

Lung Biology in Health and Disease

Volume 10

# Pathogenesis and Therapy of Lung Cancer

edited by

Curtis C. Harris

# **PATHOGENESIS AND THERAPY OF LUNG CANCER**

*Edited by*

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## FOREWORD

Most of us who are asked to name how the great advances in modern medicine and surgery have come about, would probably respond by listing some Nobel laureates and the discoveries closely linked with their names: for example, Roentgen and X-rays; Koch and the tubercle bacillus; Fleming and penicillin; Enders and culture of polio virus; Banting and insulin. Yet, once in awhile, an event that is ineligible for a Nobel Prize has had just as important an impact on medical advance as one that was eligible and won an award. One such event was Abraham Flexner's 1910 report "Medical Education in the United States and Canada" that resulted in a considerable decrease in the number of American medical schools and a considerable increase in their quality and in the scientific content of their curricula. Another was the opening of the Johns Hopkins Medical School in 1893, staffed by four professors, each outstanding as a scientist in his specialty and each believing in joining scientific research, medical education, and patient care.

Sometimes a book or a series of books has had a strong influence on the advance of medical science. One such book was the first edition of Osler's *Medicine* (1892) because Osler's emphasis on how little physicians knew for sure led John Rockefeller's adviser on philanthropy to recommend the building of the great Institute for Medical Research, which opened in 1904 and for decades was the foremost institution for research in basic medical sciences in the United States. Another was the first (1941) edition of Goodman and Gilman's "Pharmacological Basis for Medical Practice" that revolutionized teaching and research on the action and use of drugs; as one professor of pharmacology stated in 1941, no professional pharmacologist could from then on teach at a lower level than that of the superb text used by his students!

In the field of respiration and the lungs, there are some classic monographs and a comprehensive *Handbook of Physiology* that have heightened the interest of scientists, students, and physicians in this subject and stimulated them to enter pulmonary research. One can safely predict that this new series of monographs, "Lung Biology in Health and Disease," will have an even greater impact on young (and older) researchers because it is the first truly comprehensive, monumental work in this field. It does not deal just with cellular processes or just with clinical problems but with the entire spectrum of basic sciences and of lung



function, metabolic functions and respiratory defense mechanisms. The series will also include volumes that apply to modern biological knowledge to elucidate mechanisms of pulmonary and respiratory disorders (immunologic, infectious, and genetic disorders, physiology and pharmacology of airways, genesis and resolution of pulmonary edema, and abnormalities of respiratory regulation). Other volumes will deal with the biology of specific pulmonary diseases (e.g., cancer, chronic obstructive pulmonary disease, disorders of the pulmonary circulation and abnormalities associated with occupational and environmental factors) and with early detection and specific diagnosis.

This series shows the lung as a challenging organ, with many problems calling for innovative research. If it attracts some imaginative, creative, and perceptive young scientists to attack these difficult problems, the tremendous effort in writing, editing, and publishing these volumes will be well worthwhile. The volumes cannot win the Nobel Prize, but someone may who was challenged by them.

Julius H. Comroe, Jr.  
San Francisco, California

## **PREFACE**

The major cause of lung cancer, tobacco smoke, has been known for several decades. In spite of this widely recognized fact the incidence of lung cancer is increasing in both males and females. Hence, lung cancer is an example of a preventable disease, the impact of which an "informed" society has had little effect in altering. Although the reasons for this failure are complex, the obvious lesson is that the identification of environmental carcinogens is only one step toward preventing human cancer. Attention also has to be focused on the individual who has a high risk of developing lung cancer due to predisposing host factors and to cocarcinogenic environmental factors. For those individuals already exposed to an oncogenic dose of chemical carcinogens but due to the long latency period have not yet developed clinically evident cancer, attention of the clinical oncologist has to be focused on treating preneoplastic lesions by interrupting the progression of preneoplasia to cancer.

This monograph has been divided into four sections: (1) Environmental and Host Factors; (2) Respiratory Carcinogenesis in Experimental Animals; (3) Pathology and Experimental Human Studies; and (4) Biology, Clinical Manifestations, and Treatment of Lung Cancer. Each section contains chapters written by individuals who are actively conducting investigations in their area of expertise.

In the first section, Hoover reviews the epidemiology of lung cancer including the voluminous literature concerning the association between tobacco smoking and lung cancer. In addition, important clues for new studies are provided by the recent findings of areas of high cancer incidence that are associated with specific industries in counties of the United States. Lung cancer caused by occupational exposure to chemical and physical (radiation and fibers) carcinogens has recently reached public awareness. The scientific data in occupational carcinogenesis are evaluated by Frank.

Exposure to an environmental carcinogen does not necessarily cause cancer in all individuals so exposed because of differences in host susceptibility. Genetic factors determine in part the susceptibility to the oncogenic effects of carcinogens. This increasingly important area is reviewed by Mullvihill.

In the second section the authors (Nettesheim, Griesemer, Kennedy, Little, Mohr, Reznik, Boren, Paradise, and Lane) describe how experimental

animals are being used to investigate the pathogenesis of lung cancer. Animal models for both chemical and radiation carcinogenesis of the lung have been developed during the last decade. The animal models have been useful in the identification of cocarcinogens as well as host states of increased susceptibility to carcinogens. Experimental animals have also aided us in the study of tobacco carcinogenesis. A detailed investigation of the cytokinetics of the respiratory epithelium and carcinogenesis studies in cultured cells and tissues of the lung are both recent areas of research.

The third section is devoted to the pathology of lung cancer and to experimental human studies. Trump, Becci, Barrett, and McDowell are using refined morphological and cytochemical methods to study the pathogenesis of lung cancer and to improve the classification of lung cancer. Cytopathology of exfoliated cells from the lung is an important method for diagnosing lung cancer. Schreiber discusses how cytopathology can also provide us with insights into the pathogenesis of lung cancer. In Chapter 11, experimental models for studying carcinogenