. It has been suggested that carbon particles can carry into the alveoli caustic chemicals that cause emphysema. Epidemiological studies have indicated that a considerably higher incidence of COPD occurs in populations exposed to caustics such as aldehydes, which may be adsorbed on smoke particles.

Infection

Attention has also been paid to the role of respiratory infections in the development of COPD. Since infections are often a feature of advanced COPD, it was suspected that they might accelerate the disease process. These studies have indicated that although infections may precipitate episodes of respiratory failure in COPD patients, the frequency of infection does not correlate with the overall decline of lung function. The most common bacteria cultured from the sputum of patients with chronic bronchitis are Streptococcus pneumoniae and Haemophilus influenzae.

Since exacerbations of bronchitis often result from respiratory viral infections, the contribution of viral infections to COPD has also been examined. Severe bronchial damage is known to be caused by the influenza virus group, and children may have persistent symptoms as a result of residual damage from respiratory viral or Mycoplasma infections. It has been suggested that COPD patients may have had more frequent childhood infections than those who do not develop the disease. An intriguing possibility currently being examined is that childhood infection damages the lung in some yet unknown fashion that predisposes it to later development of chronic airway disease.

Although several studies indicate that the cumulative insults of smoking, recurrent respiratory infections in childhood, bronchospastic disease, and exposure to dusts and fumes in the workplace cause COPD, a precise assessment of the relationship between the development of the disease and the various separate risk factors has been difficult.

Pathogenesis

The current understanding of the pathogenesis of emphysema is based on the protease-antiprotease model proposed in 1963. According to this hypothesis, the normal balance between the

protease and antiprotease levels may be upset in favor of the proteases caused by increased release of the proteases or decreased levels of the antiproteases that result from genetic or other causes. This imbalance can lead to proteolytic damage of the lung tissue. During the last decade, many important details of this model have been developed, but the picture is still incomplete.

Since loss of elastic recoil and the concomitant destruction of elastin in the emphysematous lung have been well established, attention has been focused on the proteolytic enzymes (elastases) capable of digesting elastin. Elastases have been found in human polymorphonuclear leukocytes (PMN's) and in secretions of human and murine pulmonary alveolar macrophages (PAM's), which are cells that have access to or normally reside in the alveolar air spaces. The PMN enzyme has been purified, and it has been demonstrated that it produces emphysema when it is instilled into the airways of dog or hamster lungs. This enzyme has been found to have a broad range of activity. In addition to digesting elastin, it can degrade basement membranes of alveolar epithelium, collagen, and proteoglycans. Thus, PMN elastase is suggested as the likely candidate responsible for the extensive tissue destruction seen in emphysematous lungs. The pathogenetic role of PAM elastase, which has biological properties distinct from the PMN enzyme, is being debated.

In attempts to elucidate the mechanism underlying the destruction of pulmonary elastin in emphysema, lung PMN's and macrophages have been extensively studied, particularly their numbers, migration, distribution, and metabolic activity in the emphysematous processes. Increased numbers of pulmonary macrophages have been found in the centriacinar zones of cigarette smokers, even before the onset of significant airflow obstruction or destructive changes in their lungs. Lung PMN's, which are normally margined in large numbers in the pulmonary capillaries and are only infrequently seen in pulmonary interstitium and alveolar airspaces, have been shown to move into the airspaces in greater numbers as a result of smoking. It now appears that the recruitment of PMN's to the airspaces is partly caused by the liberation of chemical attractants (chemotactic factors) from other lung cells that have been stimulated by inhaled cigarette smoke. These chemotactic factors have also been found capable of inducing PMN's to discharge their lysosomal enzymes, including the powerful elastase contained within the cytoplasmic granules of the leukocytes. The alveolar macrophage is found to be a source of chemoattractants. Therefore, interactions between macrophages and PMN's in the lungs of cigarette smokers are suspected to play an important role in the complex pathogenesis of emphysema.

Repair mechanisms in emphysematous lung, including the regeneration of elastin, have also been examined. With the aid of

modern biochemical techniques, including recombinant DNA technology, new information has been accumulated on the structure, biosynthesis, and turnover of elastin. Evidence indicates that the integrity of the extracellular matrix substructure (collagen, elastin, proteoglycans, glycoproteins) may be important for proper alignment of the newly synthesized elastin fibers in damaged lung.

There is clear evidence that elastases present in the pulmonary milieu are balanced by endogenous antiproteases. Some of these inhibitors are locally produced, whereas others are transported into lung fluids from the circulation. Thus, human mucous secretions, including bronchial mucus, contain an important inhibitor of PMN elastase. Suggested sources of this antiprotease in the airways include seromucous glands of maxillary sinus and tracheal mucosa, serous cells of bronchial mucous glands, goblet cells, and perhaps Clara cells. The "bronchial mucous inhibitor" probably represents the major screen against PMN elastase in the human upper respiratory tract.

The major inhibitor of PMN elastase at the level of the alveoli, as already indicated, is AAT. This antiprotease has been the focus of intensive studies during the 1970's. It has been established that AAT originates in the liver and that it is transported across the endothelial-epithelial lining in alveolar fluids.

The chemistry of inactivation of PMN elastase by AAT has been elucidated to a large extent. It has been demonstrated that AAT forms a stable inactive complex with the enzyme. The inactivation process seems to involve a critical methionine residue; oxidation of this methionine residue reduces the inhibitory activity of AAT. Since cigarette smoke (from high-tar cigarettes) contains significant levels of water-soluble free radicals and peroxides capable of oxidizing the methionine residue, it has been postulated that a state of AAT deficiency may be brought about through such oxidative process by smoking. Studies have shown that lung AAT activity in the bronchoalveolar washings of chronic smokers is approximately half that of nonsmokers. It is suggested that both modes of AAT deficiency (genetic and acquired) resulting in uninhibited elastase activity lead to emphysema. This postulated common mechanism for emphysema of genetic and nongenetic origins remains to be experimentally established.

Since the development of the papain model of emphysema in the last decade, many studies have been conducted utilizing various animal models produced by enzymes and chemicals. In general, emphysema-like lesions are produced in various animal species (rats, horses, cattle, and goats) by introducing either pancreatic or neutrophilic elastase into the bloodstream or trachea, or by administration of chemical agents including NO₂, phosgene, chlorpromazine, chloramine-T, 3-methylindole, and phytohemagglutinin.

In most cases, the underlying mechanisms or common denominators remain speculative.

Progression of Disease

By the mid-1970's, a number of studies had indicated that the presence of cough and sputum did not necessarily mean that a patient would develop significant COPD. A study in which a large number of Canadian veterans were followed for 10 years demonstrated that despite the clinical diagnosis of chronic bronchitis, most led normal lives. Only 10 percent of these men developed spirometrically determined chronic airflow obstruction associated with clinical chronic bronchitis. An 8-year prospective study of London transport workers, conducted to define the early stages of COPD, led to the concept that hypersecretion of mucus and chronic airflow obstruction are two distinct conditions. Mucous hypersecretion is of much less significance, since it does not by itself lead to serious and progressive disability. In contrast, chronic airflow obstruction, which occurs in the susceptible smoker, leads to progressive disability and in a small proportion of individuals, to respiratory failure and death.

Since the beginning of this decade, it has been generally accepted that the progression of COPD usually follows the following approximate course: a young person starts smoking cigarettes and for the next 10 years, symptoms are not prominent, and then, for many smokers, a chronic cough productive of small amounts of sputum begins. After the age of 40, shortness of breath, brought on by exercise and progressive deterioration of lung function, usually occurs. Advanced disease, with severe obstruction of the airways and a varying prominence of features typical of chronic bronchitis and emphysema, most often appears after the age of 55. Continued smoking had been found to make the prognosis of the disease worse.

It has been postulated that at some early point in the disease process, the damage may be reversible. If at that stage a susceptible person can be identified and convinced to give up cigarettes, the later phases of this inevitable progressive illness, which is marked by severe airflow obstruction, disability, and death, can be prevented.

Basic Advances in Pulmonary Function Testing

Tests of Dysfunction of Small Airways

The finding of mild disease as evidenced by a number of measures of function of small airways, loss of elastic recoil in

individuals without reduction of spirometric tests, impaired gas exchange, and other changes associated with more severe disease has suggested that the findings in the sequence of symptoms outlined above appear early. Numerous investigators became interested in function tests of small airways in the early 1970's. With the use of these tests, it was shown that approximately one-third of smokers can be identified as abnormal. A number of studies showed for the first time that at least some of the functional impairment detected by these tests can be reversed if the subjects stop smoking. These studies have therefore clearly demonstrated benefits from smoking cessation. It was next suggested that these sensitive tests might help identify which smokers would have a high risk of developing severe airway obstruction if they continue to smoke.

Advances have been made in understanding the mechanics that govern airflow in the lungs and why and where flow limitation occurs. One of the most significant contributions of the last decade has been the development of the wave-speed theory of expiratory flow limitation in which the airways are likened to elastic tubes. In this model system, waves are generated in the elastic walls as air flows through the tubes, and flow becomes limited when the speed of the airflow equals the speed at which the waves in the walls propagate. The "choke point" (the location at which the limitation occurs) can be predicted if the properties of the gas, the cross-sectional area, and the stiffness of the tube are known. This concept has provided a simple approach to understanding flow limitation and the mechanisms by which airway resistance, lung elasticity, the physical properties of gases, and airway compliance and caliber interact. This concept should help in the interpretation of existing tests of forced expiratory flow and in the development of new tests.

Dysfunction and Lesions in Small Airways

A number of studies have demonstrated that small airway lesions correlate with abnormal tests of small airway function. The most important lesion appears to be inflammation, which is likely to be reversible. Cigarette smoke, having clearly been demonstrated as a powerful inflammatory agent, suggests another pathogenetic role for smoking. The fact that small airway lesions have also been observed in nonsmokers suggests that other factors may also contribute to such abnormalities.

Difficulties have been encountered, however, in correlating specific tests of small airway dysfunction with anatomical abnormalities. In surgically resected lungs and in human lungs studied postmortem, individual test abnormalities do not seem to be associated with specific anatomical lesions. The initial supposition that airway narrowing can be equated with bronchitis

and loss of elastic recoil equated with emphysema now seems simplistic. A recent study indicates that loss of elastic recoil, which is a test classically associated with the presence of emphysema, correlates well with various tests of small airway dysfunction, but less well with the anatomical changes diagnostic of mild and moderate emphysema.

It has been proposed that airflow limitation is caused by multiple abnormalities in the lung. Thus, inflammatory changes in the small airways, emphysema, loss of elastic recoil, and abnormalities in small airway function may all tend to occur simultaneously, and it may be impossible to link specific anatomical abnormalities with specific tests of lung function. It has been suggested that the loss of elastic recoil may be due to the alterations of the proteins in the extracellular matrix of the lung rather than from the actual disruption of the alveolar walls.

Mild disease in young smokers can now be demonstrated by abnormalities in small airway function, but it has not yet been established whether any of these abnormalities can predict which individuals will develop severe disease if they continue to smoke.

Tests of Large Airway Function

Although not as sensitive in detecting mild disease as the tests of small airway function, the forced expiratory volume in 1 second is a relatively good predictor of prognosis in moderately advanced disease. One population study has indicated that if the FEV_1 is above 70 percent of the predicted value, death rate is similar to the population at large. In another study of pulmonary function, the median survival rate decreased as the volume of the FEV_1 declined. Prognosis has also been shown to be closely related to the rate at which the FEV_1 declines during the first few years of observation.

Since pulmonary function tests have not been able to detect preclinical emphysema, some investigators are trying to develop assays that can measure breakdown products of elastin in the blood or urine. This approach exploits the biochemical changes that presumably occur early in the disease process. Preliminary studies using immunoassays for desmosine, which is a unique amino acid in elastin, have shown that desmosine containing elastin peptides is elevated in some smokers, in patients with emphysema, and in animals that have had elastases introduced into their lungs. The clinical value of these biochemical tests remains to be established.

Advances in Treatment and Management

Management of COPD still relies heavily on avoidance of smoking and pollution, on the maintenance of good nutrition, and on physical conditioning. Drug treatment consists primarily of bronchodilators, antibiotics, and corticosteroids. Although treatment is quite similar to what it was 10 years ago, much has been learned during the interval, and a slow shift from pragmatically based to scientifically based therapy has occurred. This change includes not only the physiological aspects of therapy, but also the psychological and educational facets of treatment.

Oxygen Therapy

For many years, low-flow oxygen has been of major importance in the management of hypoxemic patients in the late stages of COPD. Although benefits of oxygen therapy (such as its ability to reduce pulmonary artery pressure to help reverse hypoxemia-induced cardiac decompensation, to increase exercise tolerance, and to improve the patient's mentation) were recognized, it was not clear whether these benefits required the administration of oxygen continuously for 24 hours a day (continuous oxygen therapy) or if they could be achieved by using oxygen for about 12 hours at night (nocturnal oxygen therapy). There was evidence that 15 hours of oxygen a day reduced pulmonary hypertension, and it was known that patients suffer their lowest blood oxygen levels during sleep. On the basis of this knowledge, the multicentered Nocturnal Oxygen Therapy Trial (NOTT) was initiated in 1976. This study compared the effectiveness of continuous versus nocturnal oxygen therapy in 203 patients with hypoxemic COPD. The data showed the overall mortality in the nocturnal therapy group to be nearly twice that of the continuous oxygen therapy group. The decreased mortality in the continuous oxygen group was striking in the most severely ill patients--those with retention of carbon dioxide and relatively poor lung function, low mean nocturnal oxygen saturation, more severe brain dysfunction, and prominent mood disturbances; but the reason for the decreased mortality in the continuous oxygen therapy group is unclear. This study is a landmark in COPD research because it demonstrated for the first time that a therapeutic intervention can prolong life. Another advance in the area of home oxygen therapy was also made during this decade. New devices were developed and marketed that concentrate oxygen, and they were found to be more economical sources of continuous oxygen. Backup and portable tank systems, however, are still required.

Other Approaches

Improvements in methylxanthine and beta-adrenergic bronchodilator therapy have been reported during this decade. New long-acting theophyllines, which are more pleasant and safer than currently used drugs, have given the physician better control in maintaining therapeutic levels of drugs in the blood. Beta-adrenergic bronchodilators with specific beta-2 activity were recently introduced into the United States. They were shown to act more specifically on airway smooth muscle and apparently to produce fewer undesirable cardiac side effects. Where excess secretions are a problem, inhaled bronchodilators are being used together with moisture and often with chest percussion or physiotherapy. The efficacy of these treatments is often questioned, but some patients seem to find them useful, and this form of treatment remains popular.

Aerosol therapy has become popular because it can provide local delivery of many of these drugs, and significant investigative efforts have been expended on theory and practice of aerosol delivery. A medicated aerosol can be generated by a nebulizer or delivered under pressure by an intermittent positive pressure breathing machine. There has been considerable debate as to the relative merits of each of these modes of delivery. Early enthusiasm for IPPB use was tempered by contradictory findings. While IPPB is undoubtedly useful in increasing alveolar ventilation and in delivering bronchodilator therapy in the majority of acutely ill patients, these effects can also be achieved by voluntary hyperventilation and bronchodilator given by nebulizer. There may be some patients for whom IPPB has additional benefits, but specific criteria have not been well-defined in controlled studies. Since this costly form of treatment continues to be prescribed by many and without good evidence justifying its administration to patients with stable COPD, a multicenter clinical trial of long-term IPPB therapy was initiated in 1977. This trial is currently comparing the relative effectiveness of an IPPB device to a powered nebulizer in about 1,000 patients. Some of the factors being assessed include pulmonary function, quality of life, neuropsychological status, and patient history. This clinical study is still in the phase of data collection, but preliminary analysis has led to some conclusions that may eventually help in the treatment of COPD. In responses to a questionnaire on severity of symptoms (cough, phlegm, wheezing, and breathlessness), only breathlessness appeared to correlate with the severity of the disease as measured by physiologic, functional, and psychosocial indicators.

Although corticosteroids, either oral or inhaled, appear to help some patients, the value of corticosteroid therapy in the treatment of COPD has been questioned. More information is needed before this issue can be settled. A randomized double blind

crossover trial of corticosteroid and placebo treatment conducted on 42 patients recruited for the IPPB study indicated that corticosteroids substantially reduce airway obstruction in some patients, especially those responding well to inhaled bronchodilators. Bronchodilator response, however, did not predict the corticosteroid response with complete accuracy. The usefulness of corticosteroids remains unclear.

Knowledge of the importance of the imbalance of the protease-inhibitor system to the development of emphysema led investigators to suggest that it might be possible to develop agents to correct the imbalance in patients who have genetically determined low blood-concentrations of AAT or who have a local deficiency of AAT in their lungs from inhaled cigarette smoke. Studies are under way to determine if it is possible to correct the protease-antiprotease imbalance in these patients and thereby arrest or reverse the progress of the COPD through inhibitor replacement therapy.

Management

The chronic, progressive nature of COPD inevitably leads to disruption in lifestyle. Moreover, physiological effects of poor oxygenation may lead to or exacerbate neurological, psychological, and psychosocial problems. Such problems may then reduce the patient's motivation or ability to undertake rehabilitation, treatment, and self-management. Progress has been made in understanding the psychosocial aspects of COPD that contribute to a deterioration of the patient's quality of life, and in determining the corrective measures that should be taken.

The NOTT studies have led to the identification of areas of neuropsychological dysfunction associated with COPD and of responses to treatment. Neuropsychological functioning has been found to be appreciably disrupted in COPD patients, but the mechanisms linking COPD with such dysfunctions have not been identified. Quality of life as well as activity levels improved among the NOTT patients receiving various combinations of rehabilitation training, social support, psychotherapy, and counseling.

Also during this decade, much attention has been given to educating the COPD patient and physician. Several programs for the layman and for the nonspecialist physician, using a variety of teaching methods, were conducted and evaluated. A number of programs have become popular, and much has been learned about their effectiveness. Studies associated with programs for patients have shown that the concern expressed by the family positively correlates with the amount of walking done by the patient, the frequency of the patient's social contact, and the

extent to which the patient uses the telephone. Similarly, the patient's smoking habits were influenced by the spouse's habits, and success in quitting has been influenced by peer habits. Lecture and therapy sessions for patients and family, and attendance at meetings has led to subjective increases in patient well-being, endurance, and level of activity, and decreases in the number and days of hospitalizations.

Several studies have attempted to identify critical components of COPD rehabilitation programs. American Lung Association workshops have significantly increased the knowledge and positive attitudes of patients. Some studies have shown that psychotherapy is as effective as pulmonary rehabilitation. This finding suggests a need for emphasis on psychological and emotional aspects in comprehensive rehabilitation treatments.

Although physical exercise for general fitness and for improvement in breathing has long been a part of patient management, it is only recently that widespread interest in the function of ventilatory muscle has been generated. The ability of COPD patients to continue breathing and to cough forcibly depends upon adequate ventilatory muscle power, and it is possible that ventilatory muscle fatigue contributes to respiratory failure in some of these patients. There are also data to support the belief that ventilatory muscle fatigue leads to breathlessness, which is a common and distressing symptom of COPD.

It has therefore been postulated that ventilatory muscle training might offer an effective treatment for COPD patients. Studies of normal volunteers have indicated that the programs are safe and that ventilatory muscles can be specifically trained to increase strength and endurance. A few weeks of endurance training of COPD patients resulted in improved endurance of ventilatory muscle, but only some of these patients showed improved performance on exercise tests. Pulmonary function did not seem to improve with exercise, and there was no consistent improvement in cardiovascular performance. It is now thought that, at least for some patients, ventilatory muscle training may improve endurance sufficiently to allow accelerated programs of general exercise reconditioning.

Some studies have revealed an association between nutritional status and respiratory muscle mass in COPD patients. This finding may have implications for their muscle function. The weight of the diaphragm, the chief ventilatory muscle, was reported to increase in some patients with chronic airflow obstruction, and to decrease in others. Diaphragm weight appears to be related to body weight, and both decrease as the disease progresses. Diaphragm weight, however, was observed to decrease faster than body weight. Patients with far-advanced COPD have often been found to waste even when their nutritional needs are carefully

addressed. Impaired nutritional status has been reported to occur in about 20 percent of COPD patients.

Advances in Prevention

Since prevention is still the only effective approach to combat COPD, programs to discourage smoking have grown during the past decade in terms of types of people they address and the range of procedures and levels of intervention they employ. Several projects have successfully encouraged pregnant women, children, and adolescents to quit smoking or to not start it. Successful alternatives to aversive conditioning, such as rapid smoking, have included instruction in self-control skills, self-help manuals, mass communication interventions, individualized encouragement by a physician, and extended group and individual treatment as part of the Multiple Risk Factor Intervention Trial (MRFIT) comprehensive program of risk reduction for heart disease. Research in chronic smoking patterns and in relapses following cessation indicates that the smoking habits of family and friends, and social support for maintaining cessation and coping with stress may be critical targets of future programs in this area. Unfortunately, the success rate for smoking cessation is still poor.

Another approach being developed is the incorporation into smoking cessation programs of an individual "risk" index. A quantitative index of risk "models" for the development of COPD has been constructed from information in several epidemiological studies. The major factors considered are sex, age, initial lung function, and smoking history. Among these, smoking is the only modifiable variable. With reliable information on the individual's likelihood of developing COPD, greater success in modifying smoking behavior may be possible. The index of risk is being validated with data from other populations, including groups of workers in high-risk occupations. Plans are under way to incorporate the index into the smoking cessation programs when it is ready for widespread use and to evaluate its efficacy in prevention and education activities related to COPD. The ability to identify individuals who are at high risk early in life of developing severe airway obstruction if they continue to smoke would help to focus the prevention effort.

State of Knowledge in 1982

Great progress had been made in understanding the chemical processes that cause this disabling progressive destruction of the lungs. Disturbance of the protease and antiprotease balance in the lungs has been found to occur locally in the lungs of smokers

as well as in the lungs of patients with AAT-deficiency. This important finding means that studies which were previously thought to be relevant to only a small proportion of patients with COPD resulting from AAT deficiency now seem to apply to the largest group of patients with COPD, the cigarette smokers. The pathology and physiology of early airway lesions is being described, and a multidisciplinary understanding of the evolution of COPD is beginning to unfold. As a byproduct of this research, some of the constituents of cigarette smoke that are destructive to the lungs are being identified. These studies have opened the possibilities that novel approaches may be possible to prevent the progression of COPD before it becomes a disabling and deadly disease.

While physicians are clearly able, with various types of interventions, to improve the quality of life of patients with COPD, only the continuous administration of oxygen to patients with severe COPD has been shown to prolong life. The NOTT study scientifically examined the effect of therapy on the quality of life as well as on mortality and physiology. Currently available treatment modalities do not stop the progress of the disease in its early stages, and attempts to prevent the disease by the elimination of cigarette smoking have been disappointing. The long-term control of this health problem lies in the development of better methods to eliminate cigarette smoking and other environmental pollutants, the removal of toxic products from cigarettes, and the introduction of agents that can restore the protease-inhibitor balance to the lungs.

Program Goals 1982 to 1987

Epidemiology and Pathogenesis

- Continue longitudinal studies of the determinants and natural history of COPD.
- Define the importance of occupation in the pathogenesis and progression of COPD, and identify hazardous occupations.
- Determine the effectiveness of therapy for mild abnormalities in ventilatory function on subsequent development of COPD.
- Determine whether acute respiratory infections or chronic respiratory diseases such as bronchitis and asthma in infancy and childhood lead to the subsequent development of COPD.

- Continue studies on the validity of protease-antiprotease hypothesis in human emphysema, and identify the enzymes responsible for lung derangements.
- Identify constituents of conventional and modified cigarettes that damage the lungs.

Pathophysiology

- Define the differences between emphysema-related and chronic-bronchitis-related chronic airflow obstruction.
- Identify the earliest lesions in COPD.
- Continue correlative studies on lung structure and physiological function in COPD.
- Determine the relative contributions of peripheral airway obstruction and alveolar destruction to the pathophysiology of clinically overt chronic airflow limitation.
- Determine the role of the respiratory muscles in the development of respiratory failure and in its treatment.

Diagnosis, Management, and Prevention

- Develop and validate biochemical and physiological tests for the early detection and progression of COPD.
- Develop and evaluate new techniques of measuring cellular oxygenation.
- Develop methods for determining the clinical relevance of infectious agents in the sputum to the clinical course of exacerbations in COPD.
- Develop and test elastase inhibitors to determine if they prevent the progression of COPD.
- Determine if it is feasible to prevent the progression of PiZ emphysema by alpha-1-antitrypsin replacement therapy.
- Develop new approaches to alpha-1-antitrypsin replacement in deficient individuals.
- Identify the skills and personal practices with which patients may best manage or accommodate their disease, the most efficient educational, psychological, and clinical procedures to encourage such skills and practices, and the

specific effects of such procedures on physical and psychosocial status and relationships.

- Identify how smoking cessation and prevention programs best achieve their effects and which stages of disease allow most effective interventions.
- Develop and test more effective methods of encouraging smoking cessation.

Research Activities 1982 to 1987

Substantial opportunities exist to develop new types of therapy for COPD that may stop the progression of the disease in its early stages. In addition, attempts to discover new and better means of prevention are likely to be fruitful. Special attention needs to be paid to environmental factors and social habits, including smoking, since these factors are superimposed on the genetic and physiological constitution of an individual and determine the course of pulmonary health. As a corollary, there is a need to develop appropriate educational methods to help translate newly gained knowledge of risk factors into preventive and protective strategies.

Much remains to be known about the physiologic, pathologic, and clinical aspects of the COPD complex. Many of the conditions that this term encompasses have common origins, coexist, occur unobtrusively, and remain indistinguishable in early stages. In fact, it is not definitely known whether the conditions are distinct diseases as presently defined or are different pathologic and physiologic states of the same ongoing process. Precise definitions of the various pathologic entities, despite their apparent similarities, are needed, for they are likely to have different prognoses and be responsive to different modes of therapy.

Development of more accurate and sensitive methodology for the diagnosis of chronic obstructive lung disease at its inception, well before clinical symptoms appear, remains an urgent and unmet need. The time of diagnosis in relation to the age of the individual and progression of the disease has a significant bearing on the modality of treatment as well as on the ultimate outcome. New approaches to diagnosis including sensitive evaluation of pulmonary function and ability to identify subtle changes at the molecular, cellular, and subcellular levels need to be devised.

To attain these goals it will be necessary to attract into pulmonary research multidisciplinary expertise including physiologists, pathologists, pulmonary physicians, cell biologists, immunologists, biochemists, and epidemiologists.

Asthma

The term "asthma" refers to a condition that is characterized by extreme sensitivity of airways to a variety of stimulants. Exposure to stimulants, or triggering agents, results in the clinical state (asthmatic episode) of decreased airflow, shortness of breath, and wheezy respiration often accompanied by productive coughing. The patient has no detectable symptoms between episodes. Attacks may be transitory or may last for several days. Even though most episodes are reversible by appropriate treatment, very severe attacks ("status asthmaticus") sometimes occur, and they can be fatal. In some patients, the airflow obstruction becomes chronic. In varying degrees, symptoms of asthma also can occur in childhood as well as in adult diseases such as bronchiolitis, bronchitis, and emphysema, which can complicate the diagnosis. Asthmatic episodes can be caused by various agents such as allergens ("allergic asthma"), drugs ("aspirin-induced asthma"), exercise, industrial and occupational chemicals, infections, and perhaps emotional factors. Based on the initiating event, asthma is categorized tentatively as extrinsic (for example, allergic), intrinsic (idiopathic, absence of clearly external precipitating events), and mixed (nonspecific, diverse triggering agents).

Asthma is thus a term for a complex disease of varied etiology, and it occurs more often in children than in adults. At one time, asthma was mistakenly thought to be more common in higher socioeconomic levels of society, but recent studies do not confirm this observation.

Over 9 million Americans, including a significant number of children, suffer from asthma. Asthma tends to run in families, and heredity has an important role in the disease. Emotional factors make the condition worse, and certain occupations offer increased risk for the disease. Geography and climate are also contributing factors.

Although asthma was first described as early as the second century, no agreed-upon definition of the disease has yet emerged. Its basic etiology is unknown, its pathogenesis is poorly understood, and its treatment is symptomatic. Prevention constitutes avoidance of the triggering factors.

The National Heart, Lung, and Blood Institute is responsible for promoting studies of the aspects of asthma that relate to the lung as a target organ (for example, pathophysiologic and biochemical aspects of bronchial smooth muscle contraction, and its therapeutic reversal through development of specific drugs). The National Institute of Allergy and Infectious Diseases (NIAID) has the major mandate to support asthma research, and particularly research that is concerned with its immunologic, infectious, and related clinical aspects. The research areas supported by each Institute are well delineated, but the results of the research often intertwine and are symbiotic and synergistic. While it is not entirely possible to separate distinctly the accomplishments of each Institute, an attempt is made in this report to identify the NHLBI efforts.

State of Knowledge in 1972

In 1970, about 3 percent of Americans (6 million) were estimated to have active asthma. The annual mortality rate was relatively small (2,500), but the economic impact was enormous. In one year, over 27 million physician visits were for asthma. The number of lost days per year ran into millions: 85 million days of restricted activity, 33 million days in bed, 5 million days of missed work, and 6.5 million days of school absences. These estimates are only approximate since the methodologies and definitions used to determine the disease and its prevalence varied greatly; some investigators used histories, and others supplemented histories with pulmonary function tests.

The three general categories into which asthma is currently divided--extrinsic, intrinsic, and mixed (nonspecific)--had been recognized for 50 years. Asthma attacks due to exercise and to exposure to cold air were known. Acute respiratory infections were also known to cause asthma, although the responsible organisms were not identified. The effects of air pollution on asthmatics were not clearly delineated in 1972, but the more important allergens had been studied. Among these were pollens from trees, grasses, and weeds; molds; house dust; and cat-, dog-, and insect-derived antigens. A long list of occupational airborne antigens was also known, including protein dusts and certain low molecular weight, volatile chemicals. There was agreement that asthma was a physiological disorder that may be exacerbated by psychological factors in some individuals.

By 1972, the physiologic abnormality in asthma (impaired free flow of air, obstruction of airways) was characterized in pathologic terms as thickening of the bronchial wall due to edema, inflammatory cell-infiltration, hypertrophy of smooth muscle (enlargement due to increase in the size of its cells), and

thickening of subepithelial basement membrane. A decrease in the number of mast cells (ascribed to their degranulation) was also known. Plugging of the airway lumen with mucus, cells, and fibrin had been described in severe cases.

Broad features of the pathogenetic events in extrinsic asthma were understood, and the importance of the mast cell had emerged by 1972. According to the mast cell theory, individuals with appropriate genetic or immunologic characteristics produce, when exposed to environmental antigens, unique and specific antibodies called IgE immunoglobulins. These antibodies become attached to certain cells, especially mast cells. During subsequent exposures, the allergen reacts with the mast-cell-bound IgE. This event results in the direct or indirect release of certain pharmacologically active "mediators." These mediators, in turn, act on smooth muscle, secretory glands, and blood vessels to produce inflammatory cell-infiltration bronchoconstriction and hypersecretion of mucus and edema, which are the cardinal features of the asthmatic attack. Histamine was the best known of the mediators. By 1972, slow reacting substance of anaphylaxis was a recognized mediator, but little was known of its structure or function. Among the other mediators were factors chemotactic to eosinophils and neutrophils, but their identity or specific functions were also not well understood. It was known that nonimmunologic mechanisms also function in regulating the release of mediators (for example, the cholinergic and adrenergic systems), but the underlying biochemical processes were poorly understood.

The mechanisms of hypersensitivity to agents such as histamine and methacholine were not known. Theories of neural mechanisms in asthma were proposed; in one theory, beta-adrenergic receptors are blocked, and in another theory, the induced changes in the normal neural mechanisms of control and exaggerated vagal reflex responses are responsible. The interrelationships, if any, between the neural- and allergy-induced bronchospasms were not known. While studies with isolated human lung tissue and animal models (guinea pig) gave much information about mediators, suitable animal models of asthma were still lacking, though the search was under way.

In 1972, management of the disease involved identifying allergens and environmental irritants and instructing the patient to avoid them insofar as symptoms required. Medications included antihistamines and bronchodilators such as isoproterenol epinephrine, ephedrine, and methylxanthines as well as the anti-inflammatory agent, corticosteroids.

Program Goals Through 1982

Among the goals set in 1972 for research on asthma were:

- Define the natural history of asthma through longitudinal followup of genetic, immunologic, pharmacologic, and pathophysiologic characteristics in different populations of asthmatics.
- Conduct genetic studies of etiology and pathogenesis in families and twins, and establish patterns of incidence.
- Investigate, through controlled prospective epidemiologic studies, the incidence and etiology of bronchial asthma; explore by epidemiologic surveys the relationship of asthma to respiratory infections.
- Elucidate mechanisms involved in control of airway patency in healthy and asthmatic subjects, including the release of chemical mediators, their modes of action, receptors, and the means of blocking these receptors as well as their relation to neural pathways and reflexes, and cyclic AMP metabolism.
- Conduct investigations into mucociliary transport and the properties of abnormal mucus.
- Develop simple and accurate means of early detection and diagnosis using physiologic, biochemical, and immunologic approaches, including pulmonary function tests, responses to bronchodilators and methacholine, and examination of sputum for eosinophils.
- Evaluate and develop pharmacological agents that are useful in therapy. Conduct studies of genetic differences in pharmacological reactivity.
- Conduct clinical trials of steroids, immunosuppressive agents (in treatment-failure patients), and anti-inflammatory agents, and evaluate hyposensitization.
- Develop animal models of asthma to permit studies that are not appropriate in humans.

Accomplishments Through 1982

It is widely assumed that the risk factors for developing this disease are a superimposition of environmental and other factors acting on the genetic makeup. Since it is important to

identify individuals who are genetically susceptible, attempts have been made to define the natural history of asthma in families with more than one asthmatic individual. Extensive population screening studies that examined whether an association exists between asthma and a variety of histocompatibility (HLA) antigens revealed no evidence for association of asthma with any of the HLA antigens tested. Serum IgE levels and, to a lesser extent, methacholine sensitivity have been established to be under genetic control although both respond to environmental changes.

Since asthma is the leading chronic disease causing school absenteeism, disrupting family routine, and prohibiting many children from participating in daily activities, various self-help programs have been examined. A recently developed educational program has shown that children and their parents can often learn to manage the condition without undue reliance on the medical system. The principal behaviors that were targeted in the educational program are those that can contribute to the onset and to an exacerbation of an attack. They include a lack of compliance with medication, failure to avoid known irritants, failure to perceive the onset of an attack, and an inability to relax and take preventive measures during an attack. Results of an evaluation of the educational program indicate that the families made significant gains in knowledge of asthma and that a year after acquiring self-management skills, the children had fewer absences from school. This encouraging study should provide an impetus for wide dissemination of self-management programs.

The methacholine test has proved to be predictive of subsequent development of asthma, and its use should allow the institution of preventive measures through screening the preasthmatic population. Standardized protocols for inhalation-provocation testing, developed through the joint efforts of various professional groups, should also be helpful.

Developments that have facilitated population studies were the standardization of questionnaires about respiratory symptoms and histories of exposure and the standardization of methodology for lung function testing. Data are now comparable, and a better understanding has been obtained of the incidence, prevalence, and natural history of asthma. The onset seems to occur during the early years, decline markedly during adolescence, and increase during early adult life. Wheezing occurs mainly in individuals with preexisting chronic bronchitis. In general, asthma that is recognized before age 40 is related to allergy to airborne antigens. When the disease occurs later, it is apparently from other causes.

Several studies have confirmed that respiratory virus infections provoke asthma. The most common agent in infants and preschool children is the respiratory syncytial virus, which

causes bronchiolitis. In older children and adults, it is rhinoviruses and parainfluenza viruses. Bacterial infections seldom, if ever, provoke asthma. The viruses may act by influencing the immune response of the host and the epithelial handling of the antigen or by increasing the sensitivity of certain neural receptors in the mucosa or the reactivity of the smooth muscle. Viruses may also cause decreased beta-adrenergic or nonadrenergic controls versus increased alpha-adrenergic or cholinergic controls.

An increasing number of new allergens particularly from industrial processes and occupation sources have been identified during this decade, and new entities are being added regularly. These include toluene diisocyanate (TDI) and trimellitic and phthalic anhydride (used in manufacture of plastics) as well as western red cedar, coffee bean dust, and several pharmaceuticals including enzymes and antibiotic dusts. In some cases specific IgE antibodies have been detected (for example, trimellitic anhydride-induced asthma). In the case of TDI, no relationship has been found between the development of the disease and antibodies, and the current suspicion is that TDI asthma is caused by nonallergic mechanisms. There is some evidence from in vitro studies that TDI may interfere with stimulation of adenylate cyclase. Thus, various forms of occupational asthma could arise from entirely different mechanisms.

Evidence has been obtained that airway obstruction of asthmatics after physical exercise may be due to the cooling of the intrathoracic airways and not to exercise itself. Mast cell mediators have been detected following exercise. It has also been demonstrated that cromolyn sodium alleviates the obstructive response to large thermal burdens without affecting lung airways.

A major accomplishment of the decade of the 1970's is the wealth of information accumulated on the cellular origin and biochemical characterization of the generation, release, structure, and function of the chemical mediators, especially histamine, eosinophil chemotactic factor of anaphylaxis (ECF-A), neutrophil chemotactic factor, platelet-activating factor (PAF), and slow reacting substance of anaphylaxis, which have been implicated in the development of airway obstruction. This information, which was not available during the previous decade, is providing a basis for a more integrated view of the sequential effects of the mediators as they pertain to the expression of bronchial asthma. The function of histamine has been further clarified. In addition to effecting the immediate and short-lasting bronchial constriction, it may have other general effects, such as altering endothelial and epithelial permeability, modulating chemotactic factors, stimulating neural sensory endings, and influencing mucociliary transport.

The slower, more prolonged bronchial constriction in asthma has been attributed to the slow reacting substance of anaphylaxis, hence its name. It has been found to be particularly potent in contracting small peripheral airways. Since its discovery in the 1940's, SRS-A was identifiable only from its pharmacologic activity. Its chemical characterization had eluded scientists because of its instability and low tissue levels. In the second half of the 1970's, there were major breakthroughs in the characterization of SRS-A, including its structure, biosynthetic pathways, and biologic function. SRS-A has been shown to be a mixture of closely related leukotrienes (derivatives of arachidonic acid). The structure of SRS-A is now established. The voluminous literature in this field suggests that the biological effects of SRS-A (and leukotrienes) are complex and vary with species, cells, and other unknown factors. When further clarification of these complexities is achieved, inhibitors of biosynthetic pathways of SRS-A should provide new approaches to the control of hypersensitivity reactions mediated by this substance.

Eosinophil chemotactic factor anaphylaxis has been deduced to be a mixture of at least two peptides, and their postulated structures have been confirmed by synthesis. It appears that these peptides may have minor importance since they exert their effects entirely on eosinophils and neutrophils and have no direct ability to contract smooth muscle. Neutrophil chemotactic factor is a high molecular weight protein with a long half-life in plasma. This property makes it a valuable indicator of mediator release.

It is now known that the complexity of chemical mediators of asthma is greater than was hitherto anticipated. Significant new information has accumulated concerning kinins, a group of enzymatically active peptides that induce contraction of smooth muscle; platelet-activating factor, which is involved in histamine release; neutrophil chemotactic factor of anaphylaxis; and prostaglandins. Identification of the structure and chemical synthesis of PAF has been accomplished, and this mediator is suggested as the major factor in the physiological alterations in anaphylaxis. Prostaglandins are also released during both antigenically and nonantigenically mediated contraction of bronchial smooth muscle. Some prostaglandins ($\text{PGF}_2\alpha$ and TXB_2) cause bronchial contraction while others (PGE_2 and PGI_2) cause bronchodilation. PGE_2 is variably a bronchoconstrictor as well as a bronchodilator. It is likely that prostaglandins play an important role in the generation and control of inflammatory contractile responses in the lung. This is an area for active research.

It has been recognized that the immediate IgE-mediated allergic reaction is followed 6 to 12 hours later by a second phase of inflammation, but the mediators and cellular events of

the second phase are not delineated. In the lungs it is manifested by a second wave of airway obstruction that is refractory to bronchodilators but responsive to glucocorticoids. Patients who show a late phase reaction to bronchial challenge develop increased reactivity to methacholine. Study of the inflammation induced by the late phase of the IgE reaction has attracted attention because it may lead to a better understanding of the eosinophilic inflammation that characterizes the non-IgE-mediated asthma responsible for most hospitalizations.

Much indirect evidence has been obtained to suggest that abnormal responsiveness of the autonomic system may contribute to asthma. It has been found that asthma subjects exhibit excessive alpha-adrenergic activity and decreased beta-adrenergic response. Several observations support the importance of the cholinergic vagal nervous system in the increased airway responses in asthma. It has been suggested that epithelial damage may contribute to the hypersensitivity of the airways of asthmatics, and to test this hypothesis, studies were conducted on the effects of viruses and ozone on the normal epithelia of healthy individuals and animals and of their response to histamine. These studies revealed that exposure to viruses and ozone increases the bronchomotor sensitivity to inhaled histamine.

In addition to the characteristic hyperreactivity of their airways, patients with asthma and other atopic diseases have been found to exhibit diminished response to beta-adrenergic agonists and increased response to alpha-adrenergic and cholinergic stimulation in a number of organs including skin, blood vessels, and pupils. Research into the mechanisms of these abnormalities has utilized peripheral blood leukocytes because of their easy accessibility. In leukocytes of patients with asthma and atopic dermatitis, the number of beta-adrenergic receptors have been reported to be reduced, but the possibility that the reduction is due to endogenous catecholamines or to exogenous adrenergic drugs has not been excluded. Treatment with beta-adrenergic drugs or incubation of tissues with these drugs reduces the number of beta receptors. Evidence does not permit a definitive biochemical explanation for cell membrane events that account for the hyperreactive airways in asthma. There may be a defect in membrane receptors, in calcium flux, in membrane phospholipid metabolism, or in some other process.

The adrenergic nervous system was found to have a function in relaxing airways in some species but apparently not in humans. Adrenergic fibers have not yet been demonstrated in humans. Recent studies have led to the description of a previously unrecognized nervous system in the airways of humans, baboons, and other species, namely the nonadrenergic inhibitory (purinergic) system. The lack of involvement of adrenergic agonists in neurally mediated relaxation of airway smooth muscle and the

absence or paucity of adrenergic nerves in human airway smooth muscle suggest that this system may be the principal mechanism for relaxing the human airways. Adenosine triphosphate (ATP) and vasoactive intestinal peptide are among the candidates proposed as its possible mediator, but this has not yet been identified. It has been suggested that asthma may be associated with defects in the purinergic system, which is also implicated in achalasia and Hirschsprung's disease and is characterized by the inability of the esophagus or intestine to contract normally. The autonomic and mast cell theories of asthma are not necessarily mutually exclusive and may complement each other.

Since chemical mediators play a predominant role in airway smooth muscle contraction, agents capable of inhibiting mediator formation or release are potentially useful in asthma therapy. Significant effort has therefore been made to develop new information on the biochemical aspects of mediator synthesis and release. Evidence indicates that cyclic nucleotides and calcium ion fluxes modulate both these processes. Increases in cAMP levels have been found to be associated with smooth muscle relaxation. Increases in intracellular calcium ions results in contraction. Thus, agents that increase intracellular cAMP (beta-adrenergic stimulants and phosphodiesterase inhibitors) or decrease calcium efflux have provided new approaches to asthma therapy. In general, the study of the biochemical characteristics of cell membranes and the importance of lipid metabolism in the control of cell function have become active areas of investigation. The discovery of the influence of phospholipid methylation in the coupling of stimulation to response has provided promising leads to further investigation.

Progress has been made in the search for an animal model of asthma that would allow experimental approaches not possible in human patients. The ideal animal model would be a naturally occurring syndrome that duplicates the biochemical, immunologic, physiologic, and pathologic characteristics of the human disease. Unfortunately, no natural animal model has been identified thus far. Antigen challenge of sensitized dogs, guinea pigs, and rhesus monkeys results in some of the pulmonary mechanical abnormalities (bronchospasm) of acute human asthma. A major shortcoming of these models, however, is that they resemble acute asthma only in the similarity of location and mechanism of bronchoconstriction during asthma attack and not in the development of hyperirritable airways or of the histologic abnormalities that characterize human asthma between asthmatic attacks. In these models, the immunologic mechanisms associated with the respiratory responses to antigen challenge resemble those that occur in human asthma in that both are related to immediate type reagin-mediated reactions. In contrast to bronchial asthma in man, antigen-induced bronchial asthma in dogs and rhesus monkeys is not associated with pulmonary hyperinflation. In addition, use

of anesthesia in these models may modify the physiologic responses to bronchial damage. Some studies indicate that the unaesthetized Ascaris suum-sensitized sheep and the Ascaris-sensitized Basenji-Greyhound crossbreed dog may prove to be useful models.

State of Knowledge in 1982

Asthma remains a serious health problem. It is estimated that the number of Americans suffering from this disease will increase to over 10 million during this decade. The economic impact from decreased productivity and increased health care expenditures will surpass a billion dollars. Because occupational exposures are a major source of the disease, new factors that trigger asthma will continue to emerge as scientists develop new industrial processes.

There is still controversy about the definition of asthma, and diagnosis continues to remain difficult because of the similarity of asthma in its early stages to many other childhood and adult pulmonary diseases. Some researchers have suggested abandoning the classification of asthma into extrinsic and intrinsic types for a more descriptive formulation based on the factors that provoke the episodes--namely, exercise, infections, airborne irritants, aspirin, and emotions.

While asthma runs in families, heredity alone does not seem to explain its development. An interplay of physiologic, environmental, and genetic factors seems to be involved in its etiology. The role of childhood lung injury in the development of asthmatic hyperreactivity is currently undefined. A large body of information on the pathophysiology of the disease has been accumulated, but much more remains to be learned. The natural history of the disease has yet to be reconciled with the sequence of abnormal airway changes. The importance of mast cells within the bronchial tissues, the complex biochemical and morphologic changes in the airway smooth muscle, the development of the inflammatory reaction rich in mononuclear cells and eosinophils, and the importance of autonomic- and antibody(IgE)-mediated events remain poorly understood. What has already been learned about the pathophysiology has led to the development of some useful drugs, but more specific and effective drugs based on a clearer understanding of their pharmacological functions are still needed. Despite the progress in therapeutic approaches, it is still difficult to predict the course of the disease in any particular individual.

Psychosocial factors have an importance, and there is great potential for newer approaches to self-management of the disease. Since the environment, both physical and emotional, influences the

onset and occurrence of the disease, asthma patients are uniquely affected by interactions between family, peers, and society. Interventions at the level of these complex interactions need to be developed and tested.

Program Goals 1982 to 1987

Goals relevant to the NHLBI mandate in asthma are:

Epidemiology

- Identify risk factors related to development, prevalence, severity, and persistence of asthma, such as infectious agents and air pollutants.
- Determine whether asthma in early life predisposes to the development of chronic obstructive pulmonary disease in both smokers and nonsmokers.
- Develop improved epidemiologic methods and criteria to identify asthmatic subjects and to determine the severity of the disease.

Pathogenesis

- Further clarify the specific individual and interdependent functions of the various cells implicated in tissue injury and repair in asthma as well as the chemicals involved in their interactions.
- Further examine the biochemistry of mediator release with special emphasis on cell membrane phospholipid metabolism and intracellular calcium ion concentrations in airway hyperirritability in asthma.
- Determine the pathogenesis of virus-induced attacks of asthma.
- Determine the ways in which industrial hazards cause lung disease, and determine host factors leading to predisposition in these diseases.
- Continue research into neural and humoral controls in airway dysfunction in asthma.
- Continue research into the genetics of asthma.

- Delineate neurophysiologic pathways involved in expression of asthma due to emotional factors and stress.

Pathology

- Determine the pathologic basis for the progression of asthma to an irreversible phase, and develop special morphologic techniques to localize the role of specific molecules.
- Elucidate the pathology of the late phase of the allergic asthmatic response.

Clinical Studies

- Define the long-term risk and benefits of medications used for treatment, including physical, educational, and neuropsychologic effects.
- Foster investigations into the causes and prevention of death in severe asthma.
- Encourage development and introduction of new anti-mediator release drugs.
- Encourage more widespread use of standards of care in emergency rooms and outpatient settings.

Prevention and Self-Management

- Further clarify interactions among asthma and psychosocial factors, such as self-management skills, expectations of families and friends, and family characteristics.
- Identify the most critical (useful) methods of influencing skills, attitudes, and social factors in encouraging asthmatics to lead normal lives, and elucidate educational procedures that may best influence them.
- Identify improvements in health care delivery that would reduce overuse of emergency rooms by asthmatic children and adults.
- Delineate neurophysiologic pathways involved in the expression of asthmatic reaction to environmental factors and stresses.

Research Activities 1982 to 1987

Continued support of basic science is critical to a better understanding of neural and humoral control of smooth muscle and other cells in health and in diseases such as asthma. Basic and clinical investigations of the control processes of IgE antibody formation and means of inducing tolerance need to be continued. In dissecting the mechanisms of the allergic inflammation, continued attention to the functions of the cells implicated in asthma is warranted, including eosinophils, mast cells, neutrophils, macrophages, and platelets. Current advances in the understanding of the biochemistry and physiology of mediators and of the release reactions in mast cells should be exploited for developing pharmacologic agents that are capable of controlling specific mediator release and influencing the biochemical pathways in the mast cell.

In order to further these activities, comprehensive programs should be initiated to examine the total multifactorial nature of asthma and its variety of host and environmental interactions. Interdisciplinary approaches should be encouraged that involve biochemical, morphologic, immunopathologic, neurophysiologic, psychologic, epidemiologic, clinical, and industrial expertises. Improved techniques should be developed to translate the research findings into clinical practice and into education of the patient, family, and community.

Contributors

PULMONARY DISEASES ADVISORY COMMITTEE MEMBERS

Charles E. Reed, M.D., Chairman
Professor of Medicine
Mayo Medical School
Chairman, Section of Allergic
Diseases and Internal Medicine
Mayo Clinic and Foundation
Rochester, Minnesota

A. Sonia Buist, M.D.
Professor of Medicine and
Physiology
Department of Physiology
Oregon Health Sciences
University
Portland, Oregon

Edwin B. Fisher, Ph.D.
Associate Professor of
Psychology
Washington University
College of Arts and Sciences
St. Louis, Missouri

Allen B. Cohen, M.D.
Professor of Medicine and
Physiology
Temple University
School of Medicine
Philadelphia, Pennsylvania

Edward E. Mays, M.D.
Oakland, California

Arnold S. Monto, M.D.
Professor of Epidemiology
University of Michigan
School of Public Health
Ann Arbor, Michigan

CONSULTANTS

Warren M. Gold, M.D.
Professor, Department
of Medicine
University of California,
San Francisco
San Francisco, California

Peter T. Macklem, M.D.
Chairman, Department of
Medicine
Royal Victoria Hospital
Montreal, Quebec
Canada H3A 2B4

Lawrence M. Lichtenstein,
M.D., Ph.D.
Professor, Department
of Medicine
The Johns Hopkins University
School of Medicine
Baltimore, Maryland

William Thurlbeck, M.D.
Department of Pathology
University of British
Columbia
Vancouver, British
Columbia
Canada

DIVISION STAFF

J. Sri Ram, Ph.D.
Chief, Airways Diseases Branch
Division of Lung Diseases
National Heart, Lung, and
Blood Institute

Hannah Peavy, M.D.
Airways Diseases Branch
Division of Lung Diseases
National Heart, Lung, and
Blood Institute

Zakir Bengali, Ph.D.
Airways Diseases Branch
Division of Lung Diseases
National Heart, Lung, and
Blood Institute

Richard J. Sohn, Ph.D.
Airways Diseases Branch
Division of Lung Diseases
National Heart, Lung, and
Blood Institute

5. Pediatric Pulmonary Diseases

Contents

PEDIATRIC PULMONARY DISEASES.	131
RESPIRATORY DISTRESS SYNDROME OF THE NEWBORN	132
State of Knowledge in 1972	133
Program Goal Through 1982.	135
Accomplishments Through 1982	135
State of Knowledge in 1982	139
Program Goals 1982 to 1987	139
Research Activities 1982 to 1987	139
BRONCHOPULMONARY DYSPLASIA	140
State of Knowledge in 1972	141
Program Goal Through 1982.	141
Accomplishments Through 1982	142
State of Knowledge in 1982	144
Program Goal 1982 to 1987.	145
Research Activities 1982 to 1987	145
BRONCHIOLITIS	146
State of Knowledge in 1972	146
Program Goal Through 1982.	147
Accomplishments Through 1982	147
State of Knowledge in 1982	148
Program Goals 1982 to 1987	149
Research Activities 1982 to 1987	149
CYSTIC FIBROSIS	149
State of Knowledge in 1972	150
Program Goals Through 1982	151
Accomplishments Through 1982	151
State of Knowledge in 1982	153
Program Goals 1982 to 1987	154
Research Activities 1982 to 1987	154
DISORDERS OF THE CONTROL OF BREATHING	155
State of Knowledge in 1972	157
Program Goal Through 1982.	158
Accomplishments Through 1982	158
State of Knowledge in 1982	161
Program Goals 1982 to 1987	161
Research Activities 1982 to 1987	162
PEDIATRIC LUNG DISEASE AND PREDISPOSTION TO CHRONIC LUNG DISEASE IN ADULTS.	163
State of Knowledge in 1972	163
Program Goal Through 1982.	163
Accomplishments Through 1982	163
State of Knowledge in 1982	164
Program Goal 1982 to 1987.	164
Research Activities 1982 to 1987	165
CONTRIBUTORS.	166

5. Pediatric Pulmonary Diseases

Respiratory disorders are among the most common and serious health problems that affect infants and children, and during the past 10 years, morbidity and mortality from a number of pediatric lung disorders decreased markedly. New and serious problems, however, are now being recognized because of therapeutic and scientific advances.

In 1972, pediatric pulmonary research was limited and fragmented. With the exception of basic research in neonatal respiratory distress syndrome* and cystic fibrosis, there was very little activity in such areas as lung growth, structure and function, defense mechanisms, function of the mucociliary apparatus, and other nonrespiratory lung functions.

Lack of personnel trained in pediatric pulmonology was a significant problem in 1972. Less than 40 percent of pediatric departments in the country had a trained pulmonologist on the staff, and training programs in pediatric lung disease numbered fewer than a dozen. The technology necessary for studying lung function in children was being developed, and it was essentially a research tool available only to a small number of investigators. Pulmonary function testing in children was not a widely used clinical tool. Studies of normal and diseased lungs were beginning to characterize the functional differences that exist between the immature lung of a child and its adult counterpart.

During the last decade, pediatric pulmonology grew at a remarkable rate. Supported and stimulated by advances in the knowledge of lung biology, the specialty is now recognized in the biomedical academic community, and pediatric pulmonologists can be found with increasing frequency among medical school faculty. Pulmonary divisions are in over 75 percent of pediatric departments, and more are being established. More than 30 training programs currently exist in pediatric pulmonary disease.

*Originally called hyaline membrane disease (HMD). Throughout this section of the report, the term RDS is used.

As a result of transfer and widespread application of knowledge of perinatal and postnatal events, the mortality rate for RDS has decreased by at least 50 percent. A new problem, however, has arisen among very immature infants who now survive the disease. Many of these infants can develop chronic respiratory problems, such as bronchopulmonary dysplasia (BPD). These problems are difficult to manage because of a lack of fundamental knowledge about lung injury and repair in the developmental period. In addition, compelling evidence indicates that residual damage from childhood lung injury can predispose adults to chronic pulmonary disease.

Lung function in children is now being studied more frequently, and sleep studies have become an integral part of the clinical evaluation of children with certain types of respiratory problems. The recognition of defects in the control of breathing has established a group of respiratory disorders not considered 10 years ago, and the spectrum of pediatric pulmonary diseases now includes disorders not previously recognized. The most important ones are discussed here in detail.

Respiratory Distress Syndrome of the Newborn

Respiratory distress syndrome is a lung disease affecting mainly premature infants. The premature lung is not fully developed at birth and, as such, is unable to maintain normal exchange of gas. The syndrome is manifested clinically by cyanosis, flaring of the nostrils, retractions of the rib cage, and acidosis. Airway collapse (atelectasis) causes increased work in breathing. The infant with RDS "grunts" in breathing in order to reverse the tendency of the alveoli to collapse. RDS is the leading cause of respiratory failure and death in premature infants. Its onset occurs at birth, and within a few days, most infants proceed either to recovery or to further complications, including death.

Prematurity is the most common cause of death among newborns, and RDS is the most common cause of death among premature infants. In the United States, over 1 percent of all live births, which amounts to more than 40,000 infants per year, are reported to develop RDS. Prior to modern improvements in intensive care for the newborn, mortality from RDS was greater than 50 percent. Over the past 10 years, the rate has been reduced in many tertiary care centers to less than 20 percent. The incidence of RDS according to gestational age is approximately 60 percent for infants born at less than 28 weeks, 30 percent for infants between 28 and 34 weeks, and less than 5 percent for those 34 weeks and older. Infants with RDS are at significant risk for developing hypoglycemia, hydrocephalus, pneumothorax, retrolental fibroplasia,

and bronchopulmonary dysplasia, all of which can lead to high levels of morbidity and mortality. Before mechanical ventilation became an accepted treatment for RDS, a significant number of its survivors were noted to have serious learning disabilities. While the incidence of neurologic deficits has been greatly reduced by modern intensive care, the very small and premature infants still remain at considerable risk for brain damage.

A small portion of infants with RDS who have been treated with mechanical ventilation and who have survived have been found to have persistent pulmonary function deficits, even up through 7 or 8 years of age. The significance of these deficits is not fully understood, but it has been shown that more than 20 percent of survivors of RDS suffer an increased incidence of lower respiratory infection. This increased persistent susceptibility to lung infection following recovery from RDS may be secondary to the disease itself, but it is considered likely that both the changes in pulmonary function and the susceptibility to infection may be the result of exposure of the immature respiratory system to various modes of respiratory therapy.

State of Knowledge in 1972

Before 1970, it was presumed that RDS (called hyaline membrane disease at the time because of its typical pathological picture) was related to deficient oxygen diffusion in the air-spaces of the lung because of the presence of the eosinophilic "hyaline membrane" found lining the alveoli of infants dying from RDS. Although many hypotheses had been proposed, it was generally accepted by 1972 that a deficiency of surfactant synthesis or secretion by the alveolar lining cells was the primary etiology of the disease. It had been established that the hyaline membrane is not present at birth but develops over a period of hours to days as a result of injury to lung epithelial cells and subsequent exudation of plasma into the alveolar spaces. Cellular debris, fibrinogen, and other plasma products coalesce to form the membrane. A deficiency of gas diffusion was demonstrated in the lungs of infants with RDS. This defect was not due to hyaline membrane but to alveolar collapse secondary to the primary defect--that is, to surfactant deficiency.

There were several significant findings in the late 1960's and early 1970's. Almost simultaneously, methods for detecting premature lung development and for managing premature lung function became available. Amniotic fluid was found to contain lung fluids that spill out of the mouth and the trachea of the fetus. By sampling amniotic fluid and utilizing newly developed

techniques for measuring dipalmitoyl phosphatidylcholine in micrograms, the obstetrician could predict the maturity of the fetal lung and then plan for (or attempt to delay) an impending premature delivery. At about the same time, a clinical team developed a new method of respiratory therapy that decreased mortality in those infants whose premature delivery could not be prevented. Drawing upon their knowledge of the physiological functions of surfactant, the team devised a breathing system by which a positive pressure could be safely introduced into the trachea. This pressure helped prevent alveolar collapse and thereby maintained adequate gas exchange until the neonatal lung could begin producing its own surfactant. The physician was now able to predict RDS, prepare for an impending high-risk birth, and draw upon new techniques to manage the sick infant. The survival rate of newborn infants with RDS who weighed more than 1,200 grams increased from 65 percent to over 90 percent within the 2-year period of 1969 to 1970 (figure 9). Mechanical ventilation and continuous positive airway pressure (CPAP) became accepted modes of therapy for RDS by 1972. New problems, however, were created, which became of great significance in the late 1970's and continue to date. They are discussed under bronchopulmonary dysplasia.

By 1972, the results of the work conducted on the hormonal control of lung maturation were published. Corticosteroids released from the adrenal cortex of the fetus appeared to have an important function in fetal development. Receptors for these hormones were found in lung tissue, and circulating levels of the hormones were shown to increase during gestation. Exogenously delivered corticosteroids were shown to be capable of accelerating the rate of development. For the first time, pharmacological management of prematurity appeared possible.

In 1972, it was known that RDS was much more common in infants of diabetic mothers than in the normal population. Experimental investigation had demonstrated that hyperinsulinemia decreased surfactant activity. Infants of mothers whose diabetes was poorly controlled were exposed in utero to hyperglycemia. They subsequently developed pancreatic islet cell hypertrophy and produced a compensatory hyperinsulinemia, which, in turn, suppressed lung surfactant. Asphyxia, hypoxia, hypercapnia, hypothermia, and acidosis had also been shown to increase the incidence and severity of RDS by inactivating surfactant or inhibiting its production by the alveolar lining cells.

Since RDS is primarily a disease of prematurity, prevention of premature birth was recognized as the ideal method for controlling or reducing its incidence. Advances in prenatal care in the early 1970's included the use of ultrasound, nonstress and stress testing, better control of diabetic pregnancies, amniotic fluid analysis for fetal lung maturity, the prenatal use of

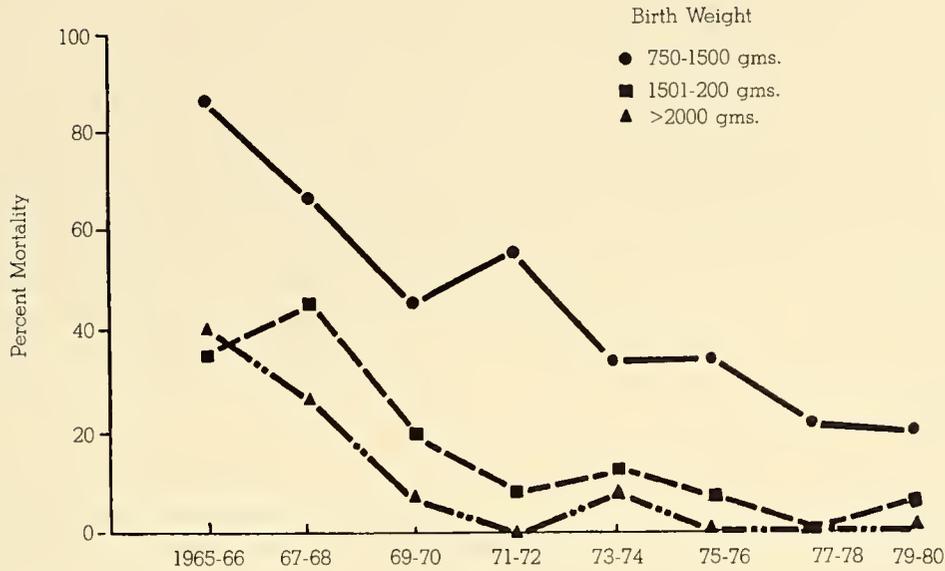


Figure 9. Mortality From Neonatal Respiratory Distress Syndrome

steroids for the induction of fetal lung surfactant, and the use of pharmacologic agents for stopping premature labor. In addition, transportation programs were developed that permitted women with impending premature delivery to be cared for at tertiary care centers specializing in the treatment of high-risk pregnancies. These programs, in which newborn intensive care could be given at birth, were later shown to be beneficial in preventing prematurity and also in providing optimal neonatal care for the infant with RDS.

Program Goal Through 1982

- Improve detection, management, and prevention of RDS and its sequelae.

Accomplishments Through 1982

When results of animal studies and human investigation during the early 1970's suggested that corticosteroids were of major importance for functional development of the lung, considerable

enthusiasm was generated for testing whether pharmacological intervention with corticosteroids shortly before birth could prevent RDS. Administration of steroids such as betamethasone to pregnant women 24 to 48 hours prior to delivery was first shown by investigators in New Zealand to reduce the incidence and severity of RDS. This use of steroids was questioned, however, because of potential side effects, including increase of toxemia and of fetal and maternal infection. In addition, animal studies demonstrated a host of other potentially serious side effects, including growth retardation by accelerated cellular maturation and differentiation in combination with inhibited cellular replication, impaired brain growth and myelination of the central nervous system, a decrease in placental size, a decrease in adrenal size, impaired immune function, and a decrease in collagen formation and collagenase activity.

Because of these concerns and the growing desire in many hospitals to use steroids prenatally, a large collaborative randomized, double-blind clinical trial was initiated in 1976 to determine: if prenatal administration of dexamethasone (a synthetic steroid) could reduce the incidence of RDS; if this therapy had any immediate adverse effects on mother or infant; and if the therapy had any long-term adverse effects on the infant that could be detected within the first 3 years of life. Between March 1977 and March 1980, 7,893 patients from five participating clinical centers were screened for eligibility in the study. Volunteer patients between 26 and 37 weeks gestation who were anticipated to deliver between 24 hours and 7 days were considered for the study, and 696 women were randomized to receive either the steroid or a placebo.

Analyses of the outcome of these pregnancies with regard to the first two objectives have shown that the incidence of RDS was reduced in the steroid-treated group as a whole by approximately 33 percent (from 18.3 to 12.6 percent), which is similar to the results reported in the New Zealand study. Further analyses, however, surprisingly revealed that the incidence of RDS was reduced only among singleton, female infants. No effect of the steroid treatment was observed in multiple births or in male infants. Furthermore, the effect appeared to be influenced by race, for whites showed little effect compared to nonwhites. No difference in mortality was seen between the treated group and the placebo group, and no immediate adverse effects were noted as ascertained by rate of infection in mothers and infants and by neurological evaluation of the infants. Prior to the immediate outcome of the trial, there appeared to be a growing trend among obstetricians to use steroids prenatally in cases of threatened premature deliveries. Since results of this collaborative trial to date indicate, however, that this form of prevention is dependent upon sex, race, and other characteristics of the infant and the mother, its potential usefulness in the future is likely

to be dictated by these factors. These, and the still unknown long-term effects of this therapy, seem to indicate that corticosteroids should be used selectively and cautiously.

Preliminary long-term followup data of survivors of RDS show encouraging results. Of infants with RDS, over 80 percent of the survivors at age 5 had normal intelligence and either minimal or no neurologic damage; very low birth weight infants were noted to have the least encouraging prognosis. Since the number of infants in these studies is still rather small, caution should be used in generalizing from these data.

Over the past decade, the improved outlook that occurred for prematurely born infants can be attributed to several new technologies. Two noninvasive diagnostic and monitoring techniques have been particularly helpful: computerized tomography, which is used in the early diagnosis and followup of intracranial hemorrhages, and the transcutaneous oxygen monitor, which permits continuous recordings of oxygenation of blood. Other technologies, such as ultrasound and echocardiography, have also been helpful in the diagnosis and management of intracranial events and cardiac complications, particularly in patent ductus arteriosus (PDA), a lesion that has been shown to be intimately associated with the natural history of RDS. The recent use of brainstem-evoked potential to establish growth and maturation of the central nervous system may prove useful for detecting abnormalities that can be related to conditions of hypoxia in the newborn period.

Because the involvement of high oxygen concentrations and high pressure of inspired air is suspected in the occurrence of chronic lung disorders in infancy, interest has been focused on the possibility that ventilators operating at very high frequencies and delivering small gas volumes at lower pressures can sustain ventilation as well as or better than conventional mechanical ventilators. The principle of gas exchange during high-frequency ventilation is not yet well understood, nor is it known if such therapy may have any undesirable side effects. Therefore, considerable research on animals as well as carefully controlled clinical studies are needed before an assessment of benefits and risks can be made. In this regard, it is encouraging that prematurely delivered subhuman primates develop RDS spontaneously and can be used for deriving information on physiologic and biochemical changes in the lungs that cannot be obtained in human infants.

Advances in the nutritional support of the premature infant have been of great importance throughout the decade. Because the premature infant with RDS is born with inadequate energy stores and is generally too ill to tolerate oral feedings, the provision of adequate nutrition has been critical but difficult. The premature infant with RDS must expend a tremendous amount of

energy to breathe, to maintain body temperature, and to regenerate lung epithelium and begin production of surfactant. The premature infant must therefore have the necessary amino acids, essential vitamins, and lipids. Carefully controlled nutritional studies have yielded important information on how to prevent loss of protein and meet the caloric demand of the infant with the disease.

A continuing problem exists. Several entities have been confused with RDS in the past, and they can masquerade as RDS or complicate its course. Infants with pneumonias in general and group B streptococcal pneumonia in particular can present symptoms that are indistinguishable from those of RDS. Recent work suggests that evaluation of tracheal aspirate samples for culture, for sensitivity, for measurement of lecithin-sphingomyelin (L/S) ratio, and for the presence of phosphatidylglycerol may be helpful in differentiating pneumonia from uncomplicated RDS. PDA is another condition that can present as RDS, but the recent application of echocardiography has proven very useful in differentiating in a diagnosis. It has been shown that between 50 and 85 percent of preterm infants with RDS who weigh less than 1,200 grams have a PDA; between 15 and 35 percent of such infants with birth weights between 1,200 and 1,800 grams also have a PDA. Preliminary investigations have suggested that early closure of the PDA is associated with a decreased severity of RDS in the premature infant, and recent trials of a prostaglandin inhibitor, indomethacin, have shown successful closure of PDA. Such closure avoids potential complications of surgery.

Over the past decade, the importance of nosocomial infections and potential hazards of infections transmitted from the mother have been recognized as possible causes of respiratory problems, but further studies to better define these problems are necessary.

The rapid expansion in knowledge of the risk factors and pathophysiological processes associated with RDS and improvements in care of the newborn with RDS have necessitated educational programs that bring physicians and other health professionals up to date on the latest technology for treatment of the disease. For this reason, model educational programs have been developed to raise the level of care given in community hospitals to RDS infants. These programs have been shown to be successful in increasing the knowledge and skills of practicing physicians and in decreasing mortality in participating hospitals. Based on this work, a national educational program is being developed by the Academy of Pediatrics, and hospitals across the country are adopting the training modules to improve the community care of infants with RDS.

State of Knowledge in 1982

Although mortality from RDS was decreased substantially in the past decade by the transfer of knowledge of perinatal and postnatal events to medical practice, it is still the leading cause of death among premature infants. The prevention of RDS by administration of drugs to the mother to prevent premature delivery or to accelerate the maturation of the lungs continues to be a high priority issue to be pursued from the point of view of basic science as well as clinical management. Improved knowledge of the role of surfactant and of its synthesis and secretion has enabled investigators to initiate studies of artificial surfactant as a possible mode of therapy. Development and testing of improved noninvasive methods for assuring proper oxygenation of the neonate as well as improvements in ways of providing respiratory support are considered important steps toward decreasing the morbidity of RDS.

It is encouraging that the incidence of major mental deficiencies appears to be small among survivors of RDS, but there is concern that chronic lung disorders may represent a considerable problem, especially among the very immature survivors.

Program Goals 1982 to 1987

The primary goals in the area of neonatal respiratory distress syndrome will continue to be:

- Improve the detection, management, and prevention of RDS.
- Evaluate prospectively infants who survive RDS, and establish relationships between perinatal and postnatal events and respiratory disorders later in life.

Research Activities 1982 to 1987

The following activities are given as examples:

- Study animals with conditions that mimic those seen in infants with RDS to further elucidate physiologic and biochemical changes in the respiratory system that accompany or follow RDS.
- Analyze tracheal aspirates of infants with RDS in order to detect abnormalities that might predict or contribute to the sequelae of RDS.

- Establish a better understanding of the relationship between nutritional status of mother and infant and the occurrence and prognosis of RDS.
- Evaluate risks and benefits associated with prenatal corticosteroid administration for the prevention of RDS.
- Investigate other pharmacologic approaches to prevention.
- Improve and develop noninvasive techniques for assessing adequate ventilation and circulation in the fetus and the premature infant.
- Develop and evaluate noninvasive techniques such as nuclear magnetic resonance, spectrophotometry, and brainstem-evoked potential for assessing cellular oxygenation in key organs.
- Evaluate the risks and benefits of high frequency ventilation in the management of respiratory insufficiency in the neonatal period.
- Evaluate critically the use of artificial surfactant in the management of RDS.
- Understand the mechanisms of respiratory muscle fatigue and its role in respiratory insufficiency.
- Conduct prospective followup of infants who have received ventilatory support, and establish relationships between neonatal and pediatric pulmonary disorders.

Bronchopulmonary Dysplasia

Bronchopulmonary dysplasia is a chronic lung disorder first recognized in 1967 in infants surviving therapy for severe RDS. Prior to that time, infants who were likely to develop BPD did not survive in large enough numbers to constitute a significant clinical problem. The condition has now been recognized throughout the world. The term BPD was coined to describe changes that were shown radiologically to represent abnormalities in the architecture of the lung leading to poor gas exchange and in many instances progressing continuously from birth to irreversible respiratory failure, sometimes many months later.

State of Knowledge in 1972

In 1972, the etiology and pathogenesis of BPD were unknown. Several factors, however, had been identified as probable contributors to its development. The two most important of these factors were prematurity and some degree of respiratory difficulty in the immediate postnatal period. BPD appeared to develop more frequently in infants with RDS and with birthweights of less than 2,000 grams who survived longer than 1 week.

Clinically, BPD was characterized by roentgenographic changes. Nothing was known about the natural history of the disease other than the fact that the most severely affected infants were dying of cardiopulmonary complications, sometimes many months after birth. It was thought to be a form of Wilson-Mikity syndrome, which is a type of respiratory distress seen in premature infants. Factors such as endotracheal intubation and positive airway pressure were considered as risks. Initial efforts at preventing the disease were therefore centered on reducing the level of supplemental oxygen during treatment of RDS. Similarly, some investigators were advocating the use of negative pressure ventilation to prevent lung damage thought to result from positive pressures.

Pathologically, the different stages of BPD were not characterized very well, and in many instances the transition between RDS and BPD was unrecognizable. Agreement on diagnosis was found only in severe cases.

Therapy of BPD emphasized the need for reduced levels of supplemental oxygen. Other interventions such as decreasing left-to-right shunts of the patent ductus, decreasing fluid administration, and using drugs such as diuretics and bronchodilators were not considered in most cases.

Program Goal Through 1982

Goals specifically addressed to BPD were not identified prior to 1982. The course and sequelae of RDS, however, were pursued:

- Improve the detection, management, and prevention of RDS and its sequelae.

Accomplishments Through 1982

Prevailing evidence at present suggests that the origin of BPD is multifactorial, but the extent of involvement of the various factors associated with its development has not been determined. Those most frequently implicated have been identified as:

- Prematurity
- Respiratory distress of any cause
- Mechanical support of ventilatory function
- Oxygen therapy
- Excessive fluid administration
- Immaturity of the antioxidant enzyme system in the lung
- High perfusion pressures associated with extrauterine life on an immature lung
- Patent ductus arteriosus and other cardiovascular lesions causing pulmonary hypertension and increased lung water
- Barotrauma
- Infectious agents
- Genetic predisposition.

Because the different forms of therapy currently in use, such as diuretics, digitalis, and beta-adrenergics, have not been shown conclusively to be of benefit, it is difficult or impossible in many cases to know which forms should be continued and which forms should be abandoned.

It has been observed that many infants with BPD who survive the critical first few postnatal weeks become oxygen dependent. As the ventilatory assistance is withdrawn, the inspired oxygen concentration can be decreased only to a level somewhat above that found in room air. Attempts to further wean the infant from oxygen have resulted in insufficient arterial oxygenation (hypoxemia). If this problem is not relieved, echocardiographic and radiographic evidence of pulmonary hypertension can be observed, which can lead eventually to cor pulmonale. In many instances such infants have been discharged while still receiving oxygen through specially developed nasal cannulae.

The use of transcutaneous oxygen monitors, which is a non-invasive technique, has been an invaluable aid in monitoring the oxygen needs of these infants, both as inpatients and during outpatient visits. Oxygen therapy is continued for as long as there is a need to maintain adequate oxygenation as documented by repeat measurements of transcutaneous oxygen tensions and echocardiograms. Newly developed noninvasive techniques to monitor pulmonary artery pressures (pulsed Doppler duplex scanner) have begun to be used as a more sensitive method of monitoring oxygen requirements.

The short- and long-term effects of oxygen therapy in this critical period of growth and development are not yet known. Its psychological impact on infant and on family life are currently under study, since infants have been kept on continuous oxygen therapy for as long as 3 years before being weaned from therapy or succumbing to the disease (figure 10). The financial burden of this therapy alone can be devastating because the care of these



Figure 10. Child Receiving Oxygen Via Specially Developed Nasal Cannulae

infants is further complicated by special nutritional and developmental needs. It has also been found that many have multiple handicaps that require physical therapy and special education. Studies of the role of nutrition in the etiology and course of BPD are now under way.

State of Knowledge in 1982

The true incidence of BPD in the newborn infant population is not yet established. Estimates from neonatal centers around the country vary from 5 to 50 percent. Several problems make it difficult to estimate true incidence. The most important problem is the lack of precise diagnostic criteria. BPD is probably a disease process of continuously distributed severity that becomes clinically apparent in only a small proportion of cases. These difficulties in diagnosis are not likely to be resolved until more objective, uniform radiographic and pathological criteria are accepted by the medical community or until inroads are made into the etiology of the condition.

In spite of these difficulties, BPD is being recognized with increasing frequency by most neonatal centers. Survival statistics for premature infants have steadily improved over the past decade, and as many as 50 percent of infants born weighing less than 900 grams survived in 1981 whereas less than 5 percent survived in 1971. Many of these infants overcome tremendous odds only to succumb to BPD. It is not uncommon for BPD infants to require intensive care, which can cost as much as \$1,000 per day for as long as 12 months. Once discharged, many require supplemental oxygen therapy for many more months. The problem becomes unique when one realizes that the majority of these infants have no other major handicaps. Moreover, although many BPD patients have a greater susceptibility to recurrent respiratory problems during infancy, recent studies show that many survivors have normal or near normal pulmonary function and capacity for exercise.

Recently, premature baboons were kept alive long enough to demonstrate changes consistent with BPD in human infants. This is an exciting development, but utilizing it will require an investment since the animals require costly intensive care similar to that given human neonates. This model offers the opportunity to control several variables and to study the role of individual factors in the pathogenesis of BPD. This opportunity is not currently available in human neonates. In addition, several *in vitro* systems offer the potential for studying the effects of injurious agents on specific cells and tissues of immature and developing lungs.

Program Goal 1982 to 1987

- Improve the understanding of the etiology and pathogenesis of BPD, and utilize this information to prevent its occurrence and reduce its morbidity and mortality.

Research Activities 1982 to 1987

The following activities are given as examples:

Diagnosis and Natural History

- Define precisely the clinical, physiologic, radiologic, and histologic criteria for diagnosing BPD.
- Conduct studies of the natural history of BPD with precise and uniform diagnostic criteria.
- Conduct prospective controlled studies of lung function in premature infants.

Prevention and Therapy

- Conduct a systematic investigation of variables that might contribute to the production of BPD.
- Evaluate agents that may prevent or be used to treat BPD and its sequelae such as vitamin E, antioxidants, digitalis, diuretics, bronchodilators, and oxygen.
- Determine the role of nutrition in the etiology, pathogenesis, and course of BPD.

Etiology and Pathogenesis

- Investigate in premature animals the growth and development of the immature lung, its adaptation to the extra-uterine environment, and the effects of injury and repair during lung maturation.
- Investigate in animal models of RDS the relative importance of factors that have been implicated in the development of BPD.

Bronchiolitis

Bronchiolitis is the most common lower respiratory tract infectious disorder of infants under 1 year of age. It is characterized by acute onset of signs and symptoms of diffuse airway obstruction, including varying degrees of wheezing, rapid respiratory rates, air trapping, hyperinflation of the lungs, and cough. Fever is not a significant problem. These acute manifestations can span the full spectrum of severity, from a mildly symptomatic course to respiratory failure and death.

State of Knowledge in 1972

It was known in 1972 that most cases of bronchiolitis were caused by infection with the respiratory syncytial virus (RSV). Other viral pathogens had been identified with lesser frequency. RSV was known to have a predilection for the lining and structures of the smallest airways and to set up an inflammatory reaction consisting of swelling, tissue breakdown, infiltration with inflammatory cells, and, possibly, contraction of bronchial smooth muscle. Bronchial secretions and plugging of the airways by mucus were not considered important components. Because of the difficulties in obtaining material for examination other than postmortem, little was known about the pathology of early stages or of mild cases of the disease.

Bronchiolitis was a common clinical problem among infants, but the extent of its epidemiologic impact was not appreciated. Little was known about rates of prevalence of the infection.

The management of acute bronchiolitis was very similar to present day therapy. No specific antimicrobial agents were available for the treatment of RSV or any of the other viruses thought to be responsible for bronchiolitis. As is true today, most cases required only supportive therapy or oxygen supplementation at best. In a number of infants, the disorder did progress to respiratory insufficiency, and some infants even required ventilatory support. The role of antiinflammatory agents such as corticosteroids in the acute therapy of bronchiolitis was undefined. Similarly, bronchodilators, which were prescribed by many clinicians in the hope that they would relieve the obstructive component, were used without much data being available concerning their indications, type, route of administration, pharmacokinetics, efficacy, or safety.

Attempts at prevention of bronchiolitis by the use of inactivated whole virus vaccines ended in complete disappointment when it was discovered that immunization afforded little protection and was in fact associated with increased morbidity.

This finding prompted research for new theories of host-agent interaction and immune response in exposed infants and to efforts to develop a live virus vaccine.

Program Goal Through 1982

- Increase the understanding of the pathophysiologic features of bronchiolitis and the relationship between bronchiolitis and subsequent disorders of the respiratory system.

Accomplishments Through 1982

Over the past 10 years, the magnitude of the problem of bronchiolitis has come into clearer focus with the aid of several sources of epidemiologic data. The peak rate of attack has been determined to be over 16 per 100 per year in infants less than 6 months, with most cases occurring in winter and early spring. The risk of hospitalization for these patients has been estimated at 10 per 1,000 infants per year. The mortality for hospitalized patients with bronchiolitis is very low. Morbidity, however, is high, with intensive medical care being required in a large proportion of cases.

The exact distribution of severity among a selected population of affected infants is currently unknown. Recent studies, however, have shown high rates of occurrence among day-care center populations. In recent years, comprehensive studies in an ambulatory population of the clinical spectrum of this disease have been initiated. This group is important since hospitalized bronchiolitis patients probably constitute only a small fraction of the affected population.

Although the actual number of deaths from bronchiolitis is relatively high, the majority of infants with bronchiolitis survive. The number of deaths from RSV-induced apnea--as in the sudden infant death syndrome--is currently unknown. High mortality has been found among infants with underlying defects such as bronchopulmonary dysplasia or congenital heart disease.

The possibility has been raised in recent years that RSV infection can result in the acquisition of lifelong disability from recurrent asthma or, more importantly, predispose the adult who had bronchiolitis as an infant to the development of chronic obstructive pulmonary disease. Studies of the effects of RSV infection on lung growth and development have been initiated, and

evidence of abnormal lung function has been found in children who had bronchiolitis during infancy.

A fluorescent technique developed for identifying and promptly confirming RSV in respiratory secretions has been of great help in diagnosis and management. In addition, as more hospitalized infants are screened, a number of previously unrecognized manifestations of this infection have surfaced. The most significant of them is apnea. It appears that apnea can be a presenting complaint in an otherwise asymptomatic infant as well as a cursory manifestation of the well recognized syndrome. As this inexpensive diagnostic technique becomes more widely used, the understanding of the natural history of the disease in all of its manifestations will increase.

Isolation of patients has contributed to a decrease in the incidence of bronchiolitis in hospitals, although in some communities nosocomially acquired RSV infection is still a significant problem. The impact of day care of infants on rates of occurrence of bronchiolitis in the United States has yet to be determined. Recent studies show that the disease is easily transmitted among infants between 2 and 6 months of age. This factor could have great impact on preventive health measures in this age group.

State of Knowledge in 1982

Although the pathophysiology of this disease has been examined during the past 10 years by various techniques suitable for use in infants, much remains to be learned. In particular, a suitable means of studying pulmonary function in these infants is urgently needed. It is important to know when, and in which cases, bronchiolitis leads to irreversible changes in lung function in later childhood and adult life.

Alternative ways to study pathogenesis and pathophysiology of this illness--namely, the use of animal models and in vitro tissue techniques--have been refined in the past decade, but further refinement is needed. Studies using clinical material are unlikely to provide much help in the foreseeable future.

English studies have shown poor response to inhaled bronchodilators in bronchiolitis, but many clinicians believe that the clinical status of some patients can be improved. Controlled studies need to be undertaken. It is currently not known, for instance, what role, if any, such environmental factors as outdoor and indoor pollution, parental smoking, living conditions, and nutrition have on rates of occurrence, morbidity, and mortality.

Program Goals 1982 to 1987

The overall goals in the area of bronchiolitis will continue to be:

- Elucidate pathophysiological features of bronchiolitis and subsequent disorders of the respiratory system along with development of modes of prevention.
- Investigate the natural history of bronchiolitis.

Research Activities 1982 to 1987

The following activities are given as examples:

- Expand prospective studies of well-defined population groups of different ethnic-genetic backgrounds and geographic locations.
- Determine the exact relationship of bronchiolitis to genetically determined airway reactivity, onset, and progression of asthma symptoms.
- Elucidate the role of bronchiolitis in the development of COPD in adult life.
- Examine genetic and environmental factors in the epidemiology of bronchiolitis.
- Clarify the immunologic response of infants to RSV antigens if efforts to develop a vaccine are to prove successful, and also clarify the role of maternal immunity.
- Develop appropriate animal models for bronchiolitis.

Cystic Fibrosis

Cystic fibrosis (CF) is an autosomal recessive trait that is characterized largely by pancreatic insufficiency and chronic obstructive pulmonary disease with attending bronchial infection. The most significant component is the pulmonary involvement, which is also the underlying cause of death in over 90 percent of cases. The mechanism of the defect is not yet known. A diagnosis is made by an identification of the major clinical manifestations, a recognition of a family history of the disease, and a detection of elevated levels of chloride in the sweat. Treatment is empirical

and symptomatic. Despite the lack of specific and direct treatment, the average predicted life expectancy has been increased, but it is still only 20 years. In 1981, over 30,000 cases were recognized in the United States alone.

State of Knowledge in 1972

In 1972, cystic fibrosis was recognized as a recessive trait and was known to occur in approximately 1 in 2,000 Caucasian births in the United States and northern European countries. While the diagnosis could be made routinely by determinations of chloride levels in sweat, there was no way to detect carriers of the defective gene or to make a prenatal diagnosis. Prior to 1972, most work concerning the pathogenesis of CF related to exocrine gland dysfunction. Extensive but not very sophisticated studies of glycoproteins had indicated an abnormality of sugar composition, namely of increased ratio of fucose to sialic acid. While this abnormality was thought to contribute to abnormal physical properties of these glycoproteins and mucus, the observation could not be confirmed by all investigators. Considerable attention had focused on the role of interactions of calcium and glycoproteins and on subsequent alterations of CF mucus that contained excessive amounts of calcium. The relationship between this interaction and mucous abnormalities, however, was not delineated. Studies of sweat gland function had determined that the primary secretory fluid was normal and that the high content of sodium and chloride in excreted sweat was due to inhibition of reabsorption of sodium as the primary fluid was being transported along the secretory duct. Studies in the late 1960's and early 1970's indicated that a factor present in saliva and sweat of patients with CF was able to block sodium reabsorption by sweat gland ducts. Despite all attempts, this factor could not be isolated because of its lability and apparently unusual properties. Other studies suggested that alterations in autonomic regulatory function might contribute to the hypersecretory phenomenon characteristic of CF. Specific abnormalities, however, were not consistently defined.

Other observers had recognized that chronic lung infection is a major pathogenic factor in CF and that Staphylococcus aureus and Pseudomonas aeruginosa are the major pathogens in the tracheo-bronchial tract. It was further recognized that the mucoid pseudomonas is characteristic, if not unique, for cystic fibrosis. Nutrition was considered a clinical problem unrelated to the basic pathophysiology of the disease.

New research directions were stimulated by the observation that CF serum contained an activity that inhibited ciliary motility. Attempts to use this activity to identify the CF gene

proved to be unsuccessful because the tests were either difficult to reproduce or not specific for cystic fibrosis.

Clinical studies had largely been focused on the treatment of pulmonary infection of obstructive lung disease. New and effective antipseudomonas antimicrobials in the form of gentamycin and carbenicillin had been introduced and proved to be superior to previous agents. Studies of the efficacy of therapy indicated that mist tents probably did not contribute substantially to the well-being of most patients.

Program Goals Through 1982

- Identify cystic fibrosis factors in patients and genetic markers in heterozygous carriers of the cystic fibrosis gene.
- Elucidate normal mechanisms involved in mucociliary clearance, and determine how these are modified in cystic fibrosis.
- Develop therapies and procedures for management of patients with cystic fibrosis.

Accomplishments Through 1982

A large number of studies have appeared concerning the etiology and pathogenesis of cystic fibrosis. While none has pinpointed what appears to be the mechanism of the defect, major breakthroughs have occurred in the basic understanding of the normal regulation of the airway structures that are involved in the secretory process, and technologic advances make it possible to study diseased tissue.

The major abnormality in CF is in mucous synthesis or secretion. Thus, considerable emphasis has been placed on the observation that mucus from the respiratory tract, intestinal tract, and uterine cervix is relatively dehydrated compared to mucus from normal individuals. In the lung, abnormalities of mucus result in airway obstruction, which is the usual cause of death in CF. Secretion from glands and surface cells of the airway combine with water to form the airway secretions, which are moved up the airway to the mouth by sweeping action of the cilia. Understanding the abnormalities in CF requires understanding of normal regulation of mucous secretion, water movement, and ciliary motion. A decade ago, little was known in these areas, but major

progress has been made through multidisciplinary approaches and several technical breakthroughs.

Since water makes up most of the airway secretions, the regulation of water is of utmost importance. Techniques used in other epithelia (for example: gut and kidney) have recently been applied to the airways. These studies have shown that water movement in the airways is controlled by a "pump" that actively moves ions across the airway surfaces; water follows passively. Methods have been developed to measure the minute volumes of water that are secreted. Some evidence suggests that abnormalities in ion transport may be an underlying mechanism in the pathogenesis of CF. In fact, the abnormalities in sweat secretion are used to diagnose the disease. Microtechniques are now being used in animal models of disease and in human tissue to explore possible abnormalities in the ion transport. Circulating factors may prevent the operation of normal ion pumps, or the cells themselves may lack normal pumps.

Most airway mucous secretions are derived from the submucosal glands. Again, multidisciplinary research has begun to identify the mechanisms by which humoral mediators and drugs regulate secretions. Glands contain serous cells and mucous cells. The first are believed to produce thin, watery secretions, and the second are believed to produce thick secretions. Recent studies have suggested that the functions of these two cell types are controlled separately. Major headway has also occurred in identifying the chemical nature and the determinants of the physical properties of mucus. Studies have indicated that mucous glycoproteins are more than normally sulfated in CF, and the abnormality is accompanied by increased average lengths of the oligosaccharide chains on these glycoproteins. The clinical implication of these abnormalities needs further exploration.

Cilia must beat in a specific, coordinated fashion to move a stream of liquid and to clear mucus. The filamentous structure of cilia has recently been discovered, and the power supply for ciliary motion has been shown. In patients with CF, a number of circulating factors have been reported. Each factor has been examined, and a number of biologic activities have been suggested, but none of the factors has been adequately purified or shown to be related to the genetic defect in CF. These factors include the ciliary inhibitory factor, which inhibits glycoprotein-debranching enzyme; a lectin-like activity, which promotes release of mucus from ciliated epithelium; and a substance with isoelectric focusing band at pH 8.4. Attempts to apply these observations to the identification of CF heterozygotes have met with only limited success, largely because of wide variability of response and overlap between the responses generated by homozygote, heterozygote, and control populations. None of these tests as yet has proven capable of consistently identifying CF in utero.

Efforts have been made to study mechanisms that lead to lung infection in cystic fibrosis. Abnormalities of pulmonary alveolar macrophages and lymphocyte defense systems occur, but they appear to be secondary to lung infection. So far, research has not found immunologic deficits. The function of the pancreas in lung abnormalities has been investigated, and it has been found that the "cystic fibrosis syndrome" is not dependent on the state of exocrine pancreatic function, as was once suggested.

Biochemical studies have suggested abnormalities in specific enzyme function (for example: protease activity and protease inhibitor), and mitochondrial dysfunction relating to intracellular distribution of calcium has been reported; but these studies have so far not provided specific insights into the pathogenesis of the disease.

Because of the difficulty of studying tissues from patients with CF, considerable effort has been exerted in developing an animal model of the disease. Thus far, no genetic model has been found, and none of the "induced" models mimic the cystic fibrosis clinical syndrome. Nevertheless, several forms of pharmacologic intervention have provided important clues concerning the modification of normal structure and function.

State of Knowledge in 1982

A considerable amount of information has been generated in a 10-year period concerning cystic fibrosis. The mechanism of the defect, however, remains unknown, and means to identify the CF gene in utero is yet to be developed. Research on the pathophysiology and pathogenesis of the disease seems unfocused, largely because of an inability to identify abnormalities that can be readily related to the clinical syndrome. In addition, it is difficult to eliminate from studies secondary effects of chronic lung disease and nutritional deficiencies. Lack of an adequate animal model has further precluded rapid advances.

Applied research has also been relatively slow in CF. Attempts to launch collaborative, large-scale studies of the various therapeutic modalities have been unsuccessful. New antibiotics have been developed, and more effective delivery of supplementary pancreatic enzyme has been engineered. Treatment, however, remains essentially the same as it was in 1972. Implication of hypersensitivity reactions in the pathogenesis of CF lung disease has opened new avenues of inquiry.

Program Goals 1982 to 1987

The long-range goals in CF research are:

- Search for mechanisms of the defect of CF that lead to pulmonary abnormality.
- Identify genetic markers for cystic fibrosis.
- Improve the care of patients that will enable them to lead a longer and better quality life.

Research Activities 1982 to 1987

The following activities are given as examples:

Basic Studies

- Attempt to characterize the basic science of metabolic defects centering on the function of cell membranes in affected secretory tissues: water and ion transport, biosynthesis and composition of mucus, and intracellular secretion and its control (cAMP and calmodulin). (See also research activities for nonventilatory functions of the respiratory system, page 76.)
- Identify genetic markers such as specific cell components that can be quantified in cells isolated from homo- and heterozygotes.

Clinical Studies and Patient Care

- Promote the availability of specific and sensitive lung function tests for early detection of impairment.
- Investigate means to combat pseudomonas infection effectively: better antibiotics and better modes of delivery of antibiotics directly to the affected area of the lung.
- Improve the delivery of oxygen during acute episodes of lung impairment.
- Identify and evaluate new and improved mucolytic agents.
- Investigate the relationship between nutrition and degree of respiratory impairment.

- Conduct prospective evaluation of CF patients to compare morbidity and mortality in males and females.

Disorders of the Control of Breathing

The term "disordered breathing" has recently been coined to refer to a number of seemingly unrelated clinical problems thought to have common pathophysiological derangements. The abnormalities are believed to reside in mechanisms responsible for sustaining normal ventilatory function in the face of changing metabolic needs that occur with growth, exercise, and sleep.

Many of these disorders are found only in newborn infants or those less than 1 year of age. Others are common among adults with certain forms of lung disease. Some are manifested by abnormalities of breathing patterns during sleep ("sleep-disordered breathing"), while others do not seem to be related to the state of consciousness. Table 12 is a list of clinical conditions (in children as well as in adults) that are thought to result from abnormalities in the control of breathing.

Of the specific disorders listed, apnea of prematurity, sleep apnea syndromes, and sudden infant death syndrome (SIDS)* are particularly prevalent in children. The disorders are described in detail below. (Disorders of breathing in children with chronic lung disease do not differ significantly from those in adults and are therefore not discussed here.) One group of lung-obstructed infants that has not been studied to date--namely, those with bronchopulmonary dysplasia--constitutes a significant problem, which is discussed separately.

The term "sleep apnea" has been used to describe a group of patients that manifest a distinct collection of symptoms that are the result of apneic episodes occurring during sleep.

Sudden infant death syndrome, also referred to as crib death, cot death, or sudden unexplained death of infancy, is the leading cause of death of infants between 1 and 12 months of age in the United States, where there are 2 deaths from SIDS per 1,000 live births, a total of about 7,000 deaths per year. A SIDS death is defined by an appropriate history and postmortem findings. When an infant who is in apparently good health dies suddenly and unexpectedly during a normal sleep period and the postmortem

*Although SIDS research is solely within the purview of the National Institute of Child Health and Human Development, the discussion here is included for the sake of completeness.

Table 12. Conditions Associated With a Disorder
in the Ventilatory Control System

Sleep-Related Disorders	Wakefulness-Related Disorders
Apnea of prematurity	Central hypoventilation
Sleep apnea	CNS depression
Obstructive	Neurologic disorder
Central	CNS trauma
Mixed	Intracranial diseases
Obesity-hypoventilation (Pickwickian)	Myxedema
Sudden infant death syndrome (SIDS)	Ventilatory pump failure
Primary alveolar hypoventilation (Ondine's curse)	Obstructive lung disease
	Respiratory muscle failure from disease or drugs
	Failure of pulmonary reflexes to recognize added loads to breathing
	Interruption of afferent or efferent neural traffic from and to the respiratory system
	Rib-cage abnormalities

examination reveals no apparent cause of death, the infant is considered a SIDS victim. The definition itself reflects most of the obstacles to determining the cause and finding a cure. Namely, all cases of SIDS are diagnosed after death. The history is an important but very subjective part of the total picture, and at least until very recently, no firm pathological abnormalities could be considered diagnostic of the condition. In essence, infants who die unexpectedly and who fulfill these criteria are placed in this category by a process of exclusion.

State of Knowledge in 1972

Most of the problems identified in table 12 had been recognized by the medical profession prior to 1972, but it has been only in the past 10 years or so that many of them have been categorized in this fashion. The sudden infant death syndrome and the obesity-hypoventilation syndrome (formerly Pickwickian) are good examples. Similarly, only in the past decade has the importance of sleep apnea and sleep-disordered breathing been clinically recognized as contributing to such problems as hypersomnolence, idiopathic cor pulmonale and pulmonary hypertension, apnea of prematurity, and periodic breathing.

Apnea associated with premature birth had been recognized as a prevalent phenomenon prior to 1971. Multiple clinical factors had by then been implicated as increasing the occurrence of apnea among premature infants. These included sepsis, hypoglycemia, meningitis, respiratory distress syndrome, and seizures. Why apnea occurs in conjunction with these disorders needed to be clarified. Studies of the control of breathing and the response of infants to carbon dioxide and hypoxia had been performed in the 1950's and 1960's in an attempt to correlate abnormalities of this system with the occurrence of apnea. Although premature and term infants, when compared to adults, were known to respond differently to hypoxia, little correlation was found with the incidence of clinical apnea.

By 1972, sleep was recognized as a nonhomogeneous state of consciousness, and the different sleep stages and patterns of brain electrical activity had been described. Little was known, however, about the profound changes that occur in ventilatory function during sleep. The different sleep patterns of premature and term newborn infants were being actively studied, and the prevalence of apneic spells during the different sleep stages were beginning to be recognized. The Pickwickian syndrome was a condition well described by 1972, but its pathophysiology was unknown. Similarly, central hypoventilation syndrome (Ondine's curse) was known to be related to sleep, but no explanation for this problem was available. The relationship between sleep-induced hypoxemia and cor pulmonale or pulmonary edema was not recognized. In addition, certain signs and symptoms occasionally found in children were not yet explained in terms of a sleep disordered breathing pattern.

In 1972, SIDS was a recognized cause of death, but almost nothing was known about its epidemiology or natural history. In many cases at the time, little or no effort had been made to investigate the medicosocial background or the events leading to death, or to search for finer clues during postmortem examinations, mainly because in most situations they were medicolegal deaths and the autopsy was performed by a local coroner's office

where personnel were not familiar with the entity of SIDS. SIDS registers were established in some countries, but none were available in the United States.

Although SIDS cases were considered rare, little data were available on its true U.S. incidence and distribution. In many instances, abuse or neglect was incorrectly suspected. Clues as to its possible etiology were lacking. Few hypotheses were even advanced. In the early 1970's, it was recognized that the first step in elucidating the nature of SIDS was to obtain accurate epidemiological and pathological data on a national scale.

Program Goal Through 1982

Before 1982, disorders of control of breathing were not identified in a separate goal. Control of breathing during development was pursued according to the following goal:

- Increase knowledge of structural and functional changes during prenatal and postnatal growth and development of the respiratory system and of the effects of endogenous and exogenous factors.

Accomplishments Through 1982

Many pioneering studies on control of breathing during sleep and wakefulness have been conducted in the past decade. (See also section 3, Physiology: Control of Breathing, pages 43-57.)

Apnea of Prematurity

Especially important for pediatricians are the advances that have been made in understanding the processes of maturation involved at the time of birth in initiating breathing and in the maintenance of adequate ventilation in the neonatal period, especially during sleep, since newborn infants spend a great deal of time sleeping. Progress has been made in understanding what constitutes normal sleep in this population and what the relationships are between sleep and such problems as apnea of prematurity, periodic breathing, and respiratory pauses. In addition, the coordination of airway patency with movements of breathing and swallowing has been confirmed to be of particular importance in infants.

Recently qualitative and quantitative studies of apneic episodes have been performed, and the relationship of the episodes

to sleep/wakefulness stages and breathing parameters have been established. These important studies have been possible partly because of developments of techniques for measuring ventilatory parameters for noninvasively monitoring oxygen and carbon dioxide tensions. These techniques have been of help not only in identifying events leading to apneic episodes but also in a number of instances in providing possible clues to etiologies of pauses in breathing. To date, the most important accomplishments relate to the recognition and recording of factors such as respiratory drive and metabolic rate, which may be involved in neonatal apnea.

Advances have also been made in understanding the epidemiology of neonatal apnea. A high mortality rate has been observed among RDS infants who develop apnea, and the incidence and severity of apnea have been correlated with birth weight. These two factors, prematurity and RDS, account for a large proportion of apneic infants.

Specific and effective palliative therapy for neonatal apnea has been found in the form of theophylline, which is a stimulant of the central nervous system. Since its first application in 1974, the use of this drug has become widespread and has proved relatively safe. More recently, caffeine has been shown to be a major metabolite of theophylline in newborns, and therapy with caffeine is now an acceptable alternative.

Sleep Apnea Syndrome

Significant advances were made in the past 10 years in the recognition of the disorders that are related to sleep-induced pauses in breathing. Three basic types of pauses have been described and characterized according to frequency and duration: central, obstructive, and mixed. Therapy in many cases has resulted in a resolution of the problem. In the pediatric age group, sleep apnea due to obstruction of the airway in some children with enlarged tonsils and adenoids has defined a population with clear indications for tonsillectomies. Also, the impact of sleep pattern on school performance has now been recognized. Whether or not a correlation can be demonstrated between sleep patterns and intellectual performance in the child who is only minimally affected remains to be shown.

Sleep studies that utilize sophisticated monitoring of cardiorespiratory and electroencephalographic signals have expanded the understanding of the control of breathing. In particular, the elucidation of the function of the muscles that modulate airway patency (such as certain tongue muscles) has made it clear that they, too, must be considered as "muscles of inspiration." Sleep has also provided a state in which to study such physiological concepts as the rhythmicity of breathing

efforts, the function of certain muscular reflexes, the modulation of breathing brought on by cortical or higher conscious and subconscious neural processes, and the adaptations that occur to accommodate behavioral respiratory movement and the adaptations that are imposed by the metabolic needs of the organism.

Sudden Infant Death Syndrome

Considerable interest in SIDS in the biomedical community and particularly in the pediatric forensic and academic pathology communities has resulted in the emergence of a much clearer pathological picture. Extensive epidemiological data have been accumulated that have led to a more precise definition of the magnitude of the problem and served as the basis for many hypotheses about SIDS. To date, however, the cause of death remains a mystery.

In 1973, the National Center for Health Statistics adopted a special code for SIDS, and data are available for the years 1973 to 1979. SIDS was recognized as a major health problem in 1974 when Congress passed the Sudden Infant Death Syndrome Act of 1974 (P.L. 93-270). The Act fixed responsibility for conducting SIDS research with the National Institute of Child Health and Human Development, and it mandated a program to collect and disseminate public and professional information and educational materials through grants and contracts for SIDS research and data collection, and to provide counseling services to families of SIDS victims.

The natural history of SIDS as presently understood is as follows: The infant, usually well nourished and well developed, is reported by parents to have been in good health until the time of death. There is usually no history of serious respiratory illnesses although some infants are reported to have stuffy or congested noses or slight colds. Peak incidence is around 2 to 4 months of age. Males are more often affected than females, black infants more than whites, twins more than singletons, and infants of low birth weight or of premature birth more than normal full-term infants. Infants of mothers who smoke seem to be at higher risk. Breast-fed babies may be at slightly greater risk than bottle-fed babies, as may be babies born to low socioeconomic households. Subsequent siblings of SIDS victims are at considerably greater risk than infants from unaffected sibships.

The picture of SIDS that has emerged from postmortem studies over the past 10 years is one of chronic hypoxia, at least in over one-half of the victims. The studies have prompted the search for possible mechanisms responsible for rendering the infant hypoxic. Although the evidence for hypoxia-induced pathological changes is strong, these data have not provided any clues as to the extent or

duration of this stimulus nor have they helped in establishing relationships of cause and effect.

State of Knowledge in 1982

Investigators are beginning to study the complexity of the control of breathing during sleep and wakefulness by systematically evaluating the physiological and environmental factors that may be involved. Improvement and further development of non-invasive techniques for measuring pulmonary function, tissue oxygenation, and metabolic rate will determine the extent to which such information can be gathered in human infants.

Most investigators at present would agree that it seems most likely that multiple rather than single etiologies are involved in SIDS. Given the lack of objective clinical data preceding death and the lack of uniform pathological findings, it would seem unrealistic to assume that all cases have a simple, common mechanism of death. Most hypotheses today fall among four categories. The first proposes some type of failure in the system(s) of respiratory control, particularly the part of the system(s) that controls breathing during sleep. Another group concerns the interaction between an immunologically susceptible host and some kind of infecting agent(s). A third group focuses on life-threatening cardiac arrhythmias. And, finally, a fourth group invokes some genetic or acquired biochemical defect as the cause. To date, a conclusive difference between "near-miss" SIDS and control infants has yet to be established. Studies of siblings and parents of SIDS infants are beginning to suggest genetically determined differences in their ventilatory control. Until an adequate animal model has been developed for SIDS or a specific marker identified, difficulties in identifying infants at risk are likely to remain.

Program Goals 1982 to 1987

- Elucidate the structural and functional maturation of central and peripheral components of the respiratory control system(s) and the influence of environmental factors and sleep on respiratory control in premature and full-term animals and in human infants.
- Conduct prospective studies to evaluate pharmacologic agents for their effectiveness in correcting dysfunction of respiratory control.

- Improve or develop noninvasive techniques to monitor respiratory functions and oxygen uptake and utilization and to detect early signs of dysfunction.

Research Activities 1982 to 1987

The following activities are given as examples:

- Gain further insights into the way in which breathing is adequately maintained during sleep, including the mechanisms responsible for airway patency as well as those responsible for appropriately responding to insufficient ventilation during loaded breathing or increased metabolic needs.
- Investigate the role of respiratory muscle fatigue during loaded breathing and sleep in producing apnea.
- Elucidate the mechanism of laryngeal reflexes in the production of apnea.
- Perform studies of the genetics of the control of breathing.
- Perform prospective control studies on the effect of surgical correction of airway problems on sleep-disordered breathing.
- Study the relationship between perinatal nutritional status and control of breathing.
- Develop further noninvasive techniques to monitor gas exchange and cardiopulmonary variables for use in research as well as for clinical monitoring purposes, including noninvasive techniques that can be used to assess intracellular oxygenation of key organs such as the brain.
- Develop simple, noninvasive techniques for sleep-disordered breathing problems such as telemetry systems to monitor children during sleep in the home.
- Develop new approaches to control and treat apnea.

Pediatric Lung Disease and Predisposition to Chronic Lung Disease in Adults

Most noninfectious pulmonary disease in adults results from lung injury by environmental agents. Most cases of chronic air-flow obstruction, for example, result from cigarette smoking, as may some cases of asthma. The factors that determine an individual's susceptibility to cigarette smoke and to other environmental agents, however, remain largely unknown. Pulmonary injury in childhood during the period of lung growth and development has been proposed as a risk factor for disease in adulthood. This effect might be mediated by increasing the adult's sensitivity to environmental agents or by reducing physiologic reserves through a reduction in the maximum level of function attained during lung growth. Identification of specific pediatric precursors of adult lung disease would offer a unique opportunity for prevention, and susceptible individuals could be identified before the development of disease and could avoid potentially harmful exposures, such as cigarette smoking.

State of Knowledge in 1972

Early interest in pediatric precursors of adult respiratory disease focused primarily on air pollution and on lower respiratory tract infections. British epidemiologic investigations of children and adults, conducted during the 1950's and 1960's, suggested the hypothesis that lower respiratory tract infections in childhood were a risk factor for COPD in adulthood. These studies did not provide definitive data, partly because of possible bias in recall for retrospective collection of histories of illness. Thus, by 1972, the hypotheses that had been advanced for pediatric precursors of adult lung disease remained untested.

Program Goal Through 1982

- Evaluate the role of bronchiolitis in subsequent disorders of the airways and lung parenchyma.

Accomplishments Through 1982

Epidemiologists and physiologists have continued to explore the relationship between childhood lower respiratory tract infections and the development of COPD in adulthood. Studies of determinants of levels of pulmonary function in children and in adults have generally shown adverse effects of childhood illness,

although bias in recall remains an issue in these investigations. Physiological studies of children with previous hospitalization for specific lower respiratory tract infections have demonstrated long-term sequelae of these illnesses. Whether the results of such studies are applicable to illness not resulting in hospitalization is unclear.

Recent investigations suggest the possibility of complex interactions between lower respiratory tract infections, the child's level of airway reactivity, and atopy. Passive exposure to parental cigarette smoking may also be a factor in respiratory illness and airway reactivity. Longitudinal data that clarify the temporal relationships of these factors and define their effects in adults are not available.

Prospective investigations of study populations initiated since 1972 should answer some of these questions. A cohort study of children in East Boston, Massachusetts, has been designed to assess early-life risk factors for the development of adult COPD. Epidemiologic studies in Tucson, Arizona, and Chapel Hill, North Carolina, are specifically directed at the effects of early childhood respiratory infection.

State of Knowledge in 1982

The hypothesis that adult pulmonary disease has pediatric precursors remains untested, although a number of investigations have provided promising leads. Obstacles to definitive studies have included the difficulties of documenting childhood exposures and illness and of conducting adequately based longitudinal investigations. The extent to which pediatric risk factors are precursors of adult lung disease remains speculative.

Program Goal 1982 to 1987

The primary goal is:

- Conduct epidemiologic investigations that include prospective documentation of illness and exposure during infancy and childhood and followup of sufficient length into adulthood.

Research Activities 1982 to 1987

The following activities are given as examples:

- Investigate long-term consequences of RDS and of bronchopulmonary dysplasia.
- Conduct prospective followup studies spanning infancy and childhood to assess the interactions between lower respiratory infection, environmental exposures, atopy, and airway reactivity.
- Perform further physiologic studies of children with documented respiratory illness utilizing subjects whose experience of illness is comparable to that of the general population: for example, participants in health maintenance organizations.
- Define the effects of lower respiratory tract infections in childhood on the maturing lung.

Contributors

PULMONARY DISEASES ADVISORY COMMITTEE MEMBERS

Jacqueline J. Coalson, Ph.D., Chairman
Professor of Pathology
Pulmonary Pathology Department
University of Texas Health Science Center
at San Antonio
San Antonio, Texas

Margit Hamosh, Ph.D.
Associate Professor of
Pediatrics
Georgetown University
School of Medicine
Washington, D.C.

Roger Menendez, M.D.
Assistant Professor of
Pediatrics
University of New Mexico
School of Medicine
Albuquerque, New Mexico

Jay A. Nadel, M.D.
Professor of Medicine, Physiology,
and Radiology
Chief, Section of Pulmonary
Diseases
Cardiovascular Research Institute
University of California,
San Francisco
School of Medicine
San Francisco, California

Solbert Permutt, M.D.
Professor of Medicine
The Johns Hopkins University
Baltimore City Hospitals
Baltimore, Maryland

CONSULTANTS

Thomas F. Boat, M.D.
Associate Professor of
Pediatrics
Department of Pediatrics
Case Western Reserve
University
Cleveland, Ohio

Richard King, Ph.D.
Department of Physiology
University of Texas
Health Science Center
San Antonio, Texas

CONSULTANTS (continued)

Bruce Ogden, M.D.
Assistant Professor of
Pediatrics
University of New Mexico
School of Medicine
Albuquerque, New Mexico

Jonathan Samet, M.D.
Assistant Professor of Medicine
Department of Medicine
University of New Mexico
School of Medicine
Albuquerque, New Mexico

DIVISION STAFF

Bitten Stripp, Ph.D.
Chief, Structure and Function
Branch
Division of Lung Diseases
National Heart, Lung, and
Blood Institute

6. Fibrotic and Immunologic Interstitial Lung Diseases

Contents

FIBROTIC AND IMMUNOLOGIC INTERSTITIAL LUNG DISEASES	169
State of Knowledge in 1972	170
Program Goals Through 1982	173
Accomplishments Through 1982	173
Epidemiology	173
Clinical Studies	176
Diagnosis	177
Treatment	180
Basic Research	182
State of Knowledge in 1982	186
Program Goals 1982 to 1987	187
Research Activities 1982 to 1987	188
Contributors	190

6. Fibrotic and Immunologic Interstitial Lung Diseases

Interstitial lung diseases can be defined as a group of disorders that predominantly involve the alveolar walls and the supporting structures of the lungs. Initial injury to one or more of the cellular components of the airspace wall is followed by edema, which is soon associated with cellular infiltration, that consists to some extent of neutrophils but with a predominance of lymphocytes and large mononuclear cells. The mononuclear cells can acquire the appearance of epitheloid cells and can be organized into foci of granulomatous inflammation. Hyperplasia of type II cells, presumably to replace lost type I cells, is often a prominent feature of the pathologic process. Eosinophils are usually scanty or absent, but on rare occasions they predominate. Another major feature of the process is the deposition of an excess of connective tissue within the alveolar walls. An excess of smooth muscle can sometimes be observed. Although involvement of the alveolar walls is a central feature of the interstitial diseases, the exudative and fibrosing process generally involves the alveolar spaces as well. Interstitial lung disease is frequently a widespread process, but focal variation in the severity of involvement is characteristic of the process: some areas of the lung may be entirely spared, whereas the extent of involvement in other areas varies from minimal to extensive. The development of epithelial-lined cystic spaces within fibrotic lung, a process known as honeycombing, marks the terminal fibrotic state, regardless of etiology.

A large number of agents can give rise to interstitial lung disease, including viral, fungal, mycobacterial, and protozoan infectious agents; organic and inorganic dusts; alveolar hyperoxia, noxious gases, and chemicals; and drugs and ionizing irradiation. A sizable group of diseases of unknown etiology has been recognized clinically.

In the United States, the term interstitial pulmonary fibrosis makes special use of the word "fibrosis." It embraces a number of disease processes that involve the interstitium of the lung, in which increased connective tissue may or may not be present. When it is present, the fibrosis is generally accompanied by inflammatory cells and other evidence of lung injury and repair. In Great Britain, the term fibrosing alveolitis is generally used for this group of diseases.

Although there are a number of different histologic patterns, these diseases may be considered as a stereotyped response of the lung to a broad range of injuries of known and unknown etiology. Sometimes an etiologic agent can be identified by the presence of markers, such as the nuclear inclusion bodies of cytomegalovirus infection, the actual infectious agents in the deep mycoses and mycobacterial infections, or the residuum of inhaled inorganic dusts, as in silicosis or asbestosis. In many instances, however, the histologic features of interstitial inflammation from such widely diverging etiologies as the influenza virus or a chemical injury are indistinguishable. The injury to the components of the alveolar wall and the inflammatory cell infiltration can resolve completely or can progress to fibrosis. The factors that control the severity of the fibrogenic response are unknown.

Clinical findings for this diverse group of diseases also share similarities: the frequent occurrence of basilar crackles on auscultation of the lungs, a similar and usually nonspecific appearance on chest roentgenograms, and a common pattern of derangement in pulmonary physiology. The last consists of a decrease in vital capacity, total lung capacity, compliance of the lungs, and diffusing capacity with little or no demonstrable airflow obstruction. Hypoxemia, especially during exercise, along with normal or low arterial P_{CO_2} values are also usually seen.

State of Knowledge in 1972

It was recognized that interstitial lung diseases could be divided into groups of known and unknown cause. Among the latter, idiopathic pulmonary fibrosis (IPF) usually occurred in the absence of involvement of other organ systems. However, IPF was at times associated with connective tissue vascular diseases, which include rheumatoid arthritis, progressive systemic sclerosis (scleroderma), and systemic lupus erythematosus. In patients with such diseases, the pulmonary manifestations could antedate or occur with the systemic disease. The knowledge of the natural history of these diffuse fibrotic diseases of the lungs was limited, although accelerated, slowly progressive, or even stable forms of lung involvement were known to occur. Risk factors for the development of IPF were essentially unknown, except for the coincident presence of a collagen vascular disorder. Even with this association, there were no clear predictors of a progressive form of the disease.

Other diffuse interstitial lung disorders of unknown etiology included sarcoidosis, eosinophilic granuloma, idiopathic pulmonary hemosiderosis, Goodpasture's syndrome, and pulmonary vasculitis. With the exception of sarcoidosis, essentially no epidemiologic data on these conditions were available. Epidemiologic studies of

sarcoidosis demonstrated an uneven distribution, with greatest frequency in Europe, the United States, and Australia. It was relatively rare in developing countries. Ethnic differences were recognized, with greater risk likely for northern Europeans and black Americans. In these granulomatous disorders, there was great variability in severity and in risk of progression to respiratory failure. Progressive disease was recognized to be relatively infrequent in the most common of these conditions, sarcoidosis. Involvement of nearly all organs and tissues in addition to the lungs was well known, but the determinants of extrapulmonary manifestations were not recognized.

Important among the specific known causes of diffuse pulmonary fibrosis were workplace exposure to such mineral dusts as silica, asbestos, coal, and beryllium. While the causal association between such exposures and lung fibrosis was established in occupationally exposed populations, there was a paucity of firm data on dose-response relationships with the exception of coal worker's pneumoconiosis (CWP). Increased risk of other respiratory complications, such as lung cancer with asbestosis and mycobacterial infection with silicosis, were recognized, but again, quantitative data to assess risks were not available. Similarly, although a number of specific antigens that can cause hypersensitivity pneumonia had been identified through clinical studies, almost no population-based studies had been completed. Little was known concerning genetic or other idiosyncratic factors that can increase susceptibility to the fibrotic consequences of exposure to mineral dust.

A spectrum of drugs were known to produce diffuse interstitial fibrosis of the lungs. Among the drugs receiving the greatest attention were chemotherapeutic agents such as methotrexate, busulfan, and bleomycin, which are used in the treatment of cancer. Antimicrobial agents such as nitrofurantoin, as well as oxygen, mineral oil, irradiation, and the herbicide paraquat, were also known to be potentially injurious to the lungs. Once again, risk for the development of these drug- and toxin-induced diffuse interstitial disorders of the lung had not been quantified.

By 1972, criteria for the etiologic, anatomic, and physiologic diagnoses of many of the interstitial pulmonary diseases had been established in those cases where the disease was clinically apparent. Diagnosis depended upon a combination of clinical and laboratory criteria: known exposure to a noxious agent (inorganic or organic dusts, and drugs), characteristic clinical course, roentgenographic findings, skin and serologic tests, pulmonary function studies, and, occasionally, examination of lung tissue secured usually at thoracotomy or by rigid bronchoscopy. Evaluation of the stage or progression of disease rested primarily upon signs and symptoms, chest roentgenograms, and pulmonary function

studies. Progressive disability and changes in chest roentgenograms and pulmonary function tests often were interpreted as evidence of "activity" of the disease process. Since repeated examinations of lung tissue were not feasible because of the limitations of available techniques, it was not always possible to ascertain whether "activity" denoted further involvement of the lung by an inflammatory process or by progression to fibrosis. When the disease process was well established, there was often little to offer the patient in the way of reversing or arresting it.

Tests of lung mechanics and gas exchange suitable for the study of interstitial lung disease had been developed, although the need for more precise standardization was evident. Roentgenographic abnormalities were known to appear in the absence of impaired pulmonary function, as in sarcoidosis and simple nodular silicosis. Conversely, pulmonary function measurements were known to detect the presence of interstitial lung disease prior to the appearance of roentgenographic abnormalities. Such findings were most frequent in persons at high risk of developing these diseases, such as those suffering from the connective tissue vascular disorders or persons with known inhalant exposure. Genetic factors seemed to modify the expression of many of these diseases. There was little information on the metabolism of the connective tissues of the lungs in normal or diseased individuals. Criteria for an animal model of interstitial pulmonary fibrosis had been established, and preliminary work with an animal model of interstitial lung disease using N-nitroso-N-methylurethane in the golden hamster had been reported. This model, however, was expensive to produce. It required subcutaneous injections of the drug over a period of many weeks. Animal models of the pneumoconioses were also expensive, and they were difficult to produce by inhalational exposure.

Immune injury apparently was a major factor in the pathogenesis of many forms of this lung reaction, especially in the connective tissue vascular disorders. For the hypersensitivity diseases that occurred after inhalational exposure to various organic dusts, such as mold spores or excreta from pigeons, the inciting agent was well known, although the variability in the susceptibility of subjects was confusing. Studies of the patterns of lung tissue response or injury suggested that many of the diseases, both of known and unknown causes, invoke immunologic mechanisms. The evidence supporting this concept included abnormalities identified in peripheral blood specimens, such as the presence of antibodies against the offending agent or of autoantibodies (antibodies against the individual's own tissue). Alterations in delayed skin test reactivity, in blood lymphocyte counts, and in in vitro mitogenic responsiveness of lymphocytes also suggested alterations of the immunologic system. Very few studies, however, had examined these immunologic characteristics

of the airways and lungs of affected people, and only limited studies of the immunology of the lung in experimental animals had been conducted.

Program Goals Through 1982

A major program goal has been to investigate etiologic factors and risk factors in population groups characterized by unusual prevalence of fibrotic and immunologic lung disease. It was suggested that epidemiologic studies establish dose-response relationships between etiologic agents and occupational lung disease. Studies were to be designed to determine the possible synergistic effects of other factors such as smoking or individual host characteristics.

Additional specific program goals were to:

- Investigate connective tissue metabolism in order to learn more about the neurogenic, humoral, enzymatic, mechanical, and nutritional factors that cause alterations in the connective tissues of the lung in normal and diseased individuals.
- Exploit existing animal models and develop new animal models to permit serial assessment of molecular, cellular, and pulmonary physiologic changes, as well as exploration of genetic influences.
- Encourage explorations to develop pharmacologic agents capable of interfering with certain aspects of connective tissue metabolism in order to prevent the progression of pulmonary fibrosis.
- Obtain more information about the immunologic responses and defense mechanisms of the lung, and find ways to block or retard these responses in interstitial lung disease.

Accomplishments Through 1982

Epidemiology

Because of the inadequacy of methods for collecting data on cases, the magnitude of the problem in interstitial lung diseases has been difficult to establish. Epidemiologic studies have also

been difficult to perform because of uncertainties in the identification of many of the diagnostic entities. There is considerable overlap in clinical, physiologic, roentgenographic, and even histopathologic features. While the last may have great specificity, invasive techniques are generally not feasible in epidemiologic studies. It has been estimated that the etiology of the interstitial lung diseases is unknown in approximately 70 percent of patients with the disease. Apart from some of the pneumoconioses, population-based studies have contributed little information about the magnitude of the problem of most interstitial lung diseases, particularly those disorders of unknown etiology. Data from hospital admissions provide only crude estimates of the relative frequency of clinical occurrence. In 1977, an estimated 34,500 patients reported to acute care hospitals with a primary diagnosis of chronic interstitial lung disease, and approximately 110,000 secondary diagnoses were made in this category. These conditions, however, are clearly not as prevalent as chronic obstructive pulmonary disease, including emphysema and chronic bronchitis. For sarcoidosis, ethnic differences continue to appear, and in rare instances, familial aggregation has been demonstrated. Epidemiologic studies, however, have not provided meaningful information concerning etiology.

Epidemiologic information concerning idiopathic pulmonary fibrosis is still disappointingly sparse. Determinants of the more progressive forms of the disease are elusive. Tentative clues concerning genetic factors, such as associations with histocompatibility antigens, have generally not been confirmed. Even less is known about the epidemiology of the less frequent chronic interstitial lung disorders such as eosinophilic granuloma, Goodpasture's syndrome, and the pulmonary vasculitides. In patients with collagen vascular disorders, the prevalence of interstitial lung disease ascertained by roentgenographic or physiologic methods can be as high as 50 percent. When histopathology is available, this figure can rise to 90 percent.

Cytotoxic-drug-induced pulmonary disease still receives attention, and new evidence suggests that synergism can occur between two of these drugs or between a drug and radiation in the production of interstitial lung disease. It is estimated that 10 percent of patients receiving the chemotherapeutic drug bleomycin develop interstitial disease. Overall, however, little attention has been directed to the epidemiology of drug-induced disease, and the magnitude of the problem is unknown. It is estimated that 5 to 15 percent of patients who receive chest irradiation will develop clinically apparent interstitial lung disease.

In the United States alone, several million workers are exposed to one or more of the fibrogenic mineral dusts: silica, asbestos, coal, and beryllium. Reasonable estimates of the extent of coal worker's pneumoconiosis among U.S. coal miners have been

established, and data suggest that approximately 5 percent of the 150,000 underground coal miners as well as several thousand former miners now have the disease. No reliable estimates are available regarding the prevalence of the fibrotic diseases caused by exposures to beryllium, silica, and asbestos. In the last decade, however, data on the effects of dosage levels have emerged from epidemiologic studies of miners exposed to coal dust, workers engaged in the mining, milling, and manufacturing of asbestos products, and workers exposed to beryllium and silica. Risk of progression in all of these diseases has been shown to be related to dosage. Quantitative risk assessment has also been possible for asbestos-related lung cancer. Although it is known that smoking interacts with asbestos to increase the risk of lung cancer and the severity of pulmonary function impairment, little has been learned concerning possible increased risk associated with exposure to the fibrogenic mineral dusts due to idiosyncratic factors. In simple coal worker's pneumoconiosis, silicosis, and beryllium disease, the focal fibrotic process per se does not contribute much functional impairment, whereas in asbestosis, parenchymal fibrosis is more diffusely distributed and tends to be more predictive of functional impairment.

Because of the broad range of etiologic agents and general lack of epidemiologic research in hypersensitivity pneumonia, only general estimates are possible regarding the prevalence of this disease and the populations at risk. Cross-sectional studies of farmers in the United States and the United Kingdom suggest that the prevalence of farmer's lung disease may be as high as 32 per 1,000 farmers in endemic areas such as Wisconsin. This estimate suggests that as many as 4,800 cases of farmer's lung may occur in Wisconsin alone. Studies of pigeon breeders have resulted in findings that 6 to 15 percent are affected. This finding suggests that there are up to 10,000 cases among the 75,000 breeders in the United States. Studies of air humidification and cooling systems contaminated with agents implicated in hypersensitivity pneumonia have reported that 1 to 15 percent of exposed individuals are affected. Because of the potential exposure of extraordinarily large numbers of individuals to antigens from such systems in houses, offices, and manufacturing plants, this problem may have far-reaching significance. Only a limited amount of prospective clinical data is available on the natural history of these diseases. Such studies suggest that the length of exposure following development of symptoms, the age of the person, and the level of functional impairment at diagnosis are important factors in predicting the possible progression of the disease.

Estimates of the prevalence of interstitial lung diseases still depend upon questionnaires focused on respiratory symptoms, pulmonary function tests, and chest roentgenography. These latter methods were standardized during the past decade through the efforts of the American Thoracic Society. Newer techniques

include pathologic study by light and electron microscopy and bronchoalveolar lavage. The standard classifications for roentgenographic appearances of the pneumoconioses were revised during this period, and the current International Labor Office (ILO) revision was published in 1980.* Expanded use of this system for the nonoccupational interstitial lung diseases has been initiated. Standardization of techniques and instrumentation for spirometry was accomplished and is now in wide use. A standardized questionnaire was developed that can be modified according to specific investigative needs.

Efforts to correlate disease with biochemical findings have been attempted but have met with only limited success. Angiotensin converting enzyme (ACE) may be useful in assessing activity of sarcoidosis. The value of the histocompatibility-antigen system in identifying susceptibility to various occupational or other fibrotic lung disease is uncertain. Immunologic markers in the diffuse pulmonary fibrotic disorders have shown associations with established disease, but thus far have not helped to predict outcomes.

The technology available to estimate personal time-weighted average and peak exposures to organic and inorganic particulates and gases was substantially improved during the past decade. Newer techniques have been used to establish dose-response relationships in occupational diseases. Techniques to measure the burden of mineral dust in lung tissue, while of considerable interest, have limited epidemiologic applicability. Such investigations, however, together with a better understanding of deposition, retention, and clearance of particles may improve the ability to make estimates of previous exposure, which are currently based on data from air samples. Methods of statistical analysis attempting to correlate exposure dosage with biological response must take into account such nonexposure-related confounding factors as smoking and atopic predisposition. These methods have made important contributions to the interpretation of epidemiologic data, and advances in computer technology have substantially expanded analytic capability.

Clinical Studies

While an accurate history is essential in determining the causes of illness, such as exposure to inorganic and organic dusts, drugs, and other agents, the use of such histories to

*Guidelines for the Use of ILO International Classification of Radiographs of Pneumoconiosis. Revised Edition 1980. Publication Number OSH22.

determine the onset and stage of many of these diseases is not always reliable. This lack of reliability is a consequence of the insidious onset and progression of the pathologic processes and the long interval between exposure to many known noxious substances and the clinical manifestation of the diseases. Recent investigations show that patients with interstitial diseases of unknown origin can have, years after the onset of symptoms, a marked cellular reaction with little fibrosis, or can exhibit early a marked cellular reaction combined with fibrosis. The patient often initially exhibits very few abnormal physical findings, although prior to changes in chest roentgenograms, bilateral basilar crackles are frequently found in patients with asbestosis.

Diagnosis

Because there is a crude correlation between roentgenographic pattern and the severity of pulmonary functional abnormalities, roentgenographic abnormalities have been used to identify the stage of interstitial diseases. Conversely, histologic studies have demonstrated that cellular infiltration or granulomas can be present in alveolar walls without abnormality in the lungs discernible by roentgenographic examination. In one center, about 10 percent of the patients with biopsy-proven disease had a roentgenographically inapparent form of interstitial disease. Further, roentgenographic patterns may not reflect the type and extent of morphologic changes until there is extensive fibrosis.

Studies relating the degree of functional abnormalities to roentgenographic and histologic changes in patients with sarcoidosis, IPF, and some organic dust diseases indicate that pulmonary function tests are more sensitive to the presence of minimal disease and to its progression than are roentgenographic findings. However, some patients with disease caused by inorganic dusts may have roentgenographic evidence of disease and normal pulmonary function tests. In general, patients with normal pulmonary function tests have minimal morphologic changes, and those with the greatest number of abnormal tests have the most extensive changes. While the extent of functional abnormality correlates with the overall extent of disease, the tests do not indicate whether the predominant pathologic process is chronic inflammation or fibrosis. There is no consensus as to which test or groups of tests are most sensitive to the presence of structural abnormalities in any one of these diseases.

The best method for ascertaining the extent and type of structural abnormality in patients is histologic examination of samples of lung tissue removed at open lung biopsy. This method permits the most extensive sampling and the selection of the most representative areas of the lung. Because of the nonhomogeneous involvement of the lung in the disease processes, the ability to

select areas is of considerable importance. Open lung biopsy for the study of diseases of known etiology, however, is little used because it requires hospitalization and general anesthesia and because treatment is ordinarily not influenced by biopsy findings. Studies of IPF show that patients with highly cellular histologic changes in the lung biopsy respond better to corticosteroids than do patients whose biopsies show predominantly fibrotic changes.

The flexible fiberoptic bronchoscope, developed in the late 1960's and widely introduced into the United States in the early 1970's, was a major technological advance. The instrument not only improved prospects for diagnosis of lung disease. Because of the safety of the procedure, it also made possible the recovery of significant amounts of airway secretions and cells by bronchoalveolar lavage in patients as well as in normal volunteers. Analysis of the proteins and in vitro testing of the cells obtained by lavage, and comparisons of results from corresponding peripheral blood samples have provided some recent information on the immunology of human airways.

Bronchoalveolar lavage is a procedure in which small aliquots of sterile isotonic saline are instilled into a segment of the lung and then recovered by aspiration. The procedure is associated with minimal discomfort, little morbidity, and no mortality. While this technique has not been used extensively in all types of diffuse interstitial lung disease, evidence shows that the number of cells recovered is much larger in the presence of inflammation than in its absence. Analysis of cell populations and protein content of lavage fluid provides data that are useful in differentiating the various types of inflammatory reactions. Patients with IPF, for example, can have an increased percentage of neutrophils in the lavage fluid, as do patients with asbestosis. The lavage fluid of such patients can also contain a leukocyte-derived collagenase not found in normal subjects or in patients with sarcoidosis. In patients with sarcoidosis and hypersensitivity pneumonia, there is an increased percentage of lymphocytes, principally T (thymus-derived) cells. Further, immunoglobulin M (IgM) is detectable in the lavage fluid of most patients with hypersensitivity pneumonia but not sarcoidosis. The ability to distinguish between these two disease entities, which can mimic each other, may prove important.

In summary, the analysis of cells, proteins, and enzymes recovered from airways and alveoli of patients with a variety of interstitial lung diseases has improved current concepts of immunopathogenesis, provided a means for assessing disease activity close to the actual tissue involved, and improved the accuracy of diagnosis in some diseases. Although analysis of lavage fluid rarely substitutes for a histologic diagnosis, which must be obtained by a lung biopsy, the procedure can provide information about disease activity. Since it is less traumatic than biopsy

and can be repeated at intervals during the course of illness, the procedure is a promising test for monitoring this activity.

Bronchoalveolar lavage has made airway and alveolar cells available for cell culture studies to elucidate the metabolic and secretory functions of alveolar macrophages. The method has also allowed identification of subsets of lymphocytes in the lung by immunofluorescent and cell rosetting techniques and has provided insights into the effector cell function of macrophages. These cellular studies have been analyzed in conjunction with studies of complement components in lung secretions, of immune complexes, and of substances in lungs such as Hageman factor and elastolytic enzymes. These last substances can contribute to injury of pulmonary epithelial and endothelial cell surfaces.

Immunologic methods applied to the study of blood and of lung tissue have enhanced the understanding of injury to tissue by immune mechanisms. The level of circulating immune complexes in serum seems to correlate with the extent of interstitial inflammation. Such measurements may prove useful for judging disease activity as well as for determining the basis for cellular injury caused by immune complexes. Such injury is thought to be important in such diseases as IPF and the collagen-vascular diseases. Immunofluorescent staining and electron microscopic analysis of lung biopsy tissue are useful in the identification and localization of these immune complexes. These histological techniques have helped in the understanding of the immunopathogenesis of disease, and in a very limited way, have been useful in diagnosis. Studies quantifying the immunoglobulin-secreting plasma cells in blood and in lavage cells have yielded data that correlate well with lung disease activity and give information about the site of immunoglobulin synthesis. The secretion of these cells may account for hypergammaglobulinemia and for the elevated levels of immunoglobulin in airway fluid that are characteristic of many of the interstitial diseases. Electron probe analysis of lung tissue for inorganic elements, and related techniques, help to identify agents that cause occupational forms of interstitial lung disease. In addition, the levels of serum enzymes such as angiotensin converting enzyme are useful indicators of the presence of some granulomatous tissues, such as those of sarcoidosis and those that are induced by beryllium. The most sophisticated immunologic methods now available are used to examine blood, lung biopsy tissue, and airway secretions recovered by lavage.

⁶⁷Gallium scintiscanning is another technique that can detect the presence of inflammatory cells in the lungs. Abnormal gallium uptake in the lung is present in a number of diffuse interstitial diseases of known origin (asbestosis, silicosis, coal worker's pneumoconiosis, and bleomycin toxicity) and of unknown origin, and in a variety of neoplastic and infectious diseases as well. Although it is not possible to quantify precisely the amount of

gallium uptake, there is some correlation between the intensity of uptake and the degree of cellular reaction as determined by bronchoalveolar lavage or biopsy. Uptake of gallium by mediastinal or hilar lymph nodes and by lung parenchyma has been noted in many patients with sarcoidosis. In those patients whose roentgenograms have revealed infiltration, gallium uptake has been consistent and striking even in those patients whose chest roentgenograms suggest extensive fibrosis. When gallium uptake is present in other interstitial diseases of unknown etiology, it is seldom as intense as in patients with sarcoidosis and has not been detected in thoracic lymph nodes. The combined use of bronchoalveolar lavage and gallium scanning may provide the best method thus far to estimate the intensity of inflammation.

It may also be possible to use high serum levels of angiotensin converting enzyme and lysozyme for diagnosis of sarcoidosis, although many of these patients have levels within normal ranges. Patients with silicosis and asbestosis may also have increased serum levels of these enzymes, but not to the extent that has been found in some patients with untreated sarcoidosis. It appears that elevated levels of these enzymes in sarcoidosis indicates the inflammatory phase but that normal levels do not exclude it. While enzyme levels were found to return toward normal levels in some treated patients, the return did not always parallel improvement in lung function. Serum levels of angiotensin converting enzyme activity have been found within normal limits or reduced in patients with farmer's lung and in farmers with precipitins to thermophilic actinomycetes who show no evidence of disease. Those patients with reduced levels were acutely ill from their disease at the time of the sampling.

Treatment

Some controversy still exists regarding the indications for and efficacy of treatment in this heterogeneous group of diseases. The controversy probably results from a lack of knowledge of the cause or duration of lung injury, the variability of the clinical course even in patients presumed to have the same disease, the paucity of controlled studies of long duration, and the frequent classification of patients according to roentgenographic criteria that do not clearly identify the dominant pathologic process. These uncertainties greatly reduce the value of comparisons of response to different therapeutic regimens.

Corticosteroids have been widely used and have proved successful in suppressing the inflammatory process in a number of patients with diffuse interstitial diseases of unknown etiology. The response to treatment and the prognosis appear to be better in those with a predominantly cellular reaction as determined by lung biopsy, bronchoalveolar lavage, or gallium scanning. Because of

the potential harm of corticosteroids, administration is usually withheld unless there is a deterioration in the clinical course or an increase of abnormalities appearing in roentgenograms or pulmonary function tests. Efficacy of therapy is usually monitored by these same techniques.

A number of other immunosuppressive or cytotoxic drugs have been utilized in a few patients, with improvement in some. These drugs are administered when the response to corticosteroids is unsatisfactory. They have not been employed widely because of possible severe side reactions and because some can injure the lung and produce fibrosis.

The most effective therapy in patients with hypersensitivity pneumonia is prevention of further exposure to the offending dust. In this disease, early diagnosis is essential. Corticosteroids have been recommended in severe acute and chronic progressive cases, and they may hasten resolution of symptoms and physiologic manifestations in patients with milder cases. A long-term followup study of pigeon breeders with hypersensitivity pneumonia has demonstrated that the disease was stable and did not progress, despite exposure, if pulmonary function was normal at the time of the initial study. Breeders with abnormal pulmonary function initially, however, tended to deteriorate over the years. These findings suggest that pulmonary function testing may be of value in determining the need for therapy.

Since cessation of administration is the only known method of combating injury and fibrosis caused by drugs, knowledge of the potential of these agents to induce lesions is essential. Early recognition of lung damage can be achieved by serial measurements of pulmonary function, usually lung volumes and the single-breath diffusing capacity for carbon monoxide. Cessation of the offending medication may reverse or at least arrest the process.

There is no specific therapy for diseases caused by inorganic dusts, although complications such as mycobacterial infections may respond to specific chemotherapy. Corticosteroid administration can result in partial clearing of abnormalities that appear in roentgenograms and in improved pulmonary function in patients with associated connective tissue disorders. Prevention of exposure remains the only "cure" at present. The increased incidence of pulmonary carcinoma and mesothelioma years after exposure to asbestos, as well as the disability consequent to fibrosis in all of these diseases, emphasizes the importance of prevention.

Basic Research

Collagen is important in defining the structure and function of the lungs. It is the most abundant single protein in the adult mammalian lung, comprising 10 to 20 percent of dry lung weight. There are at least five known types of collagen, each comprised of immunologically distinct protein chains. Types I and III collagen are found in the alveolar walls and other respiratory tissues of the lungs; type III is also found in the alveolar capillaries. Types IV and V are seen in alveolar and capillary basement membranes, and some type V is present in the alveolar interstitium. Type II, which is associated with cartilage elsewhere in the body, is found in the trachea and bronchi. Electron microscopic studies show that collagen fibers are composed of a large number of densely packed collagen fibrils that can be clearly identified by characteristic major crossbanding.

Elastin, which is another major structural protein, is also ubiquitous in the lungs. It is the major component of elastic fibers, which in the lungs are always found in association with collagen fibers. Elastic fibers are readily recognized microscopically by their affinity for specific histochemical stains. Ultrastructurally, mature elastic fibers reveal two components, microfibrils and elastin, the latter of which has an amorphous appearance and is responsible for the elastic properties of the elastic fibers.

This collagen and elastin network resides in an acellular, nonfibrillar matrix known as the amorphous ground substance. The components of the ground substance that are best defined are the proteoglycans, which are composed of glycosaminoglycans linked to a protein core. The importance of the ground substance in the function of the normal lung and in disease states is poorly understood.

The biochemical measurement of lung connective tissues has advanced greatly in the last decade. Total lung collagen, for instance, can be readily determined with the use of the amino acid hydroxyproline as a marker, since, in addition to its presence in collagen, only very small amounts of hydroxyproline occur in elastin and one component of complement. Collagen is by far the richest source of hydroxyproline in the body. Elastin measurement is more difficult since measurements depending on marker amino acids such as the desmosines or hydroxyproline levels require preliminary purification, the techniques for which are far from perfect. The harsher treatments may partially degrade the product and may solubilize incompletely crosslinked elastin, while the milder methods tend to yield a product contaminated with non-elastin proteins. Measurements of proteoglycans are the most difficult to perform.

Studies of collagen synthesis have made use of normal human lungs, lungs afflicted with fibrosing diseases, and animal models of these diseases. These studies, for the most part, have used lung explant and tissue cultures. Studies using intact lung have been limited by methodological problems, whereas studies using cell-free systems have proved useful in examining individual aspects of collagen biosynthesis. Such studies have shown an increase in collagen synthesis in human fibrotic lung disease and have demonstrated its temporal course in animal models. The sequence of events in the synthesis and deposition of collagen and elastin in the lungs of normal growing animals has been elucidated. The rapid ability of the lung to produce collagen has been demonstrated in studies of the residual lung after pneumonectomy. There is little information on factors that control the production of collagen.

Animal models of interstitial lung disease have been developed that bear a closer resemblance to naturally occurring human disease than the models available in 1970. Models can now be induced by exposure to ionizing radiation or chemicals (cadmium, bleomycin, paraquat, or oleic acid), by immunologic injury, by intratracheal administration of inorganic dusts, by hypoxia or hyperoxia, and by administration of noxious gas. The models have been described and defined with the aid of structural studies, pulmonary function measurements, and bronchoalveolar lavage analysis.

In the experimental animal, interstitial pulmonary fibrosis involves an increase not only in total lung collagen but also in elastin and glycosaminoglycans. Although an increase in the production of connective tissue has been clearly demonstrated, degradation of connective tissue continues to be by inference rather than by unequivocal demonstration. Animal studies have also demonstrated that connective tissue components must be expressed on a per lung basis because the expression of connective tissue components as a ratio to lung weight or some other lung constituent may conceal an increase in connective tissue components. This approach is easily followed in studies of small animals by making measurements on an aliquot of the entire lung. With the lungs of larger animals and humans, sampling must be performed carefully since, as noted earlier, the distribution of interstitial diseases is characteristically irregular. Studies in human IPF have shown a decrease in the ratio of type III to type I collagen, although changes in the ratios of collagen types III to I have not been observed in experimental models of IPF.

Inflammation in the lung is a requisite and integral part of the development of fibrotic and granulomatous lung diseases. It is one of the first events (or series of events) that occurs as a result of pulmonary exposure to a great variety of agents, ranging from infectious organisms to occupational dusts. It is, however,

a multifaceted process that involves a variety of cells and soluble products. What causes it to develop into a chronic form, leading to debilitating or even fatal disease, or to resolve without permanent injury to the lung is not yet known. Research from a wide range of viewpoints has been conducted on the phenomenon of inflammation in an effort to understand the participants and their interactions as well as the mechanisms that control the induction, maintenance, and resolution of the inflammatory process.

It is now known that one important participant in this process is the alveolar macrophage. This cell, which was once thought to serve only a protective function by phagocytosis followed by distribution or removal of bacteria or other potentially detrimental agents from the lung, has more recently been determined to participate directly in inflammation. Evidence obtained from in vitro culture studies indicates that alveolar macrophages are capable of producing potent chemoattractants for other inflammatory cells (neutrophils, lymphocytes, and other macrophages) and that they are important in initiating and maintaining an influx of cells characteristic of the inflammatory lesion.

The lysosomal enzymes produced by activated alveolar macrophages have also been examined because of their ability to damage tissue. Studies of macrophages from the lungs of rabbits with immunologically induced pulmonary injury have revealed that potentially tissue-destructive enzymes in the cells from injured animals are increased, both in number and in concentration, as compared to enzymes in the cells from normal, uninjured lungs. Alveolar macrophages obtained from silicosis patients and from animals exposed briefly to silica dust have also been shown to be activated. These findings offer further evidence in support of the importance of alveolar macrophages in pulmonary inflammatory processes.

Antibody, particularly in conjunction with complement, has also been found to be an important initiator of inflammation in the lung. Immune complexes made up of antigen, antibody, and complement have been found in the lungs and serum of patients with interstitial fibrosis, and it is suspected that these substances are significant in the disease process. Animal studies have provided corroborative evidence that antibody can mediate an acute inflammatory response, although the chronic inflammation associated with pulmonary fibrosis is more difficult to reproduce experimentally.

Immunologic processes are obviously involved in many of the diseases addressed within this program area, and it is important to determine the manner by which the lung responds to antigenic stimulation and by which various intrinsic and extrinsic factors

affect immune responses within the lung. Despite this importance, however, only scattered research efforts have been focused on these processes.

The characteristics of antibodies found in the alveoli of normal individuals have been studied with the use of bronchoalveolar lavage in order to better understand the nature and origins of these important proteins. It has been found that immunoglobulin G (IgG) is the predominant antibody in the alveoli. Immunoglobulin M, which is a relatively larger molecule, is strikingly absent from lung fluids; and immunoglobulin A (IgA), the secretory immunoglobulin, is present in moderate concentrations. Evidence suggests that, unlike IgA, IgG is not synthesized locally; it enters the alveolar spaces by transudation from the pulmonary vasculature. These findings are of significance because of earlier suggestions that IgG may have an importance in fibrotic lung disease.

In related studies, serum and bronchoalveolar lavage fluid from rabbits have been analyzed for specific antibodies that form as a result of immunization of the animals by inhalation. These studies showed that inhaled antigen is capable of stimulating both local (pulmonary) and systemic antibody production. IgA is favored, but IgG is also strongly stimulated. Contrary to studies discussed above, however, antibody-producing cells for both classes of antibody are most prominent in local and regional lymph nodes with little evidence of "seeding" of immunologically competent cells to other sites. The lack of IgG production in the lung parenchyma was confirmed. These observations may simply reflect differences between species and reinforce the need to clarify the site of antibody formation in humans.

The concept of antigenic stimulation of the lungs from the vasculature (that is, by blood-borne antigens) has also been pursued, and interesting new findings support this concept. In these experiments, horseradish peroxidase, an antigenic protein that can be visualized in the electron microscope, was injected intravenously into rabbits, and the movement of the protein was followed in the lungs of these animals. In electron micrographs it was seen to move from the vasculature within the bronchus-associated lymphoid tissue (BALT) into the tissue itself and was found located among the lymphocytes. The implication is that other antigens might move similarly and thus come into direct contact with these lymphoid tissues and provide antigenic stimulation to the "resident" lymphocytes.

The relationships between antibody formation and disease processes in humans has also been investigated. Progress has been made in understanding the immunology involved in occupational lung disease produced by trimellitic anhydride (TMA), which is a very reactive molecule used in the conjugation of hydrocarbons in the

plastics industry. TMA is not capable of stimulating antibody production by itself, but when it is autoconjugated to serum protein, it can act as a hapten and thus become immunogenic. It is now apparent that the immunology of this disease is complex, with antibody being directed against neither the hapten (the TMA) nor the protein to which it is coupled, but rather to unique determinants that arise as a result of the interaction between the two. More importantly, it has been discovered that TMA attaches to both IgA and IgG and that antibodies can be found in the serum of symptomatic plastics workers that react with TMA-substituted IgA and IgG. It is, therefore, thought that the immunoglobulins in the respiratory tract are haptenized upon exposure to TMA and that an immune response results that is directed against these altered antibody molecules. The immune complexes that result are, indeed, complex since they become antibodies against antibodies and allow for a great variety of molecular interactions.

Several laboratories have shown that inhaled protein antigen is very effective in stimulating host immune responses but is generally not able to induce pulmonary injury. These findings suggest that in the most basic sense, immunologic responses to inhaled antigens are protective and beneficial. Some other predisposing event or inciting agent appears to be necessary to produce destructive effects, either acute or chronic. Inhaled mitogen, which can stimulate and activate lymphocytes, or prior inflammation with a number of agents can lead to effects ranging from acute interstitial pneumonia to more devastating immune complex reactions, parenchymal necrosis, and pulmonary fibrosis. This combination of findings begins to explain why an agent known to be capable of inducing hypersensitivity pneumonitis or pulmonary fibrosis does so only in a fraction of the individuals exposed to the agent.

Experimental studies with a variety of agents in animal models of interstitial disease have demonstrated the potential for modifying the fibrogenic response. Agents studied include penicillamine, proline analogs, antilymphocyte serum, and nonsteroidal anti-inflammatory drugs.

State of Knowledge in 1982

Establishing the epidemiology of interstitial lung diseases is a lengthy and expensive process, and progress has been slow. Advances have been made primarily in the diseases of known cause, such as those associated with workplace exposures. The importance to public health of information concerning workplace exposures and risk of disease should not be underestimated, since an understanding of dose-response data may lead to the prevention of these diseases. Such information is also essential to establishing

criteria for acceptable minimum risk. The public health problem posed by the interstitial lung diseases should also be considered in combination with the problems of infant and adult respiratory distress syndromes, which have an interstitial component. These syndromes are discussed elsewhere. Clearly, many research findings in one group of disorders are applicable to another group, particularly with regard to basic studies of lung growth, development, and repair, studies of the connective tissues of the lungs, studies of the mediators and controllers of inflammation, studies of lung immunology, and studies of the functions of specific lung cells.

Investigations in the past few years have challenged some previously held concepts, and they have provided new knowledge and approaches for identifying the disease processes and for monitoring the course of disease and treatment of patients. It is as necessary to be precise in defining the degree and extent of cellular and fibrotic reaction as it is in establishing etiology and extent of functional derangement. Roentgenographic data and pulmonary function tests are not reliable for estimating the type of pathologic lesion. With bronchoalveolar lavage, gallium scanning, and immunologic and serologic studies, investigators may be able to distinguish between inflammation and fibrosis. These investigators may also be able to estimate the intensity and extent of inflammation in certain groups of patients. Further research on a large number of patients with a variety of diseases and serial studies in the same patients are needed for determining the sensitivity and specificity of new methods in detecting cellular reaction and monitoring progression of disease and response to therapy. Despite their limitations, roentgenography and pulmonary function testing remain the basis for patient evaluation until these needed investigations are completed.

Program Goals 1982 to 1987

Overall goals are to identify the etiology of interstitial diseases that are still of unknown cause, to obtain in human populations dose-response information on inhalants that are known to have the potential for causing lung disease, and to improve understanding of the mechanisms of lung injury and repair, with special emphasis on the determinants of pulmonary fibrosis. Specific goals for the next 5 years are as follows:

- Identify agents or pathogenetic processes that can initiate or exacerbate interstitial lung diseases, with particular emphasis on immunologic processes.

- Determine the mechanisms by which agents and processes known to cause lung disease produce such injury and, as the lung responds to injury, identify the factors in the repair process that determine restoration of the lung to integrity or result in fibrosis with gross disordering of its structure.
- Develop highly sensitive and specific methods of ascertaining the presence of disease and its activity.
- Improve methods of measuring the delivery to and retention in the lungs of injurious inhalants and other substances.
- Develop improved methods of expressing and understanding dose-response relations in the lungs, including individual variability during the response.
- Apply the new knowledge at the earliest possible time for prevention, early detection, and treatment of interstitial lung diseases.

Research Activities 1982 to 1987

During the last decade, the application of concepts and methods developed by other disciplines to understanding the lungs in health and disease has been unprecedented. This research has resulted in appreciation of the great complexity of the lungs, and especially of their extensive nonrespiratory functions and of the processes that guard their integrity. Although much of this new information is in its formative stages, the linking of new concepts with new technologies, such as fiberoptic bronchoscopy, has put within reach the possibility of exciting advances in clinical practice. It will most likely be profitable in the next 5 years to continue to encourage a multidisciplinary approach to the etiologic, diagnostic, and therapeutic problems posed by the interstitial lung diseases. Indeed, these efforts should be expanded. At the same time, opportunities for studies of clinical application of previously gained knowledge must be pursued. Examples of research efforts include the following:

- Develop and standardize, using in vitro techniques and animal models, methods of screening substances potentially capable of producing interstitial lung disease.
- Continue immunologic and nonimmunologic studies of lung injury and the processes that determine whether the repair process does or does not impair lung integrity.

- Continue to develop animal models whose properties more closely mimic human disease, permitting a broad range of longitudinal studies.
- Develop highly specific, sensitive, noninvasive methods for early detection and precise quantification of injury to the interstitium of the lung. Explore new physiological methods as well as new methods of external imaging, such as radionuclide scintiscanning, positron imaging, and computerized tomographical scanning.
- Validate and establish reliability of newly developed methods of detection, diagnosis, treatment, and prevention by multicenter cooperative efforts. An example is the need to evaluate the importance of bronchoalveolar lavage in the management of interstitial lung diseases.
- Encourage improved studies to establish dose-response relations in human populations because of the complexity of human exposure to inhalants, host-determined variations in clearance, and other confounding factors, almost always present. Specifically, further data are required on deposition, retention, clearance, and tissue persistence of inhaled substances.
- Continue epidemiologic studies, using modern methods of determining dose-response relations, to provide information on the frequency of pulmonary involvement in populations exposed to potentially toxic substances.
- Perform experimental laboratory studies to develop better methods of treating interstitial diseases and, where appropriate, test the new methods in human populations.

Contributors

PULMONARY DISEASES ADVISORY COMMITTEE MEMBERS

Gordon L. Snider, M.D., Chairman
Professor of Medicine and Head,
Pulmonary Medicine Section
Boston University
School of Medicine
Veteran's Administration Medical Center
Boston, Massachusetts

Rejane M. Harvey, M.D.
Dickinson W. Richards Professor
of Medicine
Columbia University
College of Physicians
and Surgeons
New York, New York

Herbert Y. Reynolds, M.D.
Professor of Internal Medicine
Head, Pulmonary Section
Yale University
School of Medicine
New Haven, Connecticut

James A. Merchant, M.D.
Professor, Department of
Preventive Medicine
University of Iowa
College of Medicine
Childrens Hospital
Iowa City, Iowa

Hans Weill, M.D.
Professor of Medicine
Tulane University
School of Medicine
New Orleans, Louisiana

DIVISION STAFF

Hugh B. Stamper, Jr., Ph.D.
Interstitial Lung Diseases Branch
Division of Lung Diseases
National Heart, Lung, and
Blood Institute

7. Respiratory Failure

Contents

RESPIRATORY FAILURE	191
State of Knowledge in 1972	192
Program Goals Through 1982	194
Accomplishments Through 1982	195
Basic Research.	195
Clinical Investigation and Patient Management . .	199
Clinical Trials	206
Prevention, Control, and Education.	207
Development and Utilization of Technology	208
State of Knowledge in 1982	209
Basic Research.	209
Clinical Investigation and Patient Management . .	210
Development and Utilization of Technology	211
Program Goals 1982 to 1987	211
Basic Research.	212
Clinical Investigation and Patient Management . .	213
Clinical Trials	213
Prevention, Control, and Education.	213
Development and Utilization of Technology	213
Research Activities 1982 to 1987	214
Contributors	215

7. Respiratory Failure

The term respiratory failure has different meanings and different therapeutic implications, depending on the underlying disorder. This discussion addresses a particular type of respiratory failure that occurs generally in individuals in whom the lungs were previously normal. This disorder, known as adult respiratory distress syndrome (ARDS), occurs as a final common pathway after numerous etiologies, including nonthoracic trauma and pancreatitis.

ARDS is clinically characterized by diffuse pulmonary infiltration, marked respiratory distress, impaired lung compliance, and hypoxemia that responds poorly to conventional ventilatory assistance. The changes that underlie these manifestations stem from damage to the microvasculature of the lungs, which leads to collapse of alveolar air sacs (atelectasis) and filling of the alveoli with proteinaceous fluid (edema). Both of these events seriously interfere with the capacity of the lungs to oxygenate and remove carbon dioxide from circulating blood.

The lesion of ARDS is pervasive and affects all tissues of the lung. Alveolar epithelium is thickened and gas exchange is impeded. Interstitial layers show proliferation of collagen, and the interstitium is invaded by leukocytes. The release of proteolytic enzymes from sequestered leukocytes can damage lung tissue directly and also can result in further accumulation of leukocytes from chemotaxis. There is evidence that components of the immune system and proteins from the complement and coagulation systems are actively involved in ARDS.

ARDS affects approximately 150,000 adults each year. This number is likely to increase with advances in evacuation and resuscitation of trauma victims and advances in treatment of severe medical and surgical conditions. Survivors become subject to the risk of ARDS.

In patients with chronic bronchitis and emphysema, respiratory failure generally signifies a life-threatening situation that is superimposed on chronic obstructive disease of the airways. In asthma, respiratory failure is said to occur when ventilation can no longer be sustained sufficiently for a tolerable level of alveolar gas exchange. The same generalization about ventilation and gas exchange applies to diffuse interstitial disease, in which the parenchyma of the lungs, rather than the airways, is primarily

affected. In all of the diseases enumerated above, hypoxia with or without hypercapnia is the hallmark of respiratory failure. Moreover, all such patients have antecedent pulmonary disease. The types of respiratory failure noted above are discussed in separate sections of this report under the particular pulmonary disorder.

State of Knowledge in 1972

There was widespread recognition among clinical specialists and researchers that ARDS could occur in a variety of nonpulmonary diseases or insults. This syndrome was first described as an important sequela of trauma during military combat, and it was subsequently recognized as a prominent problem within the civilian population. Debate over terminology ensued, but the term "respiratory distress syndrome" was accepted by the National Heart and Lung Institute Respiratory Diseases Task Force Report in October 1972 to denote a life-threatening condition characterized by noncardiogenic pulmonary edema.

The recognition of ARDS in civilians was often hindered or delayed by a shortage of health professionals highly trained in respiratory care. Limited dissemination of information about this syndrome and a lack of understanding of basic mechanisms further aggravated the problem.

The mechanisms of lung injury that can lead to ARDS were essentially unknown, although it was recognized that various problems such as aspiration pneumonia or severe pulmonary contusion can result in acute respiratory distress. Other events such as shock, fat embolism, or septicemia also included a component of respiratory distress. Thus, a number of conditions could be identified in which ARDS occurs in relation to a specific illness or injury.

Although the physiologic alterations associated with ARDS were easily recognized, little was known about the mechanisms of injury and repair. It was suggested that regardless of the initial causal event, stasis of pulmonary blood flow and relative ischemia injure the lung. Accumulation of leukocytes and release of lysosomal enzymes were thought to be of importance, chiefly on the basis of animal model experiments. The observation that only a small proportion of individuals who sustain certain injuries or illnesses develop ARDS suggested that, in many cases, there are protective mechanisms. Limited data suggested that short exposures to oxygen provide some protection against the oxygen toxicity that follows longer exposure, but the mechanisms underlying this effect were unknown.

Monitoring of arterial blood gases was the best means of early detection of ARDS in 1972, although abnormalities in blood gases were not specific for that condition. Methodology using radioactive tracers, thermodilution, transthoracic electrical impedance, and soluble gas techniques enabled measurement of lung water and protein accumulation. Each of these methods, however, had substantial drawbacks, and none was ready for widespread clinical application.

By 1972, it was also firmly established that the major cause of hypoxemia in adult respiratory distress syndrome is related to blood flow through regions of the lungs that contain little or no gas, either from atelectasis or edema. It had already been demonstrated that the extent of the gas-free areas can be significantly reduced by hyperinflation and especially by providing a higher distending pressure to the lungs at end expiration (positive end-expiratory pressure, or PEEP). The decrease in the extent of gas-free areas improved oxygenation of the systemic arterial blood by effectively reducing the degree of right-to-left shunt through the lungs. The improvement in oxygenation and even the roentgenographic appearance of the lungs were at times so dramatic that it was tempting to assume that the underlying pathophysiologic processes responsible for the respiratory insufficiency were abated. There was a significant possibility, however, that the underlying disease remained the same or even progressed, in spite of the improvement in oxygenation. The answer depended on the relationship of the elevated end-expiratory distending pressure to cardiac and pulmonary hemodynamics and fluid exchange.

The fact that bacterial infections can precipitate or perpetuate ARDS was recognized, and endotoxins were suspected as the cause. It was known that acutely injured lungs are highly susceptible to bacterial infections, and thus, it was thought that altered host defense mechanisms might be a factor.

Since only some patients who survived ARDS developed pulmonary fibrosis, genetic or immunologic differences among individuals were considered as possible factors for variations in susceptibility. However, the processes through which the various types of lung cells were injured and the implications for their functions were still not understood. In 1972, almost nothing was known of the manner by which pathogenetic processes alter the architecture of the lung or the functions of different types of lung cells.

The understanding of the mechanisms of lung injury was clouded in 1972 by a paucity of information about the histopathology of ARDS. Data that were available were obtained from autopsy in patients who had received various forms of therapy. Structural observations using light microscopy suggested that ARDS has many consistent pathologic features regardless of the cause. Moreover,

although pathologic changes evolved through predictable stages, it was not clear to what extent these changes were due to the initial injury, to subsequent phenomena, or to therapeutic interventions. The long-term consequences of ARDS for individuals who survived were not known.

Sophisticated therapy for ARDS was available in 1972, but its use was limited to highly experienced professionals. Treatment focused primarily on ventilatory support and oxygenation. Effective life-support strategies were not in widespread use and were restricted to referral centers. There was much enthusiasm for complicated and expensive life-support systems because of the prevalent belief that lungs of ARDS victims could recover if death did not interrupt the healing process. Extracorporeal membrane oxygenation (ECMO), the ultimate of these life-support strategies, became available during this time, and it afforded the possibility of long-term support of lung function by artificial means.

Bronchopulmonary infection was acknowledged as one of the most frequent life-threatening complications of ARDS, and the potential hazard of contamination of the equipment for respiratory therapy was recognized and largely eliminated. The susceptibility of patients with ARDS to gram-negative infections, however, remained a continual problem, and neither effective prevention nor treatment was available.

Pharmacologic approaches to therapy for ARDS were limited. Administration of albumin and potent diuretics were thought to improve oxygenation, presumably by removing water from the edematous lungs. Experiments with animal models suggested that corticosteroids could improve the chances of survival of fat embolism, gastric acid aspiration, and shock. The mechanism of action of these drugs in ARDS, however, was speculative.

In summary, ARDS was recognized as a feature of many different types of injury or illness, and the mechanisms of lung injury, defense, and repair were not understood. Sophisticated therapy was available, but its use was limited to a few highly skilled professionals in specialized centers. Developing less costly modes of therapy and making them readily available to the medical community were greatly needed. Critical evaluation of devices and techniques for therapy and improved diagnostic monitoring and rehabilitation methods were also needed.

Program Goals Through 1982

The program goals were twofold. One goal was to improve management of ARDS through earlier recognition, more accurate diagnosis, and more effective therapies. This general approach

required study of patients with ARDS. The other goal, which focused on fundamental investigations, was to determine the cause of lung injury and to identify progressive changes that result in respiratory failure.

The following specific goals were established in 1972:

- Expand the research program on acute respiratory failure to ensure improvements in available life-support devices and the development of new ones.
- Develop devices and techniques for efficiently monitoring the respiratory function of patients with impaired lungs.
- Develop improved invasive and noninvasive instruments for analysis of blood and respiratory gas in patients with lung disease.
- Disseminate information to the medical profession and to health care personnel to keep them informed of the latest techniques for detection and therapy.

With respect to basic studies, several additional goals were designated for 1976 through 1982:

- Characterize mechanisms involved in lung injury, and identify precipitating factors that result in acute respiratory failure.
- Determine how lung tissue changes associated with acute respiratory failure can be arrested or reversed.
- Assess the efficacy of current modes of therapy for acute respiratory failure in the adult, and develop more effective supportive and curative procedures.

Accomplishments Through 1982

Basic Research

Because of the realization that improved survival in ARDS depends on a better understanding of the mechanisms of acute lung injury and repair, an important reorientation of the investigation of ARDS occurred between 1972 and 1982. It became generally accepted that mortality could not be reduced solely by developing more sophisticated life-support systems. With this shift in emphasis, multidisciplinary centers of research were established

to elucidate mechanisms involved in lung injury, to identify the precipitating factors that result in ARDS, to determine how degenerative changes can be arrested or reversed, and to develop better methods for the detection and clinical management of acute respiratory failure in the adult.

Animal Models

Many attempts have been made since 1972 to simulate ARDS, or some features of the syndrome, in animal models. The injurious effects of gases or chemicals on the lungs of a variety of small laboratory animals have now been investigated, and pulmonary hemorrhage or trauma have been produced as partial replicas of human ARDS. Among the agents used were paraquat, ozone, nitrous oxide, N-nitroso-N-methylurethane, endotoxins, oleic acid, glass beads, Pseudomonas bacteria, and aspiration of hydrochloric acid.

An example of an animal model of ARDS in use is N-nitroso-N-methylurethane-induced injury in dogs. This model incorporates the essential features of human ARDS, including functional respiratory mechanical changes, although the initial insult is damage to the alveolar epithelium. The administration of the agent causes widespread necrosis of type I and type II alveolar cells and decreases the production of surfactant. The resulting increase in surface tension at the lung surface is associated with increased elastic recoil and decreased lung compliance.

Mediators of Lung Injury

Research has been focused on the importance of leukocytes, platelets, and various plasma enzymes as a mechanism common to ARDS initiated by diverse causes. The activation of the blood complement system is one common denominator in lung injury that has been explored. Activated complement can cause aggregation and sequestration of polymorphonuclear leukocytes in the pulmonary capillary bed. This finding has important therapeutic potential because corticosteroids can inhibit the aggregation of PMN's and the release of their proteolytic enzymes. Another important area of research is the function, in endothelial injury, of proteolytic enzymes or superoxide radicals released from PMN's in initiating ARDS.

Even with extensive studies in patients and animal models the mechanisms for lung injury are not clearly defined. Concentrated efforts of many investigators, however, have helped to confirm certain facts about the basic pathophysiologic changes in ARDS. An important consideration is that many different substances that can be inhaled, absorbed, or infused can cause diffuse lung injury. It seems clear that the pulmonary capillary endothelial

cells are particularly vulnerable to injury by agents either in the circulation or in the alveoli. Various potential mechanisms of endothelial injury remain to be systematically explored. Paramount among them is excess oxygen. The way in which excessive concentrations of inspired oxygen cause lung damage has been studied extensively in recent years. Oxygen toxicity appears to be a balance between the production of free toxic oxygen radicals and the production of enzymes such as superoxide dismutase that neutralize the reactive toxic radicals. In the normal cell, the rate of superoxide formation and the capacity of the dismutase enzyme to effectively scavenge normal levels of free radicals are balanced. An increase in free radical production or a decrease in dismutase activity can lead to the lethal consequences of oxygen toxicity. To date, most studies have concentrated on the activity of the superoxide dismutase. It may be more profitable, however, to concentrate on the event that initiates oxygen toxicity, namely the production of the toxic radicals. It has been found that it is difficult to modify oxygen toxicity pharmacologically with the use of superoxide dismutase. The large size of the dismutase molecule may cause the difficulty. The size prevents it from reaching the cell interior, where most of the free radicals are thought to be produced. If it can be determined what cell types and metabolic pathways are responsible for free radical production in oxygen toxicity, drugs that are specific metabolic inhibitors and that can easily cross cell membranes should be useful in preventing the toxicity. In the course of treatment, enriched oxygen mixtures for prolonged periods injure the lung, and the most sensitive cells appear to be endothelial cells. Other inhaled agents such as NO₂ and ozone cause damage that does not differ fundamentally from that induced by oxygen. Thus, many of the directly acting agents may damage endothelium by a common mechanism.

Indirect injury to the lungs is more difficult to assess, since it presumably results from activation of enzymes or cells in circulation. Microembolization of the lungs by fibrin, platelets, and PMN's is believed to be an important initiating event in ARDS. The major problems are the definition of the temporal sequence of events and the identification of the source of the injurious agents.

A number of clinical and experimental observations suggest that complement activation and granulocyte adhesion result in endothelial damage. PMN's are attracted to injured lungs and sequestered there, but it is still not known if they are primarily responsible for endothelial injury. For example, depletion of PMN's does not prevent the hemodynamic responses and ultrastructural pathology of ARDS in an animal model of E. coli septicemia.

Considerable evidence shows that activation of complement stimulates accumulation of PMN's in the lung, and that by

activating PMN's, this peptide facilitates the adherence of leukocytes to the endothelium. Activated complement can cause aggregation of human leukocytes in concentrations similar to those required for chemotaxis. Generation of superoxide radicals from PMN's has been proposed as one mechanism of endothelial injury. Proteolytic enzyme release, however, is also probably an important factor.

Platelets have also been implicated in the production of ARDS. The aggregation and trapping of platelets within the pulmonary capillary bed can contribute to early damage by the formation of microemboli. It is thought that release of vasoactive mediators causes bronchoconstriction and increased vascular resistance. Platelets may also influence the development of ARDS both directly and indirectly through generation of thromboxane and other products of arachidonic acid metabolism. Since thromboxane formation can be inhibited by aspirin, this avenue of research also has therapeutic potential. In addition, there is some indication that neurogenic factors are involved, possibly in concert with platelet-derived mediators. Platelet products can also damage endothelium and cause increased adherence of leukocytes to the endothelial surface. Finally, the release of factor VIII antigen (von Willebrand factor) into the blood of patients with ARDS raises the possibility that this protein may influence platelet adherence to the pulmonary endothelium and affect the course of the disease. Clearly, the function of platelets is undefined and warrants further exploration.

A recurring theme in studies of endothelial injury is the existence of potential protective mechanisms and the capacity for repair. It is well known that platelets and leukocytes do not adhere to normal undamaged endothelium. This property is probably related to several factors, including the surface of the endothelium, the production of specific factors that block aggregation and coagulation, and the uptake and degradation of thrombogenic materials in the circulation.

One of the most important factors in the antithrombotic potential of endothelium, however, is its ability to synthesize and release prostacyclin. It is now generally accepted that the endothelial antiplatelet-aggregating factor is prostacyclin. Endothelial cells form prostacyclin from arachidonic acid through specific enzymatic steps. Studies of cultured endothelial cells show that prostacyclin can be released by proteolytic enzymes and vasoactive mediators.

The release of prostacyclin by pulmonary endothelium is probably a normal, physiologic function. Experiments with animal models and perfused lungs show that there is a continual spontaneous release of prostacyclin from the lungs. Knowledge of this release has led to the concept that prostacyclin acts as a

circulating hormone to prevent thrombus formation. Vascular cells other than endothelium, however, can synthesize prostacyclin, and there is experimental evidence for enhanced synthesis by smooth muscle cells in injured vessels.

Lung Structure and Function

Various approaches have been attempted to correlate abnormalities in lung structure and function, in both clinical and experimental ARDS. Pulmonary fibrosis, a common sequela in patients who recover from ARDS, has been studied in animal and human biopsy and in autopsy materials to determine the structural characteristics of connective tissue components. Collagen biosynthesis has been studied in animal models of fibrosis and of ARDS. Various models of lung injury, such as those produced by bleomycin and by the aspiration of hydrochloric acid, have been intensively examined for clues to healing and potential reversibility.

Recent clinical studies show that patients with active ARDS have abnormal lipid components in their pulmonary surfactant but that with resolution of the disease, the lipid profile returns to normal. Since the phospholipids from ARDS patients resemble those from neonates with the respiratory distress syndrome, it is thought that this lesion reflects damage to the type II alveolar epithelial cells. The regeneration of type II alveolar cells in the adult syndrome appears to be necessary for resolution, just as maturation of type II cells is required for normal lung development in the neonate.

Clinical Investigation and Patient Management

Early Detection

Identification of diffuse lung injury before the onset of clinically apparent respiratory failure permits early application of preventive and therapeutic measures. Efforts toward early detection have sought to identify lung injury biochemically through changes in certain specific markers and physiologically through alterations in lung water and gas exchange functions.

ARDS is due fundamentally to diffuse injury of the alveolar-capillary membrane. This injury is manifested in animals by loss of the selective permeability of the membrane to macromolecules. That is, blood proteins gain ready access to the interstitial spaces of the lungs and appear in high concentration in lymph draining from the lung. While similar measurements are not possible in humans, the protein concentration of pulmonary edema

fluid in patients with ARDS is greater than in patients with hemodynamic pulmonary edema.

Analysis of fluid obtained by bronchoalveolar lavage has revealed remarkable enzymatic activity in patients with ARDS. Bronchoalveolar fluids from ARDS patients, but not from controls, are capable of cleaving several substrate proteins, including complement and coagulation proteins. Cleavage of at least some of these proteins by lavage fluids can generate biologically active fragments that promote further inflammation. Polymorphonuclear elastase may be significant in activating the mediators of inflammation, although the source of the responsible enzymatic activity remains unsettled. Bronchoalveolar lavage fluid in ARDS is also rich in alpha-1-antitrypsin, the major serum antiprotease. The balance between inhibitors and enzymes can change during the course of ARDS, with the greatest protease activity occurring early in the process. Although it is uncertain whether this biochemistry will provide useful indicators of prognosis and therapy, these findings do indicate that understanding the importance of the mediators will be a critical aspect of future research.

Precipitous decreases in the number of circulating PMN's occur in many clinical forms of ARDS. In experimental models of ARDS, this decrease is caused by massive sequestration of PMN's in the pulmonary vasculature. Although rapid accumulation of PMN's in the lung can follow activation of chemotaxins on the alveolar surface, intravascular sequestration in the lung can also follow activation of humoral factors in the blood. Activation of blood complement by dialysis membranes promptly causes sequestration of PMN's in the lung. Activation of the complement system can be caused by a variety of substances possibly related to ARDS, such as endotoxin or pancreatic enzymes. In the presence of activated complement, PMN's become "sticky" and adhere to vascular endothelium and to each other. Aggregation of PMN's in vitro appears to reflect the degree of complement activation, and the magnitude of PMN aggregation in vitro appears to have predictive value for the development of ARDS in some clinical situations. A central question is whether complement-mediated PMN accumulation is a major cause of lung injury leading to ARDS or is the effect of lung injury caused by other mechanisms. However, lung injury associated with intravascular sequestration of PMN's, which can occur clinically during hemodialysis and in experimental animals during infusion of endotoxin, appears mild and self-limited. Such a finding suggests that this injury alone is insufficient to explain the severe functional and morphologic changes associated with ARDS.

Thrombocytopenia, which occurs when the number of platelets in the blood falls below the normal level, is another common feature of ARDS. Usually a decrease in the number of platelets is not associated with full evidence of intravascular coagulation.

Platelet survival times are shortened, and intrapulmonary sequestration occurs both in patients with ARDS and in animal models of diffuse lung injury. The role of platelet sequestration in initiating diffuse lung injury remains unclear.

The formation of platelet thrombi also plays a role in ARDS. Platelet thrombi are regularly present in the lungs of patients dying of ARDS, and with the use of selective angiographic techniques, intraluminal obstructions have been identified in ARDS victims. Although these vascular lesions appear to be major contributors to the development of pulmonary hypertension in ARDS patients who receive prolonged ventilatory support, their importance to the outcome of ARDS is not yet clear.

Fibronectin is a high molecular weight protein found in blood, in secretions, and on the surface of a variety of cells. ARDS is associated with decreased plasma concentrations of this protein. This change has been postulated to have several effects, including decreased activity of the reticuloendothelial system and leakage of plasma proteins through intercellular junctions. Improved gas exchange has also been noted in ARDS patients after the intravenous administration of fibronectin.

The concentration of factor VIII antigen, presumably released from damaged pulmonary endothelial cells, is markedly increased in the blood of patients with ARDS. Concentrations have been reported to decrease to normal in individuals who survive. It has not been determined whether measurement of factor VIII antigen is a useful predictor of ARDS among high-risk patients.

Once ARDS is clinically evident, changes in arterial gas tensions are one of the best indices of the course of ARDS. Devices are now available which permit continuous monitoring of blood oxygen content with indwelling arterial catheters and transcutaneous electrodes. Blood carbon dioxide content can be inferred from similar transcutaneous measurements and from continuous monitoring of expired gases. These measurements, however, may not reflect respiratory gas exchange in vital organs and tissues.

In experimental models, notably sheep, an increase in pulmonary vascular permeability is manifested initially as an increase in lung lymph flow (that is, before the amount of extravascular water increases). It is unlikely, however, that this degree of lung injury is associated with appreciable deterioration of lung function. The subsequent stages (that is, the accumulation of excess water in the interstitium and alveoli) are apt to compromise pulmonary performance. (Techniques that have been devised to measure the accumulation of extravascular water in the lung are discussed in section 8.) Clinically, accumulation of lung water is detected most readily by changes in the chest roentgenogram. Although the chest roentgenogram provides a useful guide to the

presence of increased lung water, it is insensitive to an early accumulation.

Morphologic Changes

The morphology of diffuse alveolar damage in ARDS evolves through several stages. The stages are similar regardless of etiology. Initially, the findings are dominated by septal and alveolar edema. After 7 to 10 days, infiltration with inflammatory cells and proliferation of resident epithelial cells and fibroblasts occurs. Within 2 weeks, fibrosis is present in virtually all lungs and its extent increases with survival. This fibrosis has a predilection for alveolar ducts as well as the pulmonary interstitium. Ultrastructural examination reveals marked changes in the alveolar epithelium with loss of type I cells leading to denudation of the basal lamina and proliferation of type II cells. Endothelial injury, although obviously present as indicated by leakage of fibrin and erythrocytes, appears less pronounced morphologically than the epithelial injury.

Infection

Nosocomial gram-negative bacillary pneumonia continues to cause serious morbidity and mortality in ARDS. Accumulation of these bacteria in the respiratory tract correlates closely with the binding of bacilli to the surface of respiratory epithelial cells. Few gram-negative bacilli adhere to epithelial cells from healthy subjects, whereas large numbers adhere to cells obtained from seriously ill patients. Similar changes occur in experimental animals after several types of stress. The mechanism underlying this change in cell surface properties appears to involve proteases in secretions and cell surface proteins. Protease activity of upper respiratory secretions, the source of which has not been elucidated, increases rapidly after serious illness and stress. In association with this increased protease activity, fibronectin is lost from the surface of upper respiratory cells. These changes have a high correlation with increased adherence of gram-negative bacilli to these cells. The nature of this binding is not completely understood.

Nosocomial pneumonias are difficult to diagnose accurately in the setting of ARDS since roentgenograms of all patients show lung infiltrates. Most have fever and leukocytosis, and most have pathogenic bacteria in respiratory secretions. Selective sampling of the periphery of the lung using a protected brush technique during bronchoscopy appears to provide a sensitive means of differentiating airway colonization from parenchymal lung infection. Other invasive techniques, such as transthoracic lung aspiration,

have limited application in patients with ARDS who are being mechanically ventilated.

The mortality from superimposed gram-negative bacillary pneumonia in patients with ARDS is high, and it is difficult to estimate accurately because of impreciseness of diagnosis. Available antimicrobial agents that are effective against these organisms in vitro have not had a major influence in reducing mortality in this setting.

Processes of Repair

The collagen content of the lung increases remarkably in patients with ARDS who are maintained on mechanical ventilation for prolonged periods. Total lung collagen may increase twofold to fourfold within 4 weeks of the onset of lung injury. The concentration of collagen, expressed in terms of lung weight or total protein, is often normal or low. The normal or low collagen concentration reflects the large increase in water and noncollagenous proteins in these lungs. It is not clear whether accumulation of collagen is related to the type of lung injury that leads to ARDS. Morphologically, the type of initial injury does not appear to influence whether fibrosis occurs, but all cases with prolonged survival show this change. This observation suggests that treatment modalities may be important determinants of fibrosis. Lungs of patients treated with extracorporeal membrane oxygenation have not differed morphologically from patients treated in a conventional manner with high airway pressures and inspired oxygen concentrations. Both groups of patients, however, received positive pressure ventilation for periods of time, and both groups received supplemental oxygen throughout. Biochemical measurements of lung collagen have shown significant individual differences with increased amounts of collagen present in those subjects who required the greatest positive pressure for ventilation and inspired oxygen concentration. This correlation, however, may reflect only a greater extent of lung damage in patients whose lungs later accumulate collagen.

Information on the biochemistry of the synthesis of collagen has greatly expanded in recent years. It is now possible to inhibit synthesis experimentally in several ways. Beta-aminopropionitrile (BAPN) inhibits the enzyme lysyloxidase, which is required for the cross-linking of collagen chains. In experimental animals, administration of BAPN prevents an accumulation of collagen after acute lung injury. Analogs of proline block the synthesis of collagen by interfering with the necessary hydroxylation. Proline analogs also inhibit an accumulation of collagen after lung injury in animals. In each of these models, however, the alterations in lung mechanics associated with acute lung injury were not affected by inhibition of the formation of

collagen. This finding suggests that the changes in connective tissue may have a relatively minor importance in determining the mechanical behavior of lungs after diffuse alveolar damage.

Clinically, it appears that pulmonary fibrosis that develops during therapy for ARDS may be reversible since in most cases lung volumes return slowly to normal in individuals who survive. Gas exchange improves more slowly, and some patients demonstrate a permanent loss in lung diffusing capacity. Long-term followups are now available on a number of ARDS survivors, and fibrosis has not been reported to progress in any patient who was successfully weaned from ventilatory support.

Treatment

Support of ventilation and gas exchange by mechanical devices remains the mainstay of treatment for patients with ARDS, and such devices have undergone major improvements in the past decade. Those now in use allow clinicians to control lung volume by regulating end-expiratory pressures, the humidity and temperature of inspired gases, inspired flow rates, and the concentration of oxygen, as well as tidal volumes and frequency of breathing. In addition, most devices have suitable alarms that promptly warn of changes in a patient's condition or a malfunction of the ventilator unit. The mode of ventilation can be swiftly adjusted to meet changing clinical needs, ranging from fully controlled mechanical ventilation, to augmentation of the patient's own respiratory efforts, to providing only occasional sighs, and all the while the device maintains a flow of warmed, humidified gas with the appropriate concentration of oxygen. These improvements in ventilator technology have made it possible to adjust the pattern of ventilatory support to the patient's needs rather than force the patient to adapt to a machine. This advance contributes to patient comfort, diminishes the need for pharmacologic intervention, and hastens the patient's recovery. These sophisticated techniques are no longer confined to major medical centers; they are widely practiced throughout the country. Suitable devices are readily available, and information about the management of these patients has been widely disseminated.

The role that excessive concentrations of inspired oxygen play in causing additional lung damage is now generally understood. New ventilatory techniques, especially the application of positive end-expiratory pressure, promote more efficient gas exchange in the lung, which results in a reduction in the concentration of inspired oxygen needed to oxygenate arterial blood. Inexpensive devices for measuring the concentration of oxygen that a patient receives are widely available, and such monitoring is routine in most hospitals.

Advances in ventilatory support have been paralleled by rapid advances in understanding the critically important interactions between the respiratory and circulatory systems. A key aspect of the latter has been the introduction into clinical medicine of balloon-tipped flotation catheters (Swan-Ganz catheters), which can be inserted into the pulmonary artery at the bedside. These catheters have made it possible to distinguish pulmonary edema due to heart failure from that due to the diffuse alveolar-capillary damage of ARDS. In addition, the capability for close monitoring of cardiovascular function afforded by pulmonary artery catheterization has led to more directed therapeutic interventions. However, the use of positive airway pressure to distend lungs and to provide adequate ventilation is associated with problems that thus far appear to be unavoidable. Because positive pressure inflation of the lungs sometimes reduces cardiac output, delivery of oxygen to tissues can be impaired. Positive pressure ventilation of the lungs can also cause various forms of barotrauma, including interstitial emphysema, pneumothorax, and pneumomediastinum. In addition, the possibility that high distending pressures may stimulate the formation of connective tissue in injured lungs has been raised by observations of neonates with hyaline membranes.

Avoidance of high airway pressures may be possible by ventilating the lungs with high frequencies and with very small tidal volumes. This technique has been successful in experimental animals and in limited trials in humans. Devices designed to provide high frequency ventilation are under development, but they currently have several shortcomings compared to conventional ventilators. Furthermore, although this technique is promising, its suitability for long-term maintenance of humans with various forms of ARDS is unknown.

Ventilatory support, oxygen therapy, and cardiopulmonary monitoring are widely applied in a generally uniform fashion. Other therapeutic modalities are not as uniformly applied. For example, the intravenous administration of large amounts of crystalloid-containing fluid during resuscitation of victims of trauma and shock is common, but it has also been identified as an important predisposing factor in the development of ARDS. Albumin and other oncotic agents are administered intravenously in treating ARDS, although neither the theoretical basis nor the clinical benefit of this approach is established. The administration of potent diuretic agents to improve oxygenation in patients with pulmonary edema is sometimes at the risk of adequate cardiovascular performance. Optimal therapy for this complication--whether by infusion of crystalloid, colloid, or pharmacologic agents--has not yet been established.

The importance of corticosteroids in the treatment of ARDS is also unsettled. In animal models, corticosteroids have been shown

to minimize lung injury associated with complement activation and polymorphonuclear leukocyte sequestration, and these findings are supported by in vitro observations of endothelial cells in culture. Administration of corticosteroids promotes survival in patients with septic shock, although not necessarily by preventing ARDS. A prospective trial of corticosteroid therapy in patients with ARDS caused by aspiration of gastric acid revealed no benefit. In large part, the difficulty in interpreting the results of corticosteroid therapy in ARDS stems from the frequent inability of clinicians to define a single cause of ARDS in a given patient. Controlled trials are only of limited usefulness until there are more precise ways of determining the causes of ARDS and there are better defined bases of therapy. Evidence of endothelial cell injury as shown by the presence of factor VIII antigen in the circulation, and evidence of PMN aggregation reflecting complement aggregation may be better than lung function measurements for evaluating therapy.

Pulmonary hypertension occurs in some patients with ARDS. It is usually associated with angiographic and postmortem evidence of arterial occlusions. Despite these findings, pulmonary blood flow can be abruptly increased by infusion of isoproterenol without a concomitant increase in pulmonary arterial pressure. This event suggests that additional vascular bed can be recruited in ARDS. Infusions of vasodilators, such as nitroprusside, lower pulmonary artery pressures in patients with ARDS but usually aggravate the arterial hypoxemia. Thromboxane B₂ has been implicated as one mediator that contributes to the pulmonary pressor response. Clearly, a variety of mechanisms is involved in the pulmonary hypertension associated with ARDS.

Clinical Trials

Beginning at about 1966, research on the development of membrane oxygenators intensified as it became apparent that because of damage to blood components, the bubble-type devices used during cardiac surgery would not be suitable for long-term cardiopulmonary support. Rapid advances were made in membrane and pump technology, and preliminary studies in animals and humans demonstrated the feasibility of long-term cardiopulmonary support with membrane oxygenators. A clinical trial of extracorporeal membrane oxygenation was initiated in 1973 in which the effectiveness of ECMO was compared with conventional therapy for ARDS. Nine participating centers enrolled 90 patients who met predetermined criteria of severe ARDS. These patients were randomized to ECMO groups and control groups, and the latter received optimal therapy by conventional means. ECMO did not significantly alter any physiologic data or outcome, and in each group 90 percent of the patients died. Evaluation of lung tissue revealed only slight differences between the groups. The alterations in respiratory care made

possible by ECMO (lower oxygen concentration, smaller tidal volumes) did not affect the evolution of histopathologic changes, and lungs of all patients who died after 2 weeks or more of treatment demonstrated fibrosis.

From these findings, it was concluded that ECMO is no more effective than less expensive, conventional methods in salvaging patients with severe ARDS as defined by the criteria used in this trial. The lack of modification of lung histopathologic features in ECMO-treated patients suggest that the sequence of changes results from the initial injury rather than from treatment modalities. However, since ECMO-treated patients continued to receive mechanical ventilation and increased inspired oxygen concentrations, albeit at lower levels than the controls, this conclusion is still open to some question.

To define further the spectrum of ARDS, additional data were collected on 490 patients between the ages of 12 and 65 years who required endotracheal intubation and at least 50 percent inspired oxygen 24 hours later. The overall mortality with respiratory failure of these patients was 61 percent. Survivors and nonsurvivors could not be differentiated on the basis of physiologic measurement of lung function or ventilatory data. The major determinants of survival were the failure of organs other than the lungs. Sixty percent of the patients developed evidence of multiple organ failure, which usually followed respiratory failure. Mortality was 40 percent for patients with respiratory failure only, but increased to 54 percent with involvement of one other organ system and 72 percent with two other organ systems. Only 15 percent of the patients died of pulmonary causes exclusively. These data raise important but currently unanswered questions about the mechanisms of injury to nonpulmonary tissues in patients with ARDS.

Prevention, Control, and Education

Since standardized criteria for reporting ARDS do not exist, reliable data on its incidence are not available. Hence, efforts at prevention and control are difficult to evaluate. The topic of ARDS, however, has received broad publicity in the scientific community, and practicing physicians have had ample opportunity to learn about it. The increasing awareness of oxygen injury to the lung and the general availability of ventilators with which oxygen concentrations can be closely controlled have certainly had some impact, but this impact is known only anecdotally.

Development and Utilization of Technology

Advances in technology have facilitated ventilatory and cardiovascular support of ARDS patients, and these sophisticated technologies are widely used. Devices for continuous monitoring of the gas exchange function of the lung by either invasive or noninvasive means are available. It is clear, however, that a critical lack of oxygen in vital tissues may not be detected by monitoring either arterial or expired gases.

The technology available for mechanical ventilation is, at present, moderately sophisticated, and it represents more than 30 years of development. Current state-of-knowledge ventilators incorporate a number of features considered to be ideal, but they fall short of the ideal in many respects. Perhaps the major deficiencies are not in the functional capabilities of ventilators, but in their untoward effects on cardiovascular function and in their damage to lung and airways. If gas exchange could be achieved without the application of high airway pressures, many of the complications of mechanical ventilation could be avoided. The use of high frequency ventilation may prove to be a means of accomplishing this goal, but such use as yet has had only limited evaluation. Conversely, however, many investigators feel that maintenance of lung inflation by application of a continuous positive distending pressure (mechanical ventilation using positive end-expiratory pressure or continuous positive airway pressure with spontaneous breathing) may beneficially influence the natural history of acute lung injury. Thus, further technological applications must await clarification of the influence of the ventilatory pattern on such natural history.

Lung volume measurement can be an important component of the management of patients with ARDS receiving mechanical ventilation. It would be beneficial to know, for example, what level of ventilation or PEEP maintains an optimal functional residual capacity (FRC). With the use of PEEP in particular, the improvement in FRC should be measured against the potentially deleterious hemodynamic effects of increasing PEEP. Despite their potential value, lung volume data have had little use. Further investigation is needed to improve techniques for measuring lung volumes in patients with acute respiratory failure. Three methods need study and validation in this context: radiography, inert gas dilution, and impedance. Computed tomography (CT) scanning may also prove to be useful. Gated-transmission-radionuclide techniques may be another potential approach not previously applied directly to quantification of volume.

Techniques currently in use for measuring the partial pressure of gases in the expired air include mass spectroscopy, infrared devices for CO₂, and fuel cells for O₂. It would appear that breath-by-breath analysis of expired gas in the intensive

care unit is not limited by technology but by lack of knowledge related to the value of such monitoring.

Transcutaneous P_{O_2} electrodes are available for use on infants. Their use on adults, however, is not as practical because mature skin circulation varies so greatly with the clinical state that transcutaneous P_{O_2} may be much lower than arterial P_{O_2} . Present sensors for use in adults are uncomfortable, unreliable, and expensive. For certain critically ill patients, invasive sensors for measuring arterial or mixed venous P_{O_2} , P_{CO_2} , and pH would be useful; their development should be encouraged, but cost and reliability must be considered.

The viability of cells depends upon a continuing supply of oxygen; however, the methods for assessing oxygen delivery that are currently in clinical use are at best crude and indirect. All measurements, whether they are from single samples of arterial or mixed venous blood, from continuously recording intra-arterial electrodes or fiberoptic catheters, from transcutaneous oxyhemoglobin saturation monitors, or from transcutaneous P_{O_2} electrodes, no matter how accurate, provide only very limited information regarding O_2 supply to cells. Moreover, there is increasing evidence that data derived from measurements of blood O_2 and acid-base variables can provide misleading or inaccurate interpretations and can result in errors in patient care. The value of measurements of intracellular events as modified by O_2 depletion and acid-base disturbances is obvious. Among methodologies that show promise are the monitoring of neural events, nuclear magnetic resonance (NMR) to evaluate cellular bioenergetics, measurements of intracellular pH, spectroscopic evaluation of mitochondrial redox states, and positron imaging to examine the outcome and kinetics of metabolic substrates.

State of Knowledge in 1982

Basic Research

ARDS is a syndrome characterized by proteinaceous pulmonary edema, severely deranged gas exchange, and morphologic evidence of diffuse alveolar-capillary damage. ARDS may be caused by identifiable exogenous agents or by endogenous mechanisms. The latter appear to be capable of increasing lung injury caused by the exogenous agents. At present, treatment is predominantly supportive and survival rates are low; however, promising new techniques for early detection and early intervention are available. Among them are methods for detecting lung endothelial damage and the presence of mediators in the circulation that can cause this injury.

Basic research relevant to clinical ARDS has focused upon identification of factors responsible for endothelial injury and exploration of the mechanisms of injury. There is now considerable interest in the normal, protective mechanisms operative in vascular endothelium and in how the events that lead to ARDS may affect such mechanisms. There is currently no fully accepted method for the quantitative measurement of endothelial injury either in vivo or in vitro. Several methods have used release of endothelial-associated markers, such as angiotensin I converting enzyme or factor VIII antigen as indicative of endothelial damage. Other methods involve uptake of labeled nucleotides or metabolites. Release of labeled ions or intracellular enzymes is also used. Each method, however, has its drawbacks. Further, methods suitable for use in an in vitro system are not always applicable to the in vivo situation.

The identification of plasma-derived mediators and the definition of their roles in ARDS remain an important area for investigation. Demonstration of coagulant activity in lavage fluids from patients with ARDS and activation of related enzyme systems have stimulated research into this previously unexplored mechanism. The finding that deposition of fibrin in the lungs of ARDS patients contributes to the defect has stimulated interest in components of the fibrinolytic system. An important gap, however, remains between basic and clinical studies of ARDS; many of the animal models and in vitro systems may differ significantly from the human disease.

Clinical Investigation and Patient Management

Despite advances in knowledge about many pathogenic processes, the treatment of ARDS remains largely supportive, and major controversies persist over optimal fluid and pharmacologic management of these patients. Bacterial superinfection of the lungs of ARDS patients remains a common and serious complication for which neither adequate prevention nor effective treatment is available.

While the mortality of ARDS remains high, exceeding 80 percent in some carefully defined patient groups, only 15 percent of patients die of exclusively pulmonary causes. Long-term followup studies of ARDS survivors indicate that lung function improves and becomes normal with time in most of these patients. These findings support the concept that, despite the acute effects of ARDS on lung function and morphology, highly effective reparative processes can restore function if the patient does not succumb to the initial insult.

Development and Utilization of Technology

The two technological advances that have had the greatest impact on the care of patients with ARDS have been the development of the current type of volume ventilators and the use of the balloon-tipped catheter to measure intrapulmonary vascular pressures. Both technologies are in widespread use. Devices to continuously monitor the gas tensions in the arterial blood, either by indwelling arterial catheters or transcutaneous electrodes, are now available. While these devices may minimize the need for repeated arterial punctures in some settings, their general applicability in monitoring patients with ARDS remains to be established. Similarly, devices for continuous analysis of expired gases are now available and are utilized in some centers. These devices are well suited for the evaluation of changes in individuals with normal lungs but have limited applicability in diseases such as ARDS in which marked regional inhomogeneity in gas exchange may exist. Several approaches to the measurement of lung water have been developed to quantify pulmonary edema. Of these, the double-indicator dilution technique using iced indocyanine green, in which heat is the diffusible indicator, is the most thoroughly tested. Equipment for making this measurement is now commercially available. It is not certain, however, that the measurement provides valuable information when alveolar flooding and gross pulmonary edema have occurred. This is the stage at which most patients with ARDS are identified.

The critical area of oxygen delivery to tissues and the biochemical events that occur as a result of a lack of tissue oxygen have recently received attention. Several technological developments may be particularly useful for the evaluation of tissue oxygenation of patients with ARDS. These include NMR; measurements of intracellular pH; noninvasive monitoring of cytochromes a, a₃, and flavoproteins; direct measurement of oxygen in tissues; and monitoring of various neural events. The feasibility of each of these technologies has been demonstrated in laboratory environments, but none has yet had a rigorous clinical evaluation.

Program Goals 1982 to 1987

The overall goal is to reduce death and disability from respiratory failure. The immediate goals remain similar to those of 1976 through 1982--namely, to improve the diagnosis and management of ARDS through better understanding of the structural, biochemical, and physiologic mechanisms of acute lung injury. Specific examples are given below.

Basic Research

Mechanisms of Injury Culminating in ARDS

- Encourage further development of animal models of the human disease.
- Explore biochemical and physiologic mechanisms of acute injury in the gas exchanging areas of the lung.
- Examine the possibility of common denominators in the pathogenesis of ARDS.
- Develop effective pharmacologic approaches for the treatment of ARDS.
- Determine the mechanisms of O₂-induced injury and determine their applicability to patients.
- Determine the interaction between oxygen and the injured lung.

Early Detection of ARDS

- Develop simplified methods for the early detection of diffuse alveolar-capillary injury.
- Establish markers for the process of injury in order to screen for patients at risk for ARDS and to monitor patients with the disease.

Processes of Repair

- Clarify the mechanisms involved in inflammation and repair of lungs damaged by ARDS.
- Develop methods for monitoring the activity of processes of repair in lung epithelial, endothelial, and interstitial connective tissue cells, especially in the gas exchanging areas of the lung.
- Develop strategies for enhancing the resolution of the disease through normal processes of repair.

Clinical Investigation and Patient Management

- Develop strategies that prevent or inhibit diffuse alveolar-capillary damage.
- Examine current therapeutic modalities for the treatment of ARDS.
- Explore optimal methods for ventilatory assistance and O₂ therapy in ARDS.
- Compare different types of medical interventions, such as steroid therapy, with other pharmacologic agents that influence the inflammatory and resolution stages of ARDS.
- Determine the contribution of nosocomial infections to ARDS, and develop methods for early detection and intervention of such infections.

Clinical Trials

- Evaluate the role of promising anti-inflammatory agents in arresting or reversing the injury process.
- Determine the optimal approach for weaning ARDS patients from ventilatory therapy.
- Establish optimal O₂ concentrations, and standardize O₂ therapy in ARDS.
- Compare high frequency ventilation with conventional ventilatory assist devices.

Prevention, Control, and Education

- Develop means of disseminating information about the causes and management of ARDS.
- Apply epidemiologic principles to the identification of patients at greatest risk of developing ARDS so that efforts at screening and early detection can be sharply focused.

Development and Utilization of Technology

- Develop techniques to measure more accurately the status of oxygen delivery at the cellular level.

Research Activities 1982 to 1987

Detection of lung injury by the assay of endothelial-associated markers in blood or the use of NMR to detect a lack tissue oxygen are examples of research areas that need emphasis.

Prevention of ARDS, or treatment in its earliest stages, appears to offer the most realistic hope of reducing morbidity of this process. Epidemiologic techniques should be used to identify groups of patients at the greatest risk so that early detection and preventive strategies can be applied in a cost-effective manner. This task is simplified by the fact that ARDS often develops in patients already hospitalized for other reasons.

Limited fundamental and clinical studies suggest that high frequency ventilation may avoid many of the purported complications of ventilatory support by conventional means. Because little is known about short- or long-term harmful side effects of high frequency ventilation, much more information is required before it is placed in general use for ARDS patients.

Contributors

PULMONARY DISEASES ADVISORY COMMITTEE MEMBERS

Alfred P. Fishman, M.D., Chairman
William Maul Measey Professor of Medicine
Director, Cardiovascular Pulmonary
Disease Division
University of Pennsylvania
School of Medicine
Philadelphia, Pennsylvania

Edward H. Bergofsky, M.D.
Professor of Medicine
Head, Pulmonary Disease Division
Department of Medicine
State University of New York
Stony Brook, New York

Marlys H. Gee, Ph.D.
Associate Professor of
Physiology
Thomas Jefferson University
Jefferson Medical College
Philadelphia, Pennsylvania

Alice R. Johnson, Ph.D.
Associate Professor of Pharmacology
University of Texas
Southwestern Medical School
Dallas, Texas

CONSULTANT

Waldemar G. Johanson, Jr., M.D.
Professor of Medicine
Department of Medicine
The University of Texas Health
Science Center at San Antonio
San Antonio, Texas

DIVISION STAFF

Carol E. Vreim, Ph.D.
Chief, Interstitial Lung
Diseases Branch
Division of Lung Diseases
National Heart, Lung, and
Blood Institute

8. Pulmonary Vascular Diseases

Contents

PULMONARY VASCULAR DISEASES.	217
PULMONARY EDEMA.	217
State of Knowledge in 1972.	217
Program Goals Through 1982.	218
Accomplishments Through 1982.	218
State of Knowledge in 1982.	225
Program Goals 1982 to 1987.	226
Research Activities 1982 to 1987.	228
PULMONARY HYPERTENSION	229
State of Knowledge in 1972.	230
Program Goals Through 1982.	231
Accomplishments Through 1982.	232
State of Knowledge in 1982.	235
Program Goals 1982 to 1987.	235
Research Activities 1982 to 1987.	237
PULMONARY THROMBOEMBOLISM.	238
State of Knowledge in 1972.	238
Program Goals Through 1982.	240
Accomplishments Through 1982.	240
State of Knowledge in 1982.	243
Program Goals 1982 to 1987.	244
Research Activities 1982 to 1987.	245
CONTRIBUTORS	246

8. Pulmonary Vascular Diseases

Pulmonary Edema

Pulmonary edema is a pathological state in which fluid accumulates outside the vascular system of the lung. Edema can develop if pulmonary capillary hydrostatic pressure exceeds plasma oncotic pressure, lymphatic drainage is impaired, or pulmonary capillary permeability to plasma proteins is increased. Since lymphatic dysfunction is rarely the primary cause of pulmonary edema, pathogenic mechanisms are generally classified as being hydrostatic or nonhydrostatic. Hydrostatic edema is caused by pulmonary capillary or left atrial hypertension. Nonhydrostatic edema, usually referred to as "permeability edema," is caused by an increase in the permeability of the vascular endothelium to proteins.

State of Knowledge in 1972

By 1972, basic studies had shown that edema fluid accumulates in the connective tissue surrounding blood vessels and airways before the occurrence of alveolar flooding. Many studies used animal models of hydrostatic pulmonary edema to test methods for detecting and quantifying edema fluid in the earliest manifestations of the disorder. These methods included: double-indicator dilution techniques to estimate pulmonary blood volume and extravascular lung water content; gas uptake studies to estimate tissue volume, using nitrous oxide or acetylene with breath-holding maneuvers or using carbon monoxide with a rebreathing apparatus; studies of small airway function such as measurement of closing volume as a functional index of pulmonary congestion and edema; and electrical impedance measurements through the chest wall to estimate changes in lung water content.

Ten years ago, little was known of the permeability characteristics of the vascular endothelium and airway epithelium. A study using tagged erythrocytes and albumin had shown that protein accumulates in the lungs of dogs with alloxan-induced pulmonary edema. This observation suggested that the detection of protein rather than water might be a more sensitive indicator of early pulmonary edema. Indicator dilution methods had shown that while the normal pulmonary endothelium is relatively impermeable to sodium ions, injury is associated with a significant loss of

sodium from the vascular bed. With the use of tracer proteins, electron-microscopic methods had shown that the epithelium is a more restrictive barrier to protein flux than the endothelium. Membrane selectivity based on molecular size had also been suggested by the higher content of albumin relative to globulin in edema fluid. Further electrophoretic characterization of proteins in plasma, lymph, and edema fluid had not been performed.

Some evidence had suggested that histamine and other endogenous vasoactive compounds or that the autonomic nervous system might be important in the pathogenesis of acute pulmonary edema. In 1972, this area of research was in early stages.

In summary, research in pulmonary edema prior to 1972 was focused on developing reliable methods to detect pulmonary edema early enough in its course to be amenable to treatment. It was well understood that a thorough knowledge of the biochemical, structural, and dynamic properties of the lung and of its vasculature and fluids was a prerequisite to the development of such techniques.

Program Goals Through 1982

Early detection of pulmonary edema is the key to effective patient management, just as increased fundamental knowledge is the key to effective prevention. The overall goals through 1982 were to elucidate the mechanisms that underlie the development of pulmonary edema and to use this knowledge in improving the diagnosis and treatment of the disorder.

Specific goals included:

- Characterize the dynamics of fluid and solute exchange in the pulmonary circulation.
- Determine the role of vasoactive mediators in the pathogenesis of pulmonary edema.
- Develop noninvasive techniques for early diagnosis and continuous monitoring of pulmonary edema.

Accomplishments Through 1982

Most of the major advances in understanding the pathophysiology of pulmonary edema have come in the last 10 years. In this short time, much of the information that has been obtained has been transferred to the clinical setting primarily through

training programs and through continuing education programs for physicians and also through clinical investigations. The development of animal models of several forms of lung vascular injury is an important part of this progress. Many of the accomplishments occurred because scientists with varied specialties including physiologists, anatomists, biochemists, pharmacologists, hematologists, pathologists, internists, and surgeons have worked together in multidisciplinary research programs.

Basic Research

Pathogenesis of Pulmonary Edema. The major obstacle to research in this field has been the lack of an animal model that would provide a continuous measurement of water and protein flux from the microvasculature into the pulmonary interstitium. In the early 1970's, methods were devised in unanesthetized sheep to collect lymph that drains from the pulmonary interstitium. Experiments using this model were the first to show that water and protein are normally filtered through the pulmonary endothelium and that the endothelium restricts flux of different proteins on the basis of molecular size and configuration. It is now known that development of pulmonary edema of either hydrostatic or nonhydrostatic (permeability) origin is characterized by an increase in lymph flow accompanied by elevated pulmonary vascular pressures in hydrostatic edema or near normal pressures in permeability edema. The essential difference is in the lymph protein concentrations relative to those of plasma protein. With hydrostatic edema, lymph protein concentrations fall as left atrial pressure increases. Over a wide range of left atrial pressures, lung vascular protein permeability is apparently unaltered. With permeability edema, lymph protein concentrations are essentially constant as lymph flow increases; thus, vascular permeability to water and proteins is increased. Lung vascular permeability can be increased by such agents as alloxan, alpha-naphthyl thiourea, and endotoxin, and by such conditions as pulmonary thromboembolism, oxygen toxicity, acute myocardial ischemia, and barbiturate and opiate overdose.

The availability of reliable animal models that give reproducible results in experiments on lung vascular injury has made it possible to design studies to develop therapeutic methods to prevent increases in protein permeability or to lessen the severity of lung injury. In general, studies of the etiology and pathogenesis of lung vascular injury have followed one of three approaches. The first approach is focused on the possible role of endogenously produced vasoactive compounds that alter lung vascular permeability. In this group of studies, prostaglandins and other products

of arachidonic acid metabolism were shown to be mediators of pulmonary hemodynamic alterations that accompany many forms of lung vascular injury but not to be primary mediators of changes in vascular permeability. The exception may be a group of arachidonate products known collectively as leukotrienes. Although methods of measurement of these compounds and specific antagonists and agonists are not yet available, some evidence suggests that leukotrienes may mediate increases in vascular permeability. Histamine has been shown to increase permeability in both the pulmonary and bronchial circulations. Furthermore, diphenhydramine, a drug that blocks H₁ histamine receptors, alleviates but does not eliminate endotoxin-induced lung injury. Serotonin, which is a potent pulmonary vasoconstrictor, has no apparent effect on protein permeability. Bradykinin causes formation of gaps in bronchial vessels, but its effects on lung vascular permeability are not clear. Many of these vasoactive compounds are either added to or removed from the circulation by metabolic functions of pulmonary endothelial cells. In some instances, changes in endothelial metabolic functions parallel or precede changes in vascular permeability. These events suggest that measurement of some of these metabolic functions may prove useful in early diagnosis of lung vascular injury.

The second approach concerned the possible importance of the central nervous system. Both clinical and experimental evidence have suggested that neurogenic pulmonary edema probably results from increased lung vascular permeability. Several laboratories have attempted to develop animal models of this syndrome, and the models have provided data that support this conclusion. The etiology, however, may involve transient, severe increases in left atrial pressure that may be sufficient to cause "pore" stretching and increase protein clearance. Although some data exist to support this view, it is difficult to separate hemodynamic effects from permeability changes. The availability of a highly reproducible and sensitive method for measuring the perfused vascular surface area would aid interpretation of data in this type of study.

The third approach to studying lung vascular injury focused on the role of formed elements of the blood in mediating increases in vascular permeability. The elements of interest include platelets, leukocytes, and the complement system. Platelet aggregation in the lung causes a transient increase in permeability by an unknown mechanism. Sequestration of leukocytes in the pulmonary circulation may cause endothelial injury. Both thrombocytopenia and leukopenia can result from complement activation in response to sepsis or to exposure to extracorporeal blood circulating systems. "Dialysis" lung injury has been related to leukopenia after complement activation induced by exposure of blood to artificial membranes.

It is of interest that platelets and leukocytes are sources of arachidonic acid metabolites including leukotrienes. After clot formation, fibrin degradation products produced during clot lysis resolution may also result in lung injury.

Investigators have also studied the relationship between accumulation of edema fluid and changes in lung mechanics. These studies have shown that decreases in lung compliance may be explained by a decrease of gas volume as alveoli fill with edema fluid. Changes in airway resistance during septic lung injury may be mediated by prostaglandins, since increases in airway resistance are blocked by inhibitors of formation of prostaglandin.

Mechanisms of Clearance of Lung Edema Fluid. There are two extravascular lung compartments in which edema fluid accumulates, the interstitial space and the alveolar space. Studies of animal models have shown that when edema fluid is allowed to accumulate, the same protein concentrations are found in lymph, interstitial fluid, and alveolar fluid. Therefore, the alveolar epithelium, which is normally a very effective barrier restricting protein flux, is somehow changed with alveolar flooding to permit essentially free protein flux. Other studies have shown that when the extravascular compartments are filled with fluid, they function as slowly exchanging sumps for edema fluid. Furthermore, the lymph flow from the lung is not directly related to the amount of edema fluid stored in the extravascular sumps. From these data, it seems unlikely that lymphatics are a primary route for removal of accumulated extravascular protein. Protein solutions instilled into normal lungs are cleared by a process that removes water and concentrates the protein in the alveolar space. Other data show that clearance of large protein molecules like fibrinogen from the alveolar space depends on catabolism to smaller protein units. These results may provide the first insight into why severe pulmonary edema can result in interstitial fibrosis and formation of hyaline membranes.

Clinical Investigation

The occurrence of lung injury and edema is reportedly increasing in many different clinical conditions. Many of the animal models of hydrostatic and permeability edema have been developed to aid the clinical understanding of the disease. Although much progress has been made, the problems of early diagnosis and treatment of lung vascular injury and pulmonary edema are urgent ones. Furthermore, the morbidity and mortality associated with lung vascular injury are high.

Measurement of Edema Fluid Volumes. Early in the decade, the primary approach taken for early detection of pulmonary edema was measurement of extravascular lung water content. Theoretically, a very sensitive measure of lung water content would be useful as an early diagnostic tool, and sequential measurements of lung water would provide data for evaluating the efficacy of treatment. Several methods have been tested to measure lung water content. Double indicator dilution techniques, using a variety of indicators, have been studied extensively. Indicator dilution methods are quantitative, and they can yield a great deal of hemodynamic data. In addition, if nonradioactive tracers are used and blood is rapidly returned, measurements can be made in rapid succession. This method, however, is invasive, and the sensitivity and reproducibility in estimating gravimetrically measured extravascular lung water content vary widely.

Several other approaches are less invasive, but generally less quantitative. The distribution of inhaled soluble gases has been used for many years as a measure of lung water content. The method is relatively safe, noninvasive, and sensitive. It could serve as an early indicator of minimal edema fluid accumulation if there were baseline data, but unfortunately, in the clinical setting, such data are usually not available. Major disadvantages of this method include a lack of uniformity both in the performance of breathing maneuvers by patients and in interpretation of data obtained in patients with alterations in the distribution of ventilation. Lung function tests such as functional residual capacity, dynamic lung compliance, and nitrogen washout have been shown to change during development of acute pulmonary edema. Changes in lung function, however, are not specific for pulmonary edema. Application of this approach is also limited to those clinical situations in which patients can perform breathing maneuvers.

Recently, some investigators have begun developing sophisticated nuclear imaging methods to measure lung water. The technique lacks sensitivity, and, even at this early stage of development, significant improvement seems unlikely. Furthermore, this method could be used only in major medical centers because of the elaborate equipment and facilities required for data analysis.

The most commonly used tool for detection of lung edema fluid is the chest roentgenogram. This method has many advantages: it is currently in widespread use; it is noninvasive; it permits sequential measurements; it can be used in critically ill patients; it shows the relative distribution of edema fluid; and it is much less costly than methods that use high technology. Primary disadvantages of the chest roentgenogram

include its relative insensitivity to small increases in edema fluid volume and the qualitative nature of the data it provides.

In summary, the accuracy and sensitivity of currently available methods for measuring lung water in humans is about 20 to 30 percent. Although these methods permit the study of gross pulmonary edema, they do not represent a significant improvement over the standard chest roentgenogram, particularly when cost, invasiveness, and applicability in critically ill patients are considered. The chest roentgenogram remains the single most useful tool for early detection of pulmonary edema; however, it is clear from extensive experimental data that accumulation of edema fluid in the lung is not an early indication of lung vascular injury, nor is removal of lung edema fluid an early indication of reversal of the process by which edema develops. Lung water measurement in humans is an important method for assessing the rate of clearance of edema fluid, not for early detection of lung vascular injury or hydrostatic edema.

Clinical Assessment of Lung Vascular Injury. During the 1970's, the theoretical basis for early diagnosis of pulmonary edema shifted from the measurement of lung water content to the measurement of lung vascular permeability. There are several reasons for this subtle but important change of emphasis. It has been well established that significant increases in protein permeability occur with no measurable increase in lung water content and that reliable early detection of lung vascular injury contributes markedly to improved patient management. Increases in pulmonary vascular pressures or decreases in plasma oncotic pressure that are easily tolerated in a normal lung, for example, can lead to catastrophic pulmonary edema in a lung with increased permeability to protein. In addition, measurement of vascular permeability can discriminate between hydrostatic and permeability edemas. It is also now known that measurement of lung water content does not provide information on the pathogenic process.

Two methods have been developed to measure changes in lung vascular permeability in humans. The first is an indicator dilution method that uses urea as the restricted solute. Unfortunately, it has all of the limitations inherent in indicator dilution methodology. Its major problem is an inability to measure the surface area of the perfused vascular bed contributing to solute exchange. In the second method, external detectors are used to measure the transvascular flux of radiolabeled proteins. Although this method is effective in carefully controlled experimental conditions,

its applicability to the clinical setting has not been demonstrated conclusively.

A recent development in the detection of lung injury is based on experimental evidence that plasma concentrations of vasoactive substances that are either synthesized or cleared by the lung change during early stages of endothelial injury. The measure of the clearance of tracer quantities of serotonin by pulmonary endothelial cells is used as an index of cell injury. This method may be limited, however, by its dependence on changes in vascular surface area. Further research relating metabolic and barrier functions of endothelial cells will undoubtedly enhance the understanding of the pathogenesis of lung injury. Whether this approach will yield new, sensitive methods for early diagnosis of lung vascular injury is not as certain.

Patient Management. The availability of experimental models of lung vascular injury has led to an expanding literature on the efficacy of different therapeutic approaches. The major accomplishments in this area have been an increased reliance on cardiopulmonary monitoring as a guide to therapy, and the demonstration that overzealous use of oxygen and fluids is detrimental and that techniques to assist the ventilation of stiff lungs are often helpful.

As yet, no method exists to reverse an increase in vascular permeability once it is established. However, with the increase in understanding the etiology and pathogenesis of lung vascular injury, there are reasons to expect that mortality and morbidity can be reduced. Severe alterations in hemodynamics and lung mechanics accompany many forms of vascular injury. In some instances, these changes are mediated by the release of endogenous vasoactive compounds. The pharmacologic means to inhibit or attenuate acute hemodynamic and ventilatory alterations are available and include drugs now in clinical use. Because of these developments, there is the option of treating some of the changes that contribute to impaired lung function without reversing the increase in vascular permeability. Another helpful development is the availability of an improved data base that includes the incidence of lung vascular injury in many predisposing conditions in combination with morbidity and mortality statistics. This data base makes it possible to develop preventive approaches to therapy and management.

This discussion thus far has centered on preventive measures and on treatment modalities that depend on early recognition of the condition. There are major problems of a different order of magnitude for the patient with severe lung injury leading to respiratory failure. In the severely ill patient,

the prolonged oxygen therapy that is required to maintain systemic oxygen delivery is in itself a cause of lung vascular injury. The lack of animal models of respiratory failure once hindered progress in this critical area. This obstacle has now been largely overcome, and there should be significant advances during the next decade, although respiratory failure will continue to present a difficult challenge.

Prevention, Control, and Education

Improvements in patient management that have contributed to prevention of acute pulmonary edema secondary to other disorders have come largely through educational efforts directed toward physicians. There is little doubt that such programs have had some impact in lowering the incidence and severity of acute pulmonary edema secondary to trauma, burn, and sepsis. Physician education must remain a high priority in order to maintain the advantages gained through past efforts.

Development and Utilization of Technology

Nuclear magnetic resonance is a method currently being tested for its applicability in detecting increases in lung water content. The major limitation of this technology is cost even if it proves highly successful. Computerized tomography is another possible method, but it has the same limitation. Radionuclide imaging using positron emission tomography has also been proposed as a possible method to detect increased lung water content and the distribution of lung edema fluid.

Epidemiology

Pulmonary edema is a disorder that occurs secondary to other diseases. For this reason, and because sensitive methods for detection of edema fluid or lung vascular injury are not available, studies of mortality attributed to edema have not been made. Edema resulting from increased lung vascular permeability, however, is generally included in the adult respiratory distress syndrome. It is clear that complete epidemiologic studies require sensitive, safe diagnostic methods that are not yet available.

State of Knowledge in 1982

Reliable and reproducible animal models for many forms of acute lung vascular injury have been developed. It has been

clearly established that lung vascular injury is characterized by increased endothelial water and protein permeability. Animal models have been used to study the role of endogenous vasoactive compounds, the central and peripheral nervous systems, and the formed elements of the blood in mediating increases in lung vascular permeability. Therapeutic approaches have been developed to inhibit some of the hemodynamic and ventilatory changes that accompany many forms of acute lung injury. However, reversing an increase in vascular permeability once the condition is established remains a difficult challenge.

Although much new information on the metabolic functions of pulmonary endothelial cells has emerged in the last decade, the relationship between endothelial metabolic and barrier functions remains to be clarified. A definition of this relationship will provide important leads to early detection of lung vascular injury as well as new approaches to patient management. Understanding the relationship between the formed elements of the blood and the pulmonary vasculature, particularly leukocytes and endothelial cell functions, could stimulate the development of improved approaches to prevention and management. Progress will depend on interdisciplinary efforts to understand the biochemical and physiologic functions of pulmonary endothelial cells and formed elements of the blood.

Studies designed to determine the mechanisms for removing edema fluids from the alveolar space have provided intriguing new evidence for the importance of epithelial cells in the clearance of edema fluid proteins. The epithelial cells seem to have complex and discriminating transport and metabolic properties. Understanding epithelial cell functions is a necessary step in treating chronic effects of severe pulmonary edema such as interstitial fibrosis and the formation of hyaline membranes.

Program Goals 1982 to 1987

Rapid developments in research on the pathophysiology of pulmonary edema have led to a new sophistication in the questions being asked and in the methods for addressing them. Continued progress will depend on multidisciplinary approaches to problems of cell functions and interactions in the pulmonary circulation. The primary objective of the research program is to prevent acute pulmonary edema and lung vascular injury. Overall program goals include improved diagnosis and management of pulmonary edema through a better understanding of structural, biochemical, and physiologic mechanisms of lung vascular injury. Specific goals include:

Basic Research

- Determine the morphologic equivalent of increased protein permeability of the vascular endothelium.
- Determine the possible relationship between changes in metabolic functions of pulmonary endothelial cells and changes in lung vascular permeability.
- Examine the relationship between acute pulmonary hemodynamic and ventilatory alterations and the severity of lung vascular injury in the many disorders associated with the development of pulmonary edema.
- Determine the interactions between formed elements of the blood and pulmonary endothelial cells that lead to increased protein permeability, altered lung endothelial metabolic functions, and lung vascular injury.
- Determine the mechanisms responsible for reversal of lung vascular injury and for endothelial repair.
- Determine the function of the alveolar epithelium in the removal of fluid and protein from the alveolar space.

Clinical Investigation and Patient Management

- Develop methods for early detection of lung vascular injury.
- Establish methods to identify patients at risk for developing acute pulmonary edema and the pharmacologic means to prevent lung vascular injury in these patients.

Clinical Trials

- Evaluate the role of anti-inflammatory agents in the prevention and reversal of lung vascular injury.
- Evaluate the efficacy of treatment of acute pulmonary hemodynamic and ventilatory changes that accompany many forms of lung vascular injury.

Prevention, Control, and Education

- Incorporate into the training of radiologists the assessment of lung water content in chest roentgenograms.

- Determine the significance of measuring lung water content in relation to patient management.

Research Activities 1982 to 1987

The program has three primary objectives: develop suitable diagnostic methods for detection of lung vascular injury and of edema fluid accumulation; design and implement clinical trials to treat acute hemodynamic and ventilatory changes that accompany many disorders associated with pulmonary edema and lung vascular injury; and establish education programs to enable physicians to fully utilize the progress being made in patient management.

Diagnostic Methods

A significant improvement in existing diagnostic sensitivity may be obtained by incorporating into the training of radiologists the assessment of lung water content in chest roentgenograms. Detection of lung water is important diagnostically, but not necessarily as a means to determine pathogenesis. An equally important caveat is that normal lung water contents do not eliminate the possibility of an ongoing edemogenic process. A consensus should be sought concerning the necessity of measurement of lung water and its applicability to patient management.

The detection of lung vascular injury is of considerable importance in prevention of clinically apparent pulmonary edema and in management of patients with pulmonary edema. It is important, however, in the development of methods for detecting lung vascular injury that a method be widely adopted if the goals for prevention and management are to be met.

Clinical Trials

Basic and clinical research in the last decade has provided the foundation for the design of clinical trials to test the efficacy of treating acute hemodynamic changes associated with diseases such as pulmonary thromboembolism that predispose to pulmonary edema.

Education of Physicians

Expanded efforts are needed to increase the understanding of pulmonary edema in medical schools and in residency training programs. The establishment of respiratory intensive care units

in major medical centers provides facilities and faculties that aid this effort. Programs are needed to strengthen the effort.

Pulmonary Hypertension

Pulmonary hypertension and right ventricular failure are common sequelae to almost all chronic respiratory diseases. In some disorders, such as the respiratory syndromes arising from structural abnormalities of the thorax, pulmonary hypertension and cor pulmonale occur relatively early in the course of the disorder, and most patients die in right ventricular failure. In other disorders, such as chronic obstructive pulmonary disease (including chronic bronchitis and emphysema, and cystic fibrosis), mild to moderate degrees of pulmonary hypertension often exist for many years accompanied by sporadic exacerbations in the course of a superimposed acute respiratory illness. In still other disorders, particularly pulmonary thromboembolism, acute pulmonary hypertension leading to right ventricular failure can occur suddenly and be life-threatening. A list of respiratory disorders commonly associated with pulmonary hypertension appears in table 13.

Table 13. Respiratory Disorders Associated With
Pulmonary Hypertension

Obstructive pulmonary diseases (chronic bronchitis and emphysema; cystic fibrosis)
Diffuse interstitial diseases (interstitial fibrosis and granuloma)
Thromboembolic diseases
Pulmonary edema
Adult respiratory distress syndrome
Unexplained pulmonary hypertension (primary pulmonary hypertension)

State of Knowledge in 1972

In 1972, there was unreliable reporting not only of pulmonary hypertension and cor pulmonale but also of the respiratory diseases leading to them. It was difficult to determine the prevalence of chronic obstructive pulmonary disease, the most common precursor of pulmonary hypertension and cor pulmonale. Estimates of the incidence of right ventricular hypertrophy in COPD suggested that from 35 to 48 percent of patients afflicted by this respiratory disorder manifested enlargement of the right ventricle as part of the natural history of their lung disease. An extrapolation of this percentage to the entire U.S. population yields an incidence of about 123,000 cases of pulmonary hypertension and right ventricular overload (cor pulmonale) and failure. Pulmonary thromboembolism was another serious problem for which there were no reliable statistics. These estimates did not consider the incidence of pulmonary hypertension arising from other respiratory disorders (table 13). In 1972, the importance of pulmonary hypertension could be assessed only qualitatively, but enough information was available to indicate that the disease posed a considerable problem.

Pulmonary Hypertension and Cor Pulmonale

By 1972, investigators were beginning to understand many of the mechanisms that lead to pulmonary hypertension and right ventricular failure in patients with respiratory disease. An increase in pulmonary vascular resistance was recognized to be the common denominator. Uncertainties were centered around the mechanisms responsible for an increase in pulmonary vascular resistance. Three likely mechanisms were being investigated: destruction of the small vessels of the lung by disease, as in emphysema; intrinsic disease of the pulmonary vascular bed, as in pulmonary thromboembolism and primary pulmonary hypertension; and increased vasomotor activity. Of the three, the increased vasomotor activity offered the brightest prospects for therapeutic intervention because of its potential reversibility. The most promising approach to the other categories of disorders was prevention, such as therapy to prevent emphysema or anticoagulation to prevent peripheral thrombi from reaching the lungs.

The effects of hypoxia on pulmonary circulation were under intensive investigation by 1972. Of the stimuli known to raise pulmonary arterial pressure, hypoxia proved to be the most powerful one. It was an exceedingly common cause of pulmonary hypertension, especially in individuals with COPD and alveolar hypoventilation (underbreathing) from any cause. It was also shown that acidosis reinforces the pressor effects of hypoxia. As a result of these observations, it was therapeutically possible to relieve hypoxemia and acidosis in the management of respiratory

failure due to chronic respiratory disease. The lessons learned from this experience have been put to practical application in the home, the hospital, and the medical intensive care unit in managing patients with hypoxemia.

By the end of 1972, pulmonary hypertension could be diagnosed only by cardiac catheterization. This invasive technique was always associated with some discomfort and, on rare occasion, with mortality. Because of its nature, it was impractical for serial determinations of pulmonary artery pressure and for screening. A noninvasive approach to determining pulmonary arterial pressure was clearly needed.

Recognizing the importance of hypoxia in eliciting pulmonary hypertension, investigators undertook intensive studies to determine the mechanism by which hypoxia causes pulmonary vasoconstriction. The mechanism, however, remained elusive. It could not be settled with assurance whether the vasoconstriction was the direct result of hypoxia acting on the pulmonary vessel wall or was the result of an intermediary action such as the release of vasoactive substances from mast cells in the lungs. These and related studies did provide insights into the mechanisms that control pulmonary circulation. Adrenergic and histamine receptors in pulmonary vessels were identified, and beginnings were made in elucidating the electrophysiologic and contractile properties of pulmonary vascular smooth muscle. Prostaglandins were found to influence pulmonary vascular behavior, and attempts were begun to distinguish the actions of the different prostaglandins on the pulmonary circulation. Prostaglandins A and E proved to be potent pulmonary vasodilators, whereas prostaglandin F_2 was found to be a potent vasoconstrictor. Explanations were begun of interrelationships between the various receptors and external stimuli, such as hypoxia and acidosis. These insights into the vasomotor behavior of the pulmonary circulation were to have important implications for the advent of pulmonary vasodilator therapy.

Program Goals Through 1982

The many beginnings outlined above shaped the program goals from 1972 to 1982, which emphasized the need to develop animal models of pulmonary hypertension, characterize pulmonary vascular smooth muscle, develop noninvasive methods to measure pulmonary artery pressure, and establish referral centers for pulmonary hypertension patients.

Specific goals were:

- Develop animal models of pulmonary hypertension and cor pulmonale.

- Determine the structural, biochemical, and physiologic characteristics of pulmonary vascular smooth muscle, and the roles of hypoxia and vasoactive mediators in the etiology of pulmonary hypertension.
- Develop noninvasive techniques for early diagnosis and continuous monitoring of pulmonary hypertension.
- Establish referral centers for patients with pulmonary hypertension to serve as a focus for the development of clinical trials to assess current and new antihypertensive agents.

Accomplishments Through 1982

Basic Research

Central to the understanding of pulmonary hypertension and to its proper management is clarification of the mechanisms by which blood pressures can be influenced in the pulmonary circulation. Until 1972, the major emphasis was on hypoxia, hypercapnia, and acidosis, and on the response of the lung to these stimuli. Since then, it has been recognized that more elaborate control mechanisms exist, and investigations have been pursued at ultrastructural, biochemical, and molecular levels. In particular, humoral and neural influences on the behavior of the pulmonary blood vessels are being systematically explored.

Humoral agents can arise locally (such as prostaglandins and bradykinin) or can be carried to the lungs by the bloodstream (such as norepinephrine), and they are of potential importance. Considerable attention has been paid to the biogenic amines, the vasoactive polypeptides, and the prostanoids. It appears from these studies that a wide variety of circulating substances, such as norepinephrine, histamine, serotonin, and dopamine is processed by the lining of the pulmonary blood vessel.

The vessel wall may also be strongly influenced by products that are generated and released locally, such as the contents of pulmonary mast cells. Many potent vasoactive substances from mast cells, for instance, can influence vascular calibers in the lung. Another promising direction of research has been the delineation of the role of the calcium ion, both as a direct influence on pulmonary vascular calibers and as an intermediary--that is, as part of the effector mechanism during acute hypoxia. During the past decade, the use of such modulators in combination with pharmacologic blocking agents has helped to identify the types of receptor mechanisms involved in pulmonary vasomotor control and to

provide information about the organization of the system of control with respect to the different (and often opposing) neural, humoral, and direct vasoactive influences.

Clinical Investigation and Patient Management

An important advance in the management of pulmonary hypertension during the past decade was the widespread use of vasodilator agents in an attempt to lower pulmonary arterial pressure. These agents were originally used in patients with primary (unexplained etiology) pulmonary hypertension and later in patients with secondary pulmonary hypertension. The impetus for the use of these drugs was their proven efficacy in treating systemic hypertension and heart failure. Because the vasodilator drugs have a variety of influences, a clear picture of the pathophysiology of pulmonary hypertension is necessary. As a result, the new pharmacologic agents have already proved valuable not only for lowering pulmonary vascular pressures but also for providing fresh insights into the mechanisms of pulmonary hypertension.

Important distinctions have also been made between the effects of acute and chronic hypoxia on the pulmonary circulation and the effects of the adaptive changes that follow chronic exposure to high altitude. One provocative concept that has emerged is that pulmonary vasomotor reactivity may be genetically influenced. This proposed type of predisposition makes it possible to explain high altitude pulmonary edema and much of the clinical experience with variability in the pressor response to acute exposure to high altitude.

Clinical Trials

As noted above, hypoxia is the most powerful stimulus known for pulmonary hypertension. In certain types of chronic pulmonary disease, notably obstructive pulmonary disease, hypoxia is chronic and unremitting, and contributes significantly to pulmonary hypertension. Results from a clinical trial suggest that oxygen therapy can reverse pulmonary hypertension and is optimally effective when it is delivered continuously rather than nocturnally. The potential reversibility of pulmonary hypertension in hypoxemic disorders also raises the possibility of avoiding cor pulmonale and right ventricular failure, which are dread complications of severe and unremitting pulmonary hypertension.

Development and Utilization of Technology

The lack of a noninvasive method to measure pulmonary artery pressure has seriously hampered the early detection of patients

with chronic pulmonary hypertension and their subsequent therapeutic management. At the present time, measurements of pulmonary artery pressure by invasive cardiac catheterization are required to establish an initial diagnosis. Such measurements have to be repeated periodically to ascertain the effectiveness of therapy or the occurrence of side effects. Repeated cardiac catheterization is not only uncomfortable; it is potentially hazardous, especially in patients who often have exceedingly high pulmonary arterial pressures. For these reasons, emphasis has been placed in the past few years on the development of noninvasive techniques to measure pulmonary arterial pressure.

Several theoretical approaches to noninvasive measurement of pulmonary arterial pressure have been proposed, one of which consists of appraisals of the pulmonary valve closure sound. In this technique, the accentuation of valve closure, which is apparently proportional to pulmonary arterial pressure, is quantified. In a second technique, right ventricular relaxation time is measured. The higher the pulmonary arterial pressure, the more time is required for the ventricle to relax. A variety of approaches to hemodynamic modeling that permits measurement of instantaneous flow, vessel diameter, and pulse wave velocity has also been suggested. In another proposed approach ("bubble"), the bursting of bubbles of uniform size as they flow through the pulmonary artery is detected ultrasonically.

Modifications of the indicator-dilution technique have also been widely adopted for the measurement of pulmonary blood flow in humans in a serial fashion. Among the more popular indicators is cool saline, especially in the intensive care unit. At present, noninvasive techniques for determining pulmonary blood flow are not available and are as urgently needed as techniques for non-invasively measuring pulmonary arterial pressure.

Epidemiology

Pulmonary hypertension not only arises from a multitude of causes, but it also is generally a complication or end result of other conditions. Epidemiologic observations to date have been concerned primarily with underlying causes. In addition, diagnosis of pulmonary hypertension is difficult and often retrospective. It is therefore not surprising that few data are available on pulmonary hypertension. However, mortality statistics concerning pulmonary heart disease (cor pulmonale) have shown that, although cor pulmonale is not a common cause of death in certain parts of the United States, it is often a contributing factor. Experiences in other countries, notably the United Kingdom, suggest that the incidence parallels that of chronic bronchitis.

An epidemic of primary pulmonary hypertension, presumably related to the anorexigenic drug aminorex, has been reported from Switzerland, Austria, and Germany. Although the disorder is uncommon in the United States, it is of great theoretical importance. To explore fully the characteristics of the entity and to define the effectiveness of pharmacologic agents, a national registry with 35 participating centers has been established.

State of Knowledge in 1982

Interest in exploring all aspects of the regulation of the pulmonary circulation remains high for at least two major reasons: the mechanisms that regulate pulmonary vasomotor tone have been elucidated, and pharmacologic agents that may relieve pulmonary hypertension have been developed. A key area for exploration is the mechanism by which hypoxia (and acidosis) elicits pulmonary vasoconstriction. Other research areas include the role of the various humoral mediators in setting and increasing tone and of neurohumoral interactions.

Answers to these questions will clearly require the clarification of the physiology of normal and hypertrophied pulmonary vascular smooth muscle. Electrophysiologic and biomechanical studies of pulmonary vascular smooth muscle are still in early stages. Studies of receptor physiology are only beginning, particularly with respect to how neurohumoral mechanisms exert their influences. Exploration of the role of calcium ions in setting pulmonary vascular tone has begun, but the complicated nature of normal and abnormal pulmonary vascular smooth muscle presents formidable problems.

Important initial steps have been made in developing animal models. The hypoxic pulmonary hypertension that occurs at high altitude has been replicated in a variety of species at sea level. Another model of pulmonary hypertension involving predominantly intimal proliferation (monocrotaline) rather than medial hypertrophy (hypoxia), which is being developed in a variety of species, holds considerable promise. Other approaches, including immunopathologic disorders of the lungs in animals, are also under way.

Program Goals 1982 to 1987

Results of research of the past decade have strongly suggested that early detection and proper adjustment of pulmonary arterial pressure is clinically desirable in patients with chronic obstructive pulmonary disease and in those with predominant disease of the pulmonary circulation alone. To accomplish such

goals, fundamental research, clinical investigation and trials, and epidemiologic studies will be required. Program goals for the next 5 years include:

Basic Research

- Characterize more fully the pulmonary vascular smooth muscle with respect to electrophysiologic and pharmacologic properties and to receptor function in the normal and pulmonary hypertensive states.
- Elucidate the roles and interactions of humoral agents in setting pulmonary vascular tone and responsiveness to major physiologic states, such as acute and chronic hypoxia.
- Analyze the structural alterations produced in animal models of pulmonary hypertension and in patients with pulmonary hypertension.
- Evaluate the efficacy of vasodilators, calcium blockers, and cyclooxygenase inhibitors in experimental pulmonary hypertension of various etiologies.

Clinical Investigation and Patient Management

- Maintain a clinical registry of cases of primary pulmonary hypertension to characterize the natural history, pharmacologic responsiveness, anatomical-ultrastructural features, and epidemiologic and familial occurrence.
- Determine more precisely the contribution of pulmonary hypertension and right heart failure toward morbidity and mortality in COPD.
- Increase efforts to develop an accurate measurement of pulmonary arterial pressure and pulmonary blood flow by noninvasive methods.

Clinical Trials

- Utilize the results of the patient registry in primary pulmonary hypertension to devise a clinical trial of the proper pharmacologic agent or combinations of agents to reduce pulmonary arterial pressure.
- Extend such a clinical trial to other forms of pulmonary hypertension, namely that associated with COPD, collagen vascular disease, lymphangiomyomatosis, and others.

Development and Utilization of Technology

- Maintain efforts to develop a noninvasive approach for the measurement of pulmonary arterial pressure and pulmonary blood flow.

Epidemiology

- Survey the relation between pulmonary hypertension and high altitude and the possible role of genetic variation (using, among others, histocompatibility assessment techniques) in the development of pulmonary vascular hypertrophy.

Research Activities 1982 to 1987

Some of the research activities generated by the program goals will be extensions of present work, while others represent new directions. Among those envisaged for the next 5 years are:

- Validate current animal models of pulmonary hypertension (produced by hypoxia or drugs) as reasonable analogs of the hypertrophy process in at least some types of human pulmonary hypertension.
- Determine the interrelations between the structural changes of the blood vessel during development of chronic pulmonary hypertension and the corresponding electrophysiologic and pharmacologic properties.
- Continue current efforts to characterize the pharmacologic receptor system and electrophysiologic properties of the normal pulmonary circulation and the relation of these properties to important physiologic states, such as hypoxia, which not only affect this circulation acutely but also may be factors in the development of chronic pulmonary hypertension.
- Maintain a registry of patients with primary pulmonary hypertension not only to clarify this disorder but also provide the basis for a clinical trial involving pathology, pharmacology, and genetics.
- Initiate, on the basis of the experience with the registry, a clinical trial of pharmacologic intervention in primary pulmonary hypertension, and perhaps other pulmonary hypertensive states.

- Extend efforts to develop noninvasive methods for determining both pulmonary arterial pressure and blood flow.

Pulmonary Thromboembolism

A pulmonary embolus is a thrombus that has dislodged and impacted in the pulmonary vascular bed. The embolus usually comes from thrombi originating in peripheral veins or the right atrium. When death occurs in pulmonary thromboembolism, it is almost always due to obstruction of the pulmonary circulation. In the presence of congestive heart failure or preexisting pulmonary thromboemboli, even relatively small quantities of emboli can produce right heart failure, but in patients with normal cardiovascular and respiratory systems large quantities of emboli are necessary to cause right heart failure. Bronchoconstriction and small airway closure may increase the severity of the symptoms. Pulmonary infarction results if there is enough interference of blood supply to produce tissue necrosis. Because the lung has a dual blood supply, most pulmonary thromboemboli do not cause infarction.

The incidence of pulmonary thromboembolism in the United States is estimated to be 500,000 cases per year. Pulmonary thromboembolism is suspected of causing at least 50,000 hospital deaths each year in the United States and is a contributing factor in another 100,000 patients. Of these deaths, approximately 30 percent occur within 1 hour of the onset of symptoms, and approximately 60 percent occur in patients in whom the diagnosis has not even been suspected. Only approximately 7 percent of the deaths occur in patients for whom the diagnosis has been made and therapy has been instituted. Therefore, there is a great need for a simple, inexpensive screening test to detect asymptomatic deep venous thrombosis before the development of pulmonary thromboembolism.

State of Knowledge in 1972

Diagnosis

Nontraumatic methods that could be employed on a wide scale for accurate diagnosis of pulmonary thromboembolism were not yet available, and the development of such methods was considered essential for assessing the efficacy of treatment and prophylactic measures. It was additionally recognized that the development of better diagnostic procedures would be substantially aided by the

availability of a suitable primate model of peripheral venous thrombosis. Such a model would also require a comprehensive study of fibrinolysis, platelet function, and coagulation.

The development of radioactive scanning procedures to tag the clot within the lung as a possible "hot spot" was also thought to be important. Investigators considered that studies of fibrin degradation products also warranted further investigation as a diagnostic procedure. The widescale use of ^{125}I -labeled fibrinogen was not possible in the United States at that time because of the risk of transmitting hepatitis.

Therapy

Although other agents had been tried, heparin appeared to be the most satisfactory anticoagulant in therapeutic use. It had the disadvantages, however, of being effective only by injection and of sometimes being erratic in controlling anticoagulation. In 1972, a approach being studied was the use of fibrinolytic agents. The first phase of a cooperative trial of urokinase as its agent had not demonstrated efficacy in terms of either morbidity or mortality, but the obstructing thrombus underwent lysis more rapidly in the urokinase group than in the heparin control group. Heparin, however, remained the treatment of choice pending proof that thrombolytic agents had a place in therapeutic management.

A great need for the development of accurate diagnostic tests for pulmonary thromboembolism that would be suitable for widescale studies in high-risk groups was recognized in 1972, and when they became available, clinical trials of heparin in high-risk groups were to be undertaken.

Prevention

In 1972, the major approach to the problem of pulmonary thromboembolism was toward prevention. Because clots coming from thrombosis of the deep veins of the lower extremity are the main source of pulmonary thromboemboli, measures for preventing deep venous thrombosis in high-risk patients were studied.

Heparin in low doses was thought to hold considerable promise as a prophylactic measure in high-risk groups. Several studies of heparin treatment in surgical patients indicated reduced incidence of postoperative venous thrombosis. A controlled study using ^{125}I -labeled fibrinogen scanning to detect venous thrombosis, for example, reported a reduction of incidence from 41 to 15 percent in postoperative patients. Early data from another controlled

study of about 200 high-risk patients showed that venous thrombosis (again detected by ^{125}I -labeled fibrinogen) occurred in 3 percent of the treated group and in 25 percent of the placebo group.

In another approach to prophylaxis, drugs that suppress platelet function were investigated for the prevention of postoperative venous thrombosis. Controlled studies of aspirin and dipyridamole did not show a beneficial effect. An uncontrolled study of aspirin that revealed a beneficial effect had to be interpreted with caution, for it was likely that aspirin masked the clinical signs of venous thrombosis. The entire area of platelet-inhibiting drugs was under intensive study at that time. Theoretically, these agents were expected to have an effect on arterial circulation and perhaps not on venous circulation, but further evaluation was needed before firm conclusions could be drawn.

Various methods of preventing vascular stasis during surgery were investigated for their effect on occurrence of postoperative venous thrombosis. While the results were varied, there was some evidence that if stasis is prevented by postoperative use of a pulsatile flow system, venous thrombosis can also be prevented.

Program Goals Through 1982

The goals emphasized the need for a noninvasive diagnostic technique and for improved therapeutic regimens.

Specific goals were:

- Develop and evaluate noninvasive tests for the diagnosis of pulmonary thromboembolism that can be used in a wide range of patients.
- Evaluate clot-preventing and clot-dissolving drugs in individuals at high risk for pulmonary thromboembolism.
- Develop an animal model of peripheral venous and pulmonary thromboembolism.

Accomplishments Through 1982

Diagnosis

Ventilation-perfusion scans and pulmonary angiography, in combination with medical history and clinical findings, have

become the most commonly used methods to diagnose pulmonary thromboembolism. Ventilation-perfusion scans are very accurate in confirming or excluding pulmonary thromboembolism in the patient who does not have an infiltrate, but unfortunately, 50 to 75 percent of patients with angiographically documented pulmonary thromboemboli have infiltrates on their chest roentgenograms. Thus, a firm decision about the presence or absence of pulmonary thromboembolism cannot be reached with ventilation-perfusion scans alone in over one-half the patients. Pulmonary angiography is the most accurate diagnostic tool available, but it also has its limitations. The technique is time consuming and expensive, it carries some risk, and it cannot reliably detect emboli that are less than 2.5 mm in diameter and that cause complete occlusion of the vessel in which they lodge. In addition, a single injection with a pulmonary angiogram does not give adequate detail of vessels, particularly at the base of the lung. Use of multiple injections with augmented techniques, such as balloon-occlusion angiography or magnification roentgenography with subselective injections, are necessary to exclude pulmonary thromboembolism. Furthermore, clots form readily on the outside of most catheters unless they are specially treated with heparin. Thus, during the process of multiple injections to detect pulmonary thromboemboli, it is possible to form clots on the outside of the catheter, dislodge them, and then detect them.

A promising new method, inhaled ¹⁵O-labeled carbon dioxide, allows very accurate detection of pulmonary thromboemboli in humans by serial positron imaging, but because the method requires a highly specialized technology, it is not available at most centers.

Another approach to diagnosing pulmonary thromboembolism is the "hot spot" imaging technique. Substances such as indium-labeled platelets that adhere to thromboemboli have been successfully labeled with isotopes and are detected as "hot spots" by external scintillation detectors.

As screening tests for pulmonary thromboembolism, a positive finding of both fibrin degradation products and soluble fibrin complexes adds strong support to the diagnosis, and a negative finding in both of these tests practically excludes pulmonary thromboembolism. Unfortunately, many patients suspected of having pulmonary thromboembolism have only one of the tests positive.

Treatment

Two primary approaches to the treatment of deep venous pulmonary thromboembolism include anticoagulant therapy for the prevention of clot formation and recurrence, and the dissolution of clots with the use of thrombolytic agents. Other approaches

include pulmonary embolectomy and vena caval interruption, but these methods are usually attempted only when thrombolytic or anticoagulant therapy is unsuccessful.

Although far from ideal, the most commonly used anticoagulant continues to be heparin. When it is used in a manner that prevents recurrence, major bleeding complications occur approximately 15 percent of the time. Heparin has also been shown to be one of the most common causes of iatrogenic diseases in hospitalized patients. Recent studies have also compared the relative advantages and disadvantages of intermittent and continuous administration of heparin. Continuous administration appears to be associated with less major bleeding complications than intermittent administration, but only in patients at high risk for bleeding. However, continuous administration is associated with a significantly higher recurrence rate than intermittent administration.

Oral warfarin and heparin have been compared for use in long-term outpatient anticoagulant therapy. Oral warfarin was associated with bleeding complications in approximately 30 percent of the patients over a 6-month period. Low-dosage subcutaneous heparin was associated with significantly fewer bleeding complications than warfarin. There appears to be some question as to the effectiveness of both warfarin and heparin in preventing recurrence on a long-term basis.

After the acute phase, both venous and pulmonary thromboemboli usually dissolve. Available data suggest that most patients achieve partial to complete lysis within 2 to 6 weeks; however, it is clear that in some patients lysis fails to occur. Data are lacking to explain the factors that determine the rate and extent of lysis. A national multicenter trial has shown that thrombolytic therapy with standard doses compared with heparin therapy greatly accelerates the rate of lysis of pulmonary thromboemboli in the first 24 hours. Thrombolytic therapy, however, has not been shown to reduce mortality significantly. Thrombolytic therapy is approved by the Food and Drug Administration for pulmonary thromboembolism that is massive or results in unstable hemodynamics, and the two agents used in the United States are streptokinase and urokinase. In thrombolytic therapy, absolute contraindications and measures to minimize bleeding must be strictly observed.

Prevention

The prognosis for patients who survive initial treatment for pulmonary thromboembolism is good. The overall recurrence rate is approximately 5 percent, and patients rarely die because of the recurrence. The recurrence rate is even lower when the precipitating cause is no longer present.

A debate about the prevention and management of venous and pulmonary thromboembolism arises from continued uncertainty regarding its natural history. This uncertainty is a consequence of the multiple and inadequately performed or validated clinical techniques currently used to detect and follow the course of venous thromboembolism. Clearly, it is not possible to determine accurately the risk:benefit ratio of prophylactic or therapeutic regimens unless the disorder itself can be reliably detected and its course followed.

The debate is heightened by the fact that venous and pulmonary thromboembolism occurs in patient subpopulations that differ substantially with regard to age, the presence of significant coexistent cardiopulmonary (and other) diseases, and the presence of other factors that can influence the risk:benefit ratio of diagnostic, prophylactic, and therapeutic approaches. These variables alter not only the sensitivity and specificity of diagnostic techniques but also the acute and chronic pathophysiology of the disorder itself. Thus, there is not a homogeneous population of patients with venous and pulmonary thromboembolism; rather, there are subpopulations that must be addressed individually.

A large international multicenter trial has shown beyond reasonable doubt that low-dose subcutaneous heparin is effective in preventing both fatal and nonfatal pulmonary thromboemboli after major surgery. Also, another preventive measure is the use of elastic stockings to prevent deep venous thrombosis after elective knee surgery.

State of Knowledge in 1982

There remains a need for an improved noninvasive method for making the initial diagnosis of pulmonary thromboembolism, for studying the natural history of the disease, and for evaluating therapeutic regimens. At the present time, pulmonary angiography remains the "gold standard" for diagnosis. The use of ventilation-perfusion scans needs to be more carefully evaluated with the use of pulmonary angiography as the standard. A promising diagnostic technique is the development of imaging agents that adhere to venous and pulmonary thromboemboli and produce a positive image scan. The availability of animal models of experimental pulmonary thromboembolism has helped in the development of this technology. In addition, radioimmunoassays for products released during platelet aggregation, thrombin activity, and plasmin activity have been developed that may prove useful in the design of screening tests for pulmonary thromboembolism.

Anticoagulant therapy with heparin needs to be improved. With current methods, it appears impossible to avoid recurrences

that are without a significant number of major bleeding complications. A better form of outpatient therapy for prevention of recurrence needs to be developed. Though effective in preventing recurrence after initial episodes, oral warfarin therapy is associated with significant bleeding complications and is frequently ineffective in patients with recurrent venous thromboembolism.

Thrombolytic agents have been investigated extensively, but their role remains uncertain. Thrombolytic therapy needs further investigation and evaluation.

Program Goals 1982 to 1987

Diagnosis

- Improve screening tests for pulmonary thromboembolism.
- Evaluate ventilation-perfusion lung scans in comparison with pulmonary angiography utilizing standardized methods and criteria for the lung scans.
- Develop an imaging agent for the diagnosis of pulmonary embolism by a positive image lung scan technique, and compare it with pulmonary angiography in animals and humans.
- Develop specialized equipment to visualize pulmonary thromboemboli in the intensive care unit.
- Evaluate emerging techniques in the diagnosis of pulmonary thromboembolism.
- Refine techniques to identify the source of pulmonary thromboemboli.

Treatment

- Develop and evaluate better agents for an antithrombotic effect without associated bleeding complications.
- Develop and evaluate better thrombolytic agents that can lyse the fibrin in pulmonary emboli without lysis of fibrinogen and other coagulation proteins.
- Compare the relative effectiveness of thrombolytic therapy and anticoagulant therapy in patients with pulmonary thromboemboli.

Prevention

- Improve treatment for prevention of recurrent venous thrombosis and pulmonary embolism by identifying abnormalities of platelet function, coagulation, and spontaneous fibrinolysis, and by directing therapy toward the specific abnormality.
- Identify etiologic factors relating to recurrent venous thrombosis and pulmonary embolism.
- Study the natural history of pulmonary thromboembolism in medical patients as compared to surgical patients.

Research Activities 1982 to 1987

The major research activities in the next few years should be focused on improving the diagnosis and treatment of venous and pulmonary thromboembolism. Studies are expected that will define the sensitivity, specificity, and risk of diagnostic procedures. Prophylactic and treatment strategies will be further developed and evaluated in defined subpopulations of patients. Studies will also be conducted to better define the natural history of the disease and to identify etiologic factors related to its recurrence.

Contributors

PULMONARY DISEASES ADVISORY COMMITTEE MEMBERS

Alfred P. Fishman, M.D., Chairman
William Maul Measey Professor of Medicine
Director, Cardiovascular Pulmonary
Disease Division
University of Pennsylvania
School of Medicine
Philadelphia, Pennsylvania

Edward H. Bergofsky, M.D.
Professor of Medicine
Head, Pulmonary Disease Division
Department of Medicine
State University of New York
Stony Brook, New York

Marlys H. Gee, Ph.D.
Associate Professor of
Physiology
Thomas Jefferson University
Jefferson Medical College
Philadelphia, Pennsylvania

Alice R. Johnson, Ph.D.
Associate Professor of Pharmacology
University of Texas
Southwestern Medical School
Dallas, Texas

CONSULTANT

James E. Wilson, III, M.D.
Professor of Medicine
Chief, Pulmonary Section
Louisiana State University
Medical School
New Orleans, Louisiana

DIVISION STAFF

Carol E. Vreim, Ph.D.
Chief, Interstitial Lung
Diseases Branch
Division of Lung Diseases
National Heart, Lung, and
Blood Institute

Barbara Liu
Prevention, Education and
Manpower Branch
Division of Lung Diseases
National Heart, Lung, and
Blood Institute

9. Research Training and Development

Contents

RESEARCH TRAINING AND DEVELOPMENT.	247
State of Pulmonary Personnel in 1972.	247
Program Goals Through 1982	252
Accomplishments Through 1982.	252
Research Career Development Award.	254
National Research Service Award.	254
Pulmonary Academic Award	267
Young Investigator Pulmonary Research Grant.	271
National Pulmonary Faculty Training Program.	272
NHLBI Clinical Investigation Award	274
Pulmonary Personnel in 1982 and Goals 1982 to 1987.	275
Contributor	280

9. Research Training and Development

State of Pulmonary Personnel in 1972

At the beginning of the 1970's, the United States faced a serious shortage of personnel in the pulmonary field. Chest diseases had been increasing in importance, both as a principal cause of morbidity and mortality and as a great source of socio-economic cost; yet fewer and fewer young physicians were seeking training in the pulmonary subspecialty. Historically, the major focus of the chest physician's practice and research efforts had been tuberculosis. As that disease was brought under control, the field lost some of its appeal, and a personnel shortage developed.

Concern about the situation led to the initiation of a survey of pulmonary disease personnel in 1970. The survey, which was conducted by a joint committee of the American Thoracic Society and the American College of Chest Physicians in collaboration with the Subspecialty on Pulmonary Diseases of the American Board of Internal Medicine, culminated in a report distributed in November 1972.* The committee's assessment of the extent of the shortage is shown in table 14. In terms of physicians in practice, the committee found a shortage of at least 3,769 chest physicians. To meet the nation's estimated need of two adult chest physicians per 100,000 population would require more than doubling the number in practice at that time. The shortage of pediatric pulmonary physicians was even more acute: a fourfold increase in numbers would be needed to reach the goal of one physician per 100,000 population.

In terms of shortages of faculty and physician-investigators in medical schools and other research institutions, the committee estimated a need for 558 additional persons. Of that number, 149 were actual funded vacancies reported at the time of the survey; the remainder comprised the institutions' projected needs for additional pulmonary faculty within the next 2 years.

*Survey of Professional Manpower in Pulmonary Diseases, prepared for the National Heart and Lung Institute by the Manpower Survey Committee of the American Thoracic Society and the American College of Chest Physicians, November 1972.

Table 14. Personnel Shortage in Pulmonary Diseases, 1972

	Total U.S.
<u>Practicing Physicians</u>	
Goal	
2 adult chest MD's per 100,000 population	4,160
1 pediatric chest MD per 100,000 population	<u>2,080</u>
	6,240
Available	
0.95 "internist" MD per 100,000 population	1,976
0.24 "pediatric" MD per 100,000 population	<u>495</u>
	2,471*
Total Needed	3,769**
<u>Medical Schools</u>	
Funded vacancies	131
Needed, in addition, within 2 years	<u>226</u>
Total Needed	357
<u>Research Institutions</u>	
Funded vacancies	18
Needed, in addition, within 2 years	<u>183</u>
Total Needed	201
TOTAL (all categories) NEEDED	4,327

*Since this number includes a large but unknown number of full-time physicians in medical schools and research institutions who are not practicing physicians, it overestimates the total number of available physicians.

**For the reason given (footnote above), both the total practicing physicians needed and the total needed (all categories) are underestimates of the actual figures.

The situation appeared even more grave when one considered the "supply" side of the equation, that is, the number of young physicians completing pulmonary training programs at that time. For the 1971-1972 academic year, the committee found only 225 adult and 39 pediatric chest physicians scheduled to finish their training and enter the work force during that year.

The committee found that in 1971-1972, 80 of the 97 medical schools surveyed had clinical chest disease training programs. Of those, 24 schools had both adult and pediatric programs, 55 schools had only adult programs, and one school had only a pediatric program. A number of new training programs, however, were being planned; by 1974-1975, it was expected that 93 schools would have adult chest disease training programs and 32 would have pediatric programs.

Numbers of enrollments in adult and pediatric clinical training programs in 1971-1972, as well as in funded vacancies and training capacities of the programs, are presented in table 15. Trainees in these programs had received support from the National Institutes of Health (27 percent), voluntary health associations (19 percent), medical school funds (22 percent), and other sources (32 percent). The fact that adult chest medicine programs could have accommodated 35 percent more trainees than those for which they had funds (and pediatric programs, 64 percent more) suggests that funding for clinical pulmonary training was, indeed, a part of the problem in 1972. However, in light of the number of funded vacancies for which the programs were unable to recruit trainees, it would seem that a more fundamental problem lay in attracting young physicians into clinical pulmonary training programs.

The committee also collected data on programs that were oriented primarily toward research training rather than clinical training. Fifty-three medical schools had such training programs; their enrollment and vacancy figures are presented in table 16.

Table 15. Clinical Training Programs, 1971 to 1972

	Adult	Pediatric
Currently enrolled	256	29
Funded vacancies	53	10
Number that could be accommodated	420	64

Table 16. Research Trainees, 1971 to 1972

	Full-time	Part-time
Currently enrolled	131	22
Funded vacancies	24	0
Additional trainees needed	82	13

Most (53 percent) of the research trainees were affiliated with departments of internal medicine, 15 percent were in pediatrics, and 17 percent in physiology. The small numbers remaining were associated with departments of surgery, anesthesiology, anatomy, biochemistry, microbiology, and environmental health. The committee found these figures disturbing, and noted in its report:

The Committee feels that these figures reflect an unhealthy situation in which basic science is seldom directed toward pulmonary problems; this in turn impedes the likelihood of making important basic discoveries in respiration, and prevents pulmonary trainees in teaching and clinical programs from having a desirable degree of familiarity with the techniques of research and analysis provided by basic scientists. Clearly more emphasis needs to be placed in developing interest in chest disease among members of basic science departments. In this context the NIH should assume the dominant role through its research and training support so that strong links between clinicians and basic scientists will be encouraged, and interdisciplinary research in chest diseases will be carried out. (pp. 87-88)

Finally, the committee reviewed the extent to which "modern" pulmonary medicine was being practiced in hospitals and medical clinics in 1972. The findings were both reassuring and disturbing. Many facilities had acquired sophisticated equipment such as spirometers, blood gas analyzers, and diffusing capacity analyzers, but many had no full- or part-time chest physician to direct their use. Thus, while all large hospitals and clinics were rapidly acquiring the facilities and equipment of a chest service, including a pulmonary function lab, an inhalation therapy service, and a respiratory intensive care unit, staffing by pulmonary disease specialists had proceeded much more slowly.

Other parts of the survey also identified the fact that the facilities and equipment available for the diagnosis and treatment of pulmonary disorders were more "up to date" than the physicians using them. Patterns of practice, for example, revealed that physicians who had little or no formal training in chest diseases were likely to be spending as much time dealing with respiratory disorders as physicians who had had many years of training. More than 60 percent of internists surveyed felt that current training programs offered in medical schools and through residency and fellowship programs did not sufficiently prepare the general practitioner or internist for diagnosing and treating respiratory disease. That view was shared by a majority of pediatricians as well, and was felt particularly strongly by physicians in the youngest age groups. The inadequacy and underutilization of available continuing education programs in pulmonary disease was also highlighted by the survey.

The findings of the committee led to three broad goals for pulmonary personnel development in the 1970's:

- (a) To enhance the training of those physicians, whether pulmonary specialists or not, who will actually be treating patients with chest diseases. House staff, general practitioners, internists and pediatricians will continue to be called upon-- increasingly, it seems--to treat patients with pulmonary diseases, yet they do not often at present have training and awareness necessary for the "modern" management of severely ill patients;
- (b) To train a greater number of chest specialists to work in hospitals and clinics where the impact of their specialty training will be magnified through its effect on the education of their colleagues and improvement in the level of care available in the hospital itself; and
- (c) To support and sustain the basic scientific inquiries, without which improvements in patient care cannot be made, and to encourage the attention of basic scientists to matters of potential importance to clinical pulmonary research. (p. 97)

In light of these goals, and in consideration of the serious discrepancy between the number of chest physicians being trained and the number actually needed, the committee made five recommendations:

Recommendation 1: To train more medical school faculty members, both clinicians and basic scientists, with special interests related to chest diseases.

Recommendation 2: To train basic scientists and to encourage the association of clinical chest physicians with basic scientists for an interdisciplinary approach to the solution of problems of mutual concern.

Recommendation 3: To initiate and expand clinical chest training programs for internists and pediatricians.

Recommendation 4: To place greater emphasis on the ongoing education of practicing physicians not primarily interested in chest diseases.

Recommendation 5: To incorporate into these expanded programs mechanisms by which the entire system can be sensitive to future and as yet unpredicted changes in the American health scene (by expanding, contracting, or reshaping responsively).

Program Goals Through 1982

- Develop and expand multidisciplinary research training opportunities in respiratory disease.
- Attract more physicians into careers in pulmonary medicine.
- Encourage basic scientists from a variety of disciplines to bring their knowledge and skills to bear on research problems related to pulmonary disease.
- Increase the availability of highly trained pulmonary faculty for the nation's medical schools and research institutions.
- Upgrade and modernize the pulmonary component of medical school training in the United States.

Accomplishments Through 1982

The decade of the 1970's was marked by a sizable expansion of training opportunities in pulmonary medicine. As shown in table 17, the number of trainee positions funded by the Division of Lung Diseases (DLD) approximately tripled during the first 8 years of the decade, reached a high of 477 positions in 1978, and then declined to the present level of around 400 positions. Data on the number of institutional training programs funded during that

Table 17. Division of Lung Diseases Personnel Development Program
 Number of Positions Funded Directly by Institutional Grants, 1970 Through 1981

Supportive Mechanism	1970	1971	1972	1973	1974	1975	1976	1977	1978	1979	1980	1981
<u>Postdoctoral</u>												
"Old" Fellowship (F02, F03, F22)	36	32	32	20	36	31	21	6	0	0	0	0
NRSA Fellowship	0	0	0	0	0	25	59	60	58	42	54	50
"Old" Training Grant (T01)	84	128	128	128	123	112	110	85	52	12	0	0
NRSA Training Grant (T32)	0	0	0	0	0	49	115	145	202	223	202	179
RCDA (K03, K04)	18	20	21	24	20	24	38	41	39	36	37	31
Research Career Award (K06)	7	6	8	9	9	8	8	7	7	7	7	7
Pulmonary Academic Award (K07)	0	4	16	16	25	30	37	39	33	38	36	29
Pulmonary Faculty Award (K08)	0	0	0	0	0	0	5	13	22	25	31	26
Clinical Investigator Award (K08)	0	0	0	0	0	0	0	0	0	0	14	24
Subtotal	145	190	205	197	213	279	393	396	413	383	381	346
<u>Predoctoral</u>												
"Old" Training Grant (T01)	14	13	16	21	25	24	24	32	20	4	0	0
NRSA Training Grant (T32)	0	0	0	0	0	9	29	34	44	51	51	46
Short-Term Training Grant (T35)	0	0	0	0	0	0	0	0	0	0	(20)	(32)
Subtotal	14	13	16	21	25	33	53	66	64	55	51	46
TOTAL	159	203	221	218	238	312	446	462	477	438	432	392

period (table 18) show a similarly expansive pattern, though a sharper decline in total programs by 1981.

It should also be clear from these tables that the mechanisms available for supporting NIH training efforts changed greatly during the 1970's. Several long-standing mechanisms were abolished, new programs were authorized to replace them, and several innovative programs were developed in response to the special needs of the pulmonary field.

Research Career Development Award

At the NIH-wide level, the only development program to continue through the decade essentially without change has been the research career development award (RCDA). Designed to facilitate the transition of promising young physicians and scientists into independent investigators, the RCDA program provides 5 years of salary support for an intensive research experience. Over the years, the DLD has strongly supported this program, many "graduates" of which are now prominent investigators in the pulmonary field. Interestingly, the typical RCDA recipient has changed over the past decade. While 74 percent of successful applicants in the years 1970 to 1975 were physicians, only 24 percent of new awardees from 1976 to 1980 held the MD degree. Thus, the program has become mainly a mechanism to support the development of pulmonary research careers of basic scientists.

National Research Service Award

During the 1970's, there were revisions and uncertainties in NIH-wide training and fellowship programs, the most significant of which were the phase-out of all "old" training authorizations, announced in 1973, and the passage of the National Research Service Act in 1974. Since 1975, all new individual fellowships and institutional training grants have been made under the aegis of the National Research Service Award (NRSA) Program. NRSA grants, which support the bulk of NIH postdoctoral research training, provide modest stipends and strictly limited institutional costs, permit no clinical training, and require service or monetary payback from all trainees who receive support through the program.

While the NRSA program has suffered since its inception from uncertainties in funding and reauthorization, it has formed the backbone of the DLD training effort. Tables 19 through 28 provide descriptive information on all NRSA postdoctoral trainees supported by the Division since the program began in 1975.

Table 18. Division of Lung Diseases Personnel Development Program
 Number of Institutional Grants, 1970 Through 1981

Supportive Mechanism	1970	1971	1972	1973	1974	1975	1976	1977	1978	1979	1980	1981
"Old" Training Grant (T01)	31	44	44	44	45	41	32	23	14	3	0	0
NRSA Training Grant (T32)	0	0	0	0	0	20	34	40	49	55	56	47
Short-Term Training Grant (T35)	0	0	0	0	0	0	0	0	0	0	1	2
Pulmonary Faculty Grant (T17)	<u>0</u>	<u>0</u>	<u>0</u>	<u>0</u>	<u>0</u>	<u>6</u>	<u>6</u>	<u>6</u>	<u>6</u>	<u>6</u>	<u>6</u>	<u>6</u>
TOTAL	31	44	44	44	45	67	72	69	69	64	63	55

As shown in table 19, the program has trained 786 individuals--132 through individual fellowships and 654 through institutional grants. Of the total number, 65 percent were physicians and most of the remainder held a PhD in the basic sciences.

The distribution, by specialty, of the 513 physician trainees is given in table 20. The majority of trainees (420) took their residency training in internal medicine, 65 in pediatrics, and a very small number in other specialty areas.

The distribution of the 263 basic scientist trainees by the disciplines in which they had received the PhD degree is presented in table 21. (See "Table 22. Lexicon of NRSA Disciplines," for a listing of specific disciplines that fall under each NRSA discipline class.) It is apparent that the largest number of trainees (78) had done their doctoral work in physiology, a traditional pulmonary research discipline. However, other disciplines were also represented; 42 trainees came from the physics/engineering field (mostly bioengineers); 40 from chemistry, including a large number of biochemists; and 25 from anatomy, which includes cell biology and pathology.

Table 23 gives the distribution of 549 trainees (those for whom complete data were available) according to the National Program area of their research training, and tables 24 through 29 give more detailed information on training in each of the six program areas: structure and function of the lung, pediatric pulmonary diseases, chronic obstructive pulmonary disease, fibrotic and immunologic interstitial lung diseases, respiratory failure, and pulmonary vascular diseases.

Since comparable numbers from the early 1970's are not available, it is difficult to identify trends or draw conclusions from these data. Nonetheless, some interesting descriptive findings are apparent. More than one-third (196) of the trainees, for instance, were involved in studies related to the structure and function of the lung, mainly in respiratory physiology. While more than one-half of this number came from the basic science disciplines, a significant number (72) were physicians. These data suggest that the lung programs have been successful in attracting clinically trained individuals to studies of basic mechanisms affecting the normal and diseased lung.

As expected, the five disease-oriented programs have been heavily dominated by physicians: overall, 74 percent of these trainees held the MD degree. The area with the largest proportionate representation of basic scientist trainees has been fibrotic and immunologic lung diseases, which has included a number of microbiologists and immunologists. Respiratory failure has been the area with the smallest percentage of basic scientist

Table 19. NRSA Program, 1975 Through 1981
Number of Postdoctoral Trainees

Type of Doctorate	Individual Fellowships	Institutional Grants	Total
Basic Scientists	72	191	263
Physicians	58	455	513
Veterinarians	2	7	9
Dentists	<u>0</u>	<u>1</u>	<u>1</u>
TOTAL	132	654	786

Table 20. NRSA Program, 1975 Through 1981
Distribution of Physician Trainees by Specialty

Specialty	Number of Trainees
Medicine	420
Pediatrics	65
Surgery	13
Pathology	9
Anesthesiology	4
Obstetrics/Gynecology	1
Psychiatry	<u>1</u>
TOTAL	513

Table 21. NRSA Program, 1975 Through 1981
Distribution of Basic Scientist Trainees by Discipline

NRSA Discipline Class	Number of Trainees
Anatomy	25
Biology	22
Chemistry	40
Genetics	5
Microbiology/Immunology	18
Pharmacology	17
Physics/Engineering	42
Physiology	78
Psychology/Social Sciences	9
Statistics/Epidemiology	4
Toxicology	<u>3</u>
TOTAL	263

Table 22. Lexicon of NRSA Disciplines

<u>ANATOMY</u>	<u>PHYSICS/ENGINEERING</u>
Anatomy	Biomedical Engineering
Cell Biology	Biophysics
Embryology	Engineering
Experimental Pathology	Environmental Engineering
Histology	Physics
Pathology	Radiation Physics
<u>BIOLOGY</u>	<u>PHYSIOLOGY</u>
Aging Process	Communicative Sciences
Biology	Endocrinology
Botany	Physiological Optics
Developmental Biology	Physiology
Entomology	Reproductive Physiology
Molecular Biology	<u>PSYCHOLOGY/SOCIAL SCIENCES</u>
Neurobiology	Anthropology
Nutrition	Bioethics
Oral Biology	Clinical and Counseling Psychology
Radiobiology	Community and Ecological Psychology
Teratology	Demography or Population Dynamics
Zoology	Developmental and Child Psychology
<u>CHEMISTRY</u>	Economics
Biochemistry	Education and Guidance
Biomaterials	Experimental and General Psychology
Chemistry	Health Administration and Public
Health	Health Nursing
Inorganic Chemistry	Linguistics
Medicinal Chemistry	Nursing
Organic Chemistry	Personality
Physical Chemistry	Physiological Psychology and
Psychobiology	Psychobiology
Polymer Chemistry	Political Science
<u>GENETICS</u>	Psychophysics
Genetics	Social/Behavioral Sciences
Mutagenesis	Social Psychology
Disciplines	Social Sciences and Related
<u>MICROBIOLOGY/IMMUNOLOGY</u>	Disciplines
Bacteriology	Sociology
Immunology	<u>STATISTICS/EPIDEMIOLOGY</u>
Microbiology	Biostatistics
Mycology	Computer Sciences
Parasitology	Epidemiology
Virology	Information Sciences
<u>PHARMACOLOGY</u>	Mathematics
Pharmacology	Statistics
	<u>TOXICOLOGY</u>
	Aquatic
	Environmental
	Forensic
	Inhalation
	Occupational/Safety
	Toxicology

Table 23. NRSA Program, 1975 Through 1981
Distribution of Trainees by National Program Area

Type of Doctorate	Program Area							Total
	Structure and Function	Pediatric	COPD	Fibrotic and Immunologic	Respiratory Failure	Pulmonary Vascular	Unknown	
Basic Scientists	121	12	22	30	4	16	58	263
Physicians	72	40	80	70	29	44	178	513
Veterinarians	3	1	1	1	0	2	1	9
Dentists	<u>0</u>	<u>1</u>	<u>0</u>	<u>0</u>	<u>0</u>	<u>0</u>	<u>0</u>	<u>1</u>
TOTAL	196	54	103	101	33	62	237	786

Table 24. NRSA Program, 1975 Through 1981
Trainees in Structure and Function of the Lung

	Respiratory Physiology	Nonrespiratory Physiology	Lung Structure	Total
BASIC SCIENTISTS				
<u>NRSA Discipline Class</u>				
Anatomy	0	9	1	10
Biology	1	3	2	6
Chemistry	4	14	3	21
Genetics	0	0	0	0
Microbiology/Immunology	0	1	0	1
Pharmacology	1	4	0	5
Physics/Engineering	30	0	3	33
Physiology	31	6	1	38
Psychology/Social Sciences	2	1	0	3
Statistics/Epidemiology	2	0	0	2
Toxicology	<u>0</u>	<u>1</u>	<u>1</u>	<u>2</u>
Subtotal	71	39	11	121
PHYSICIANS				
<u>Specialty</u>				
Medicine	51	7	2	60
Pediatrics	3	4	0	7
Surgery	2	0	0	2
Pathology	0	0	0	0
Anesthesiology	2	0	0	2
Obstetrics/Gynecology	0	0	0	0
Psychiatry	<u>1</u>	<u>0</u>	<u>0</u>	<u>1</u>
Subtotal	59	11	2	72
VETERINARIANS	2	1	0	3
DENTISTS	0	0	0	0
TOTAL	132	51	13	196

Table 25. NRSA Program, 1975 Through 1981
Trainees in Pediatric Pulmonary Diseases

	Growth and Development	Cystic Fibrosis	Bronchiolitis	Total
BASIC SCIENTISTS				
<u>NRSA Discipline Class</u>				
Anatomy	1	1	0	2
Biology	1	0	0	1
Chemistry	2	1	0	3
Genetics	0	1	0	1
Microbiology/Immunology	0	0	0	0
Pharmacology	1	0	0	1
Physics/Engineering	0	0	0	0
Physiology	1	1	0	2
Psychology/Social Sciences	2	0	0	2
Statistics/Epidemiology	0	0	0	0
Toxicology	<u>0</u>	<u>0</u>	<u>0</u>	<u>0</u>
Subtotal	8	4	0	12
PHYSICIANS				
<u>Specialty</u>				
Medicine	10	4	0	14
Pediatrics	22	1	2	25
Surgery	0	0	0	0
Pathology	0	0	0	0
Anesthesiology	0	0	0	0
Obstetrics/Gynecology	1	0	0	1
Psychiatry	<u>0</u>	<u>0</u>	<u>0</u>	<u>0</u>
Subtotal	33	5	2	40
VETERINARIANS	0	0	1	1
DENTISTS	1	0	0	1
TOTAL	42	9	3	54

Table 26. NRSA Program, 1975 Through 1981
 Trainees in Chronic Obstructive Pulmonary Disease

	Emphysema and Chronic Bronchitis	Asthma	Total
BASIC SCIENTISTS			
<u>NRSA Discipline Class</u>			
Anatomy	3	0	3
Biology	1	0	1
Chemistry	2	3	5
Genetics	2	0	2
Microbiology/Immunology	1	0	1
Pharmacology	0	1	1
Physics/Engineering	0	0	0
Physiology	2	5	7
Psychology/Social Sciences	0	2	2
Statistics/Epidemiology	0	0	0
Toxicology	<u>0</u>	<u>0</u>	<u>0</u>
Subtotal	11	11	22
PHYSICIANS			
<u>Specialty</u>			
Medicine	30	43	73
Pediatrics	4	0	4
Surgery	1	1	2
Pathology	0	1	1
Anesthesiology	0	0	0
Obstetrics/Gynecology	0	0	0
Psychiatry	<u>0</u>	<u>0</u>	<u>0</u>
Subtotal	35	45	80
VETERINARIANS	1	0	1
DENTISTS	0	0	0
TOTAL	47	56	103

Table 27. NRSA Program, 1975 Through 1981
 Trainees in Fibrotic and Immunologic Interstitial Lung Diseases

	Number of Trainees
BASIC SCIENTISTS	
<u>NRSA Discipline Class</u>	
Anatomy	6
Biology	6
Chemistry	3
Genetics	0
Microbiology/Immunology	10
Pharmacology	3
Physics/Engineering	1
Physiology	1
Psychology/Social Sciences	0
Statistics/Epidemiology	0
Toxicology	<u>0</u>
Subtotal	30
PHYSICIANS	
<u>Specialty</u>	
Medicine	64
Pediatrics	3
Surgery	0
Pathology	3
Anesthesiology	0
Obstetrics/Gynecology	0
Psychiatry	<u>0</u>
Subtotal	70
VETERINARIANS	1
DENTISTS	0
TOTAL	101

Table 28. NRSA Program, 1975 Through 1981
Trainees in Respiratory Failure

		Number of Trainees
BASIC SCIENTISTS		
<u>NRSA Discipline Class</u>		
Anatomy		0
Biology		0
Chemistry		0
Genetics		0
Microbiology/Immunology		1
Pharmacology		0
Physics/Engineering		0
Physiology		3
Psychology/Social Sciences		0
Statistics/Epidemiology		0
Toxicology		<u>0</u>
Subtotal		4
PHYSICIANS		
<u>Specialty</u>		
Medicine		24
Pediatrics		2
Surgery		2
Pathology		1
Anesthesiology		0
Obstetrics/Gynecology		0
Psychiatry		<u>0</u>
Subtotal		29
VETERINARIANS		0
DENTISTS		0
TOTAL		33

Table 29. NRSA Program, 1975 Through 1981
Trainees in Pulmonary Vascular Diseases

	Number of Trainees
BASIC SCIENTISTS	
<u>NRSA Discipline Class</u>	
Anatomy	1
Biology	0
Chemistry	0
Genetics	0
Microbiology/Immunology	0
Pharmacology	1
Physics/Engineering	5
Physiology	8
Psychology/Social Sciences	0
Statistics/Epidemiology	1
Toxicology	<u>0</u>
Subtotal	16
PHYSICIANS	
<u>Specialty</u>	
Medicine	36
Pediatrics	2
Surgery	2
Pathology	4
Anesthesiology	0
Obstetrics/Gynecology	0
Psychiatry	<u>0</u>
Subtotal	44
VETERINARIANS	2
DENTISTS	0
TOTAL	62

trainees (12 percent) and also the area with the fewest trainees overall (only 33).

Finally, the data in table 25 raise serious concerns about the adequacy of current training efforts in pediatric pulmonary diseases. During the 7-year period under consideration, only 54 trainees can be identified in that area. The majority of these trainees were involved in studies of the growth and development of the lung, an area which includes the Division's research program on respiratory distress syndrome of the newborn. Only 3 trainees were involved in bronchiolitis research projects.

Pulmonary Academic Award

During the 1970's, the Division initiated several innovative personnel development programs designed to address the special needs of the pulmonary field. The first of these was the pulmonary academic award (PAA), which was established in 1970. At that time, there were few strong academic programs in pulmonary medicine in the United States. While a number of scientific discoveries had opened strongly promising avenues of research into the causes and cure of pulmonary disease, the field lacked the trained personnel and the structure to capitalize on those opportunities. There were clearly perceived needs to integrate the disciplines involved in the lung, to build upon the new pulmonary knowledge base, to translate that knowledge into improved health care techniques, and to assure the education of new physicians in modern pulmonary medicine. Accordingly, the Pulmonary Academic Award was established with the following objectives:

- Create and encourage a stimulating approach to respiratory disease curricula that attracts high quality students to the area.
- Assure that students receive superior, modern instruction in respiratory diseases.
- Foster academic career development of promising young teacher-investigators whose interest and training are in respiratory diseases.
- Encourage schools to recognize respiratory diseases as a subspecialty and to recruit or retain high caliber faculty with a major commitment to teaching in respiratory diseases.
- Develop and implement excellent multidisciplinary pulmonary curricula through interchange of ideas, methods, and techniques among grantee institutions.

- Enable grantee institutions to strengthen their existing pulmonary teaching program to the point that they will be able to sustain that effort with their own funds by the end of the award period.

The pulmonary academic award was essentially a career development award for teachers and as such, resulted in the creation of a rather distinctive cohort of trained personnel in academic medicine. Awards were limited to one 5-year grant per institution, and the major focus of the awardee's effort was to improve the education of medical students. Typically, the awardee sought to review, coordinate, extend, and modernize all elements of basic science and clinical courses related to the lung; to develop attractive and high caliber pulmonary elective offerings; to expand and improve the pulmonary learning resources available at the institution; to establish special pulmonary conferences and research opportunities designed to spark the interest of talented students; and to give pulmonary medicine higher visibility at the institution. As a group, the awardees also engaged in a number of collaborative activities, the most noteworthy of which was the development of a core curriculum for teaching in respiratory diseases.

It is apparent from the large number of applications for PAA's received during the past 11 years that the academic pulmonary community clearly perceived a need for such a program. To date, more than half of the medical schools in the United States have held pulmonary academic awards (see figure 11).

In 1975, an interim evaluation of the PAA program was undertaken by the Pulmonary Diseases Advisory Committee. Based on site visits to 15 award programs, the committee found that the program had been successful in the majority of cases and recommended its continuation and expansion. As noted in the report of the committee:

The award program has resulted in reevaluation and modification of the pulmonary curriculum at parent institutions, coordinating the teaching of different departments, usually with the introduction of a clinical point of view earlier in the curriculum. Generally the pulmonary curriculum has been expanded....At all institutions covered by the reports, the students interviewed found the respiratory curriculum stimulating and were enthusiastic about the awardees' efforts. Pulmonary electives were usually filled or over-subscribed. In many schools some of the students interviewed were committed to or were considering pulmonary disease as a career.

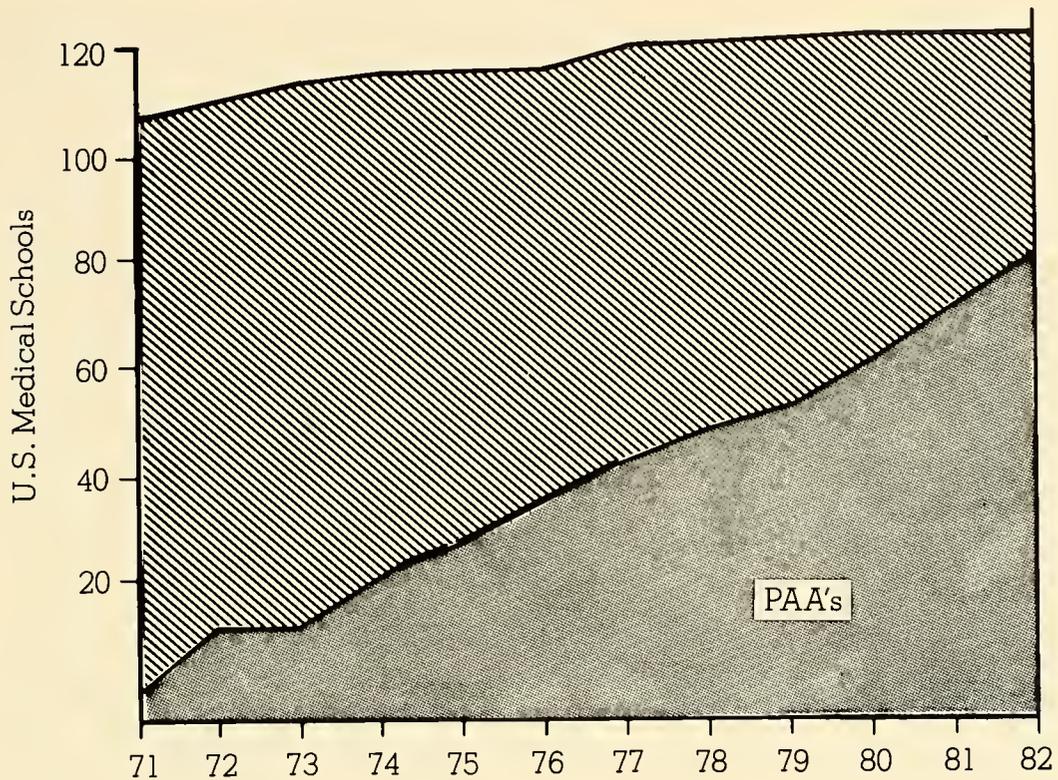


Figure 11. Pulmonary Academic Award
Growth of Program, 1971 to 1982

In 1980, a more formal evaluation of the Pulmonary Academic Award Program was conducted by the Division of Lung Diseases through a contract with the Association of American Medical Colleges. The study, which considered the first 14 institutions to receive PAA's (in 1971 and 1972), sought to compare the progress of the pulmonary programs at those schools with the progress at 14 matched comparison schools that had not held PAA's.

Detailed findings were presented in a final report.* In brief, the PAA was found to have had a measurable positive influence on the acquisition of pulmonary knowledge by medical students. That influence was observed in standardized test performance of students both in the first 2 years of medical school and in the last 2 years. The PAA program also had an easily

*Sherman, C.R., "An Evaluation of the National Heart, Lung, and Blood Institute's Pulmonary Academic Award Program," Association of American Medical Colleges, November 1981.

noticeable positive effect on the curriculum, on the quality of clinical faculty, and on the teaching of clinical science. These findings suggest that the PAA was an effective mechanism for bringing modern pulmonary education to medical students.

It was difficult, however, to find evidence that the PAA program had met its other broad goal of attracting more physicians to careers in pulmonary medicine. In the study, the PAA schools did not differ significantly from the comparison schools on measures of student interest in pulmonary disease or of student choice of a pulmonary career. It is not clear whether these findings represent a real lack in the PAA program, the effect of various confounding variables, or the insensitivity of the measures available for use in the evaluation.

The evaluators also considered the effect of the PAA on the academic career advancement of its recipients. They found that 6 of the 14 awardees advanced strongly, 5 made average progress, and 3 did not fare well. Academic career advancement was strongest at schools where an additional faculty member had been hired to relieve the pressure of responsibilities of clinical care and to build the pulmonary division's research activity. Where problems developed, the difficulty seemed to arise from the fact that the PAA permitted and encouraged its recipients to develop their careers along nontraditional lines (namely, teaching, rather than research) that were not recognized or awarded by the institution's promotional system.

It should be emphasized that this was a pilot evaluation study that considered only the first 14 schools to receive pulmonary academic awards. At the time those awards were made, the program was limited to schools with minimally developed pulmonary programs. Also, the award required such a large commitment of its recipients' time that concurrent development of research interests was generally not feasible. Those guidelines were relaxed in subsequent years; therefore, an evaluation of later pulmonary academic awards may result in very different findings.

The Pulmonary Diseases Advisory Committee recently held extensive discussions of the progress and fate of the PAA program. In addition to reviewing the evaluation report, the committee interviewed several more recent pulmonary academic awardees and examined data on the application history of the program, which showed a decline in the number of schools seeking PAA's during the last few competitions. The committee concluded that the PAA program had been a timely and effective mechanism for improving pulmonary medical education and that it had largely met its original goals. Therefore, it was recommended that the program be phased out.

Young Investigator Pulmonary Research Grant

Early in the 1970's, the newly formed Division of Lung Diseases began a series of efforts to establish a small grant program in pulmonary diseases. As noted above, there was great concern at that time that the pulmonary field had failed to capture the interest and imagination of enough bright young physicians and scientists to develop an effective national pulmonary research program. It was felt that a small grant program in pulmonary research would serve to encourage biomedical scientists and physicians to channel their research interests into the pulmonary field early in their careers; to stimulate pulmonary research by providing young investigators with the opportunity for preliminary or exploratory studies; and, overall, to extend the base for pulmonary research and increase the personnel pool of pulmonary physicians and scientists.

Plans for development of such a program were accelerated in 1973 when the administration determined that the NIH had met its training needs and that other needs could be met through the private sector. It became clear that young scientist-physicians would be able to develop investigative skills and interests only if they were able to participate directly in research. Therefore, a way was needed to encourage their interest in research, foster their initiative, and provide opportunities to learn research techniques that would otherwise have been developed in a training environment. In some fields and at some institutions opportunities were available in which young scientists could participate as research associates or assistants on program project grants, SCOR grants, or large research grants. The still underdeveloped pulmonary research field, however, could not offer sufficient opportunities through these mechanisms.

Accordingly, the young investigator pulmonary research grant was initiated in 1974 with the following objectives:

- Enable young scientists and physicians to explore their developing research interests.
- Provide young investigators with modest support for a project of their own design.
- Encourage pulmonary research in fundamental as well as clinical disciplines.

The program was restricted to candidates under the age of 35 who had not previously been the recipients of other independent NIH research support. Applicants were required to present plans for either a well defined study to answer a specific scientific question or a pilot study preliminary to development of a larger proposal. In either case, the research had to be of sufficiently

limited scope to be completed for publication within the 2-year period of the grant.

The program was enthusiastically received by the scientific pulmonary community, and served as a model for similar programs at the National Institutes of Health. In 1976, the program was expanded and reannounced as the National Heart and Lung Institute's young investigator research grant. Development of parallel programs at other Institutes soon followed: by 1980, grants of this type were available in cancer, aging, dental research, environmental health sciences, visual sciences, diabetes, anesthesiology, trauma and burn research, medical information science, clinical immunology and virology, and tropical medicine. These diverse programs were ultimately consolidated into a single, NIH-wide funding mechanism, the new investigator research award.

Obviously, the young investigator pulmonary research grant (and its later forms) has been perceived as a highly successful program filling an important gap in research training support. An empirical assessment of its specific contributions to pulmonary research manpower has not been feasible, mainly because of difficulties in identifying a suitable "control group" for an evaluation study. It is clear, however, that the program brought a number of basic scientists as well as clinicians into the field and attracted young investigators who had not previously applied their skills to the study of the lung. An informal followup of the early recipients of the award has indicated that their retention in the pulmonary research field and their success at obtaining subsequent grant support have been satisfactory. Overall, it seems that the program has been an important part in the national pulmonary research effort.

National Pulmonary Faculty Training Program

In 1975, the National Pulmonary Faculty Training Program was initiated as a means to develop pulmonary faculty at medical schools that lacked strong pulmonary programs. The program was designed in response to a recommendation of the Manpower Survey Committee, discussed above, and was based on the notion that "the fastest way to alleviate the manpower shortage, to fill existing vacancies in chest disease training programs, and to encourage and strengthen links between clinicians and basic scientists is to ensure that a large and capable faculty concerned with various aspects of respiratory diseases is present in every medical school in the United States" (p. 98). The committee felt that one reason for underenrollment in pulmonary training programs was the fact that medical students coming from schools that had few or no pulmonary faculty were not influenced by curriculum or by example to enter the subspecialty. The lack of pulmonary faculty at a

number of medical schools was felt to have other, broad-ranging consequences as well. For example, medical students at those schools inclined toward other specialties, such as pediatrics, in which chest diseases are important, would not be adequately trained. Similarly, students pursuing an interest in the basic sciences would not be inclined toward or properly educated in respiratory aspects of physiology, pharmacology, biochemistry, microbiology, anatomy, and pathology.

A two-phase program was developed in response to these concerns. First, six National Pulmonary Faculty Training Centers were established in 1975 through nationwide competition. The centers had large, vigorous, proven programs that were capable of providing research and clinical training in adult and pediatric pulmonary diseases. Then, in 1976, competition was opened for medical school pulmonary faculty training awards for which institutions lacking strong pulmonary programs could nominate "junior faculty" candidates of their own choosing. The award provided 5 years of salary support for its recipients, who spent 3 years of that time receiving research and clinical training at one of the six Pulmonary Faculty Training Centers and the remaining 2 years establishing pulmonary programs at their sponsoring institutions. The program announcement required a long-term commitment from all parties. The junior faculty awardee was required to remain at his or her sponsoring institution for 3 years after termination of the 5-year award; the sponsoring institution agreed to retain and support the awardee during that period; and the training centers were not permitted to recruit awardees during that time.

Six competitions for medical school pulmonary faculty training awards were held between 1976 and 1980. Ultimately, awards were made to 26 medical schools on behalf of 33 junior faculty trainees--a number that was quite a bit lower than the funded capacity of the Pulmonary Faculty Training Centers. In review, it has been apparent that the long commitments required of the trainees and their sponsoring institutions deterred many potential applicants from seeking support through this program. Some medical schools were unable or unwilling to commit future resources to untried investigators, and many potential junior faculty awardees were reluctant to "tie-up" the 8 years of professional life required by the program. It is also clear that the modest development of the program reflects the problems inherent in developing pulmonary faculty at schools with minimal pulmonary programs. The majority of schools that received awards had recruited their junior faculty trainees from their own ranks, most often from their residency programs. It is reasonable to suppose that many schools with undeveloped pulmonary programs would have difficulty influencing their graduates to make a long-term commitment to pulmonary medicine and research. Thus, it

could be said that the success of the program was to some extent impeded by the very problems it was designed to resolve.

Because the program made its first 5-year awards only in 1976, an assessment of the progress of its "graduates" is just at its beginning stages. There is much informal evidence that the training portion of the 5-year periods has been quite successful. The Pulmonary Faculty Training Center directors have commented favorably on the general caliber and commitment of the junior faculty trainees in their programs, and most of the trainees have expressed satisfaction with their training experiences. Reports from trainees who have returned to their sponsoring institutions have been mixed. In some cases, the return has been smooth, and active development of research and clinical programs has been well supported; in other cases, junior faculty have experienced problems establishing themselves and gaining support and guidance from their institutions. A comprehensive assessment of the program's strengths and shortcomings awaits further evaluation.

NHLBI Clinical Investigation Award

The decade of the 1970's was marked by a general decline in the proportion of physicians seeking training and research support through the various funding mechanisms of the National Institutes of Health. Concern over this phenomenon reached a peak in 1978, at which time the National Heart, Lung, and Blood Advisory Council formed a committee to study the situation and recommend remedies. The committee identified a number of reasons for which careers in research had become unattractive to newly trained physicians. Among the disincentives were the low stipends, relatively short duration, and payback requirement that had been part of the National Research Service Award Program. There seemed to be a need for a new program to draw physicians into research careers at an early stage in their professional development--a program that would compete more successfully with the attractions of clinical practice.

Accordingly, the National Heart, Lung, and Blood Institute's clinical investigator award (CIA) was formulated, and the first awards were made in 1980. This career development type of award is designed for physicians who have completed their clinical training and shown some potential for careers in research. It provides 5 years of support for a supervised research experience in a promising environment.

The Division of Lung Diseases has participated in this program from its inception and currently funds awards to 31 young physicians.

Pulmonary Personnel in 1982 and Goals 1982 to 1987

Because of the remarkable strides made during the past decade, the pulmonary personnel situation in 1982 is vastly different from that seen in 1972. Although there have been no additional surveys of personnel in pulmonary medicine, information from a variety of sources suggests that there has been considerable improvement in a number of critical areas.

As noted above, the nation faced a critical shortage of pulmonary physicians in 1972, and newly training clinicians were entering the workforce at too slow a rate to improve the situation. Data from the recent report of the Graduate Medical Education National Advisory Committee (GMENAC)* indicate that there may be a large oversupply of pulmonary specialists by 1990. Specifically, GMENAC's final estimation is that for 1990, between 3,400 and 3,700 adult pulmonary physicians will be needed. The projected 1990 supply of pulmonary specialists is 6,950--nearly double that number.

As one might expect, there has been a concomitant increase in the availability of training programs for physicians in pulmonary disease. Each year, the American Review of Respiratory Diseases publishes a listing of adult and pediatric respiratory disease training programs in the United States. A comparison of the number of programs available in 1970 with the number available in 1981 (table 30) shows the great expansion of training opportunities that has occurred. The increases in training support through the various programs of the Division of Lung Diseases have already been noted (see tables 17 and 18).

Programs supported by the Division of Lung Diseases have been highly successful in attracting physicians into research training. As shown in figures 12 and 13, the number of physicians trained through the various lung program mechanisms increased and stabilized during the decade under consideration.

Likewise, efforts to draw a variety of basic scientists into pulmonary research have been highly successful. As indicated by data presented above on the NRSA program, the Division currently trains scientists from a wide variety of disciplines. Further, considerable interaction has been developed between clinical investigators and researchers in the fundamental disciplines.

*Physician Requirements, 1990, for Pulmonary Diseases. Office of Graduate Medical Education, HRA, DHS, DHHS Publication No. (HRA) 82-623, 1982.

Table 30. Pulmonary Training Programs, 1970 to 1981

Training Programs in Respiratory Disease

Year	Number of Programs	Number of 1st Year Openings	Total Openings
1970	120	267	524
1981	181	404	920

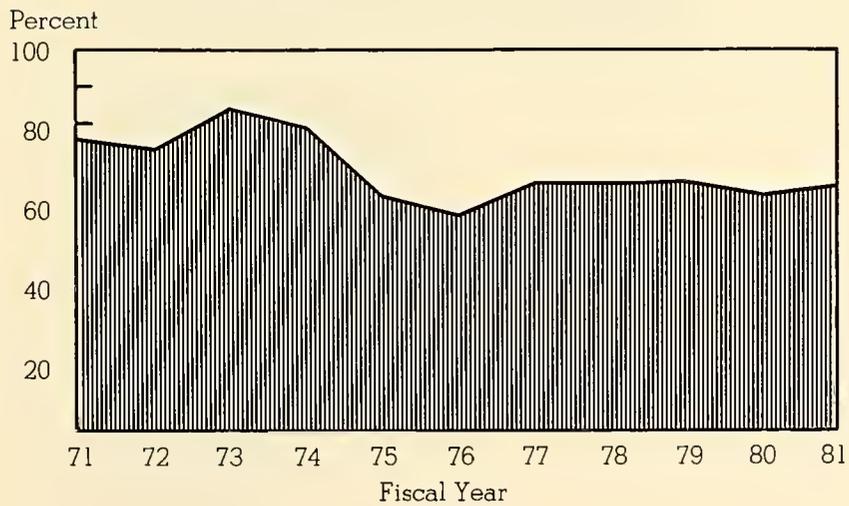
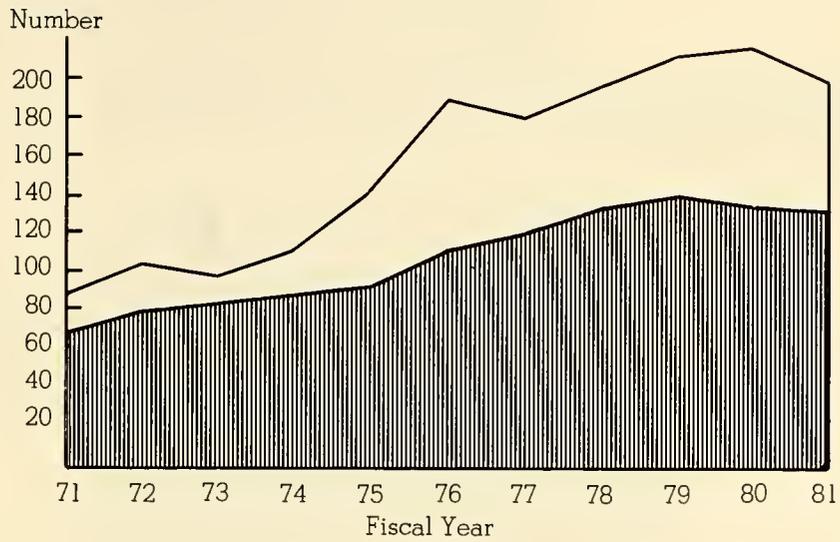
Training Programs in Pediatric Respiratory Diseases

Year	Number of Programs	Number of 1st Year Openings	Total Openings
1970	27	35	72
1981	34	57	134

Sources: ARRD 102:309-327, 1970.
ARRD 123:577-605, 1981.

Clearly, progress has been great during the past decade. However, some problems remain unresolved and some new challenges are presenting themselves as a result of the overall constricture of Federal research funding that has occurred in recent years.

- While the supply of physicians trained in adult respiratory diseases has grown tremendously, the pediatric pulmonary medicine field has been much slower to develop. Efforts must be made to increase the personnel pool for both investigative and clinical endeavors in pediatric pulmonary disease.
- Despite the generally abundant supply of adult pulmonary physicians, the academic pulmonary community still reports problems in attracting physicians into its research training programs and in filling vacant faculty positions. If the GMENAC projections of a future oversupply of pulmonary physicians have the effect of diminishing the attractiveness of the pulmonary field, the number of physicians



□ Non-MD ▨ MD

Figure 12. Postdoctoral Research Trainees: MD-PhD Distribution, 1971 to 1981

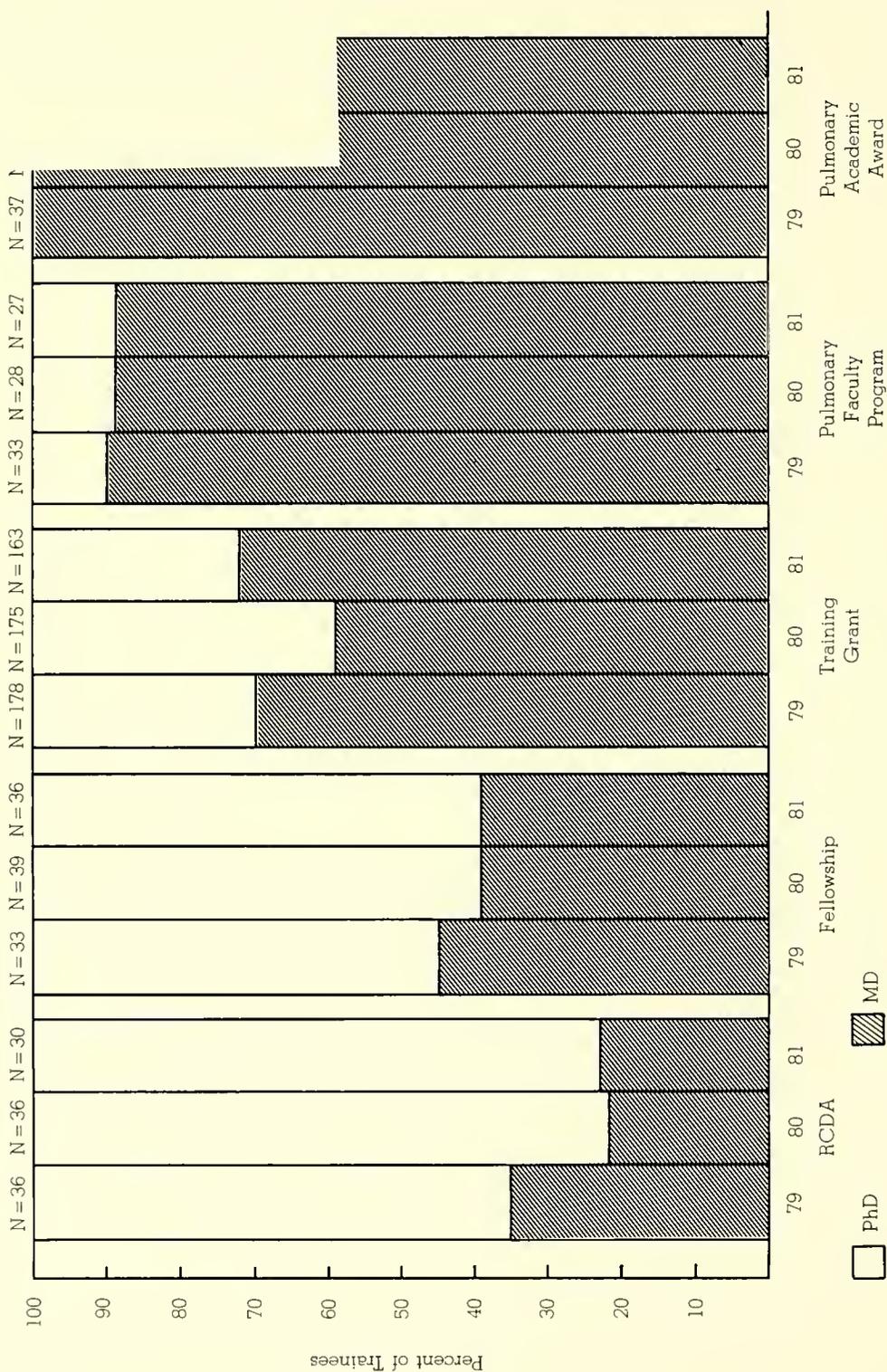


Figure 13. DLD Manpower Programs: MD-PhD Distribution, 1979 to 1981

entering academic pulmonary medicine may decline sharply. The challenge, therefore, is to develop programs that will produce a relatively high "yield" of academic physicians, that is, that will attract physicians who have a research orientation into a field where potential for practice is becoming less promising.

- As the Federal research budget has diminished in terms of real dollars in recent years, it has become difficult even for established investigators to survive in academic research and to build and maintain their investigative efforts. The perceived instability of investigative life deters many newly trained physicians and scientists from seeking research careers. It is time to reexamine the entire continuum of research training support--from post-doctoral fellowships through career development awards--and to examine their interactions with research support mechanisms. The goal is to develop new programs that will fill in the current gaps in support and thereby provide more stable prospects for careers in pulmonary research.
- As noted earlier, the Division's training programs reached a peak, in terms of numbers trained annually, around 1978 and have shrunk somewhat since that time. This situation reflects, in part, the diminished availability of funds to support training programs--a condition that is likely to prevail in the future. Accordingly, there is a need for the Division to focus its training efforts more sharply--namely, to identify specific disciplines and research areas requiring greater development, so that scarce personnel dollars may be used optimally.
- Finally, improvements in pulmonary educational programs have been great during the past decade, in part due to the influence of the Pulmonary Academic Award Program. While that program is phased out during the next few years, it is essential that the momentum of the improved pulmonary teaching effort not be lost. A careful examination of the program as a whole is necessary in order to identify the source of its effectiveness and to design new programs to stimulate the development of teacher-investigators in pulmonary diseases.

Contributor

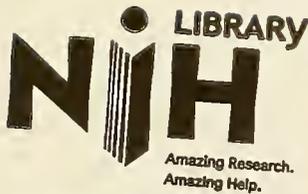
DIVISION STAFF

Barbara Liu
Prevention, Education, and
Manpower Branch
Division of Lung Diseases
National Heart, Lung, and
Blood Institute

Ten-Year Review and Five-Year Plan

National Heart, Lung, and Blood Institute

- Volume 1. Progress and Promise
NIH Publication No. 84-2356
- Volume 2. Heart and Vascular Diseases
NIH Publication No. 84-2357
- Volume 3. Lung Diseases**
NIH Publication No. 84-2358
- Volume 4. Blood Diseases and Resources
NIH Publication No. 84-2359
- Volume 5. Companion Issues
NIH Publication No. 84-2360



<http://nihlibrary.nih.gov>

10 Center Drive
Bethesda, MD 20892-1150
301-496-1080

ITED: Under provisions of applicable public laws enacted by rson in the United States shall, on the grounds of race, color, or age, be excluded from participation in, be denied the l to discrimination under any program or activity (or, on the o any education program or activity) receiving Federal finan- , Executive Order 11141 prohibits discrimination on the basis subcontractors in the performance of Federal Contracts, and states that no federally funded contractor may discriminate applicant for employment because of race, color, religion, sex, fore, the National Heart, Lung, and Blood Institute must be with these laws and Executive Orders.



3 1496 00114 9882



NIH Publication No. 84-2358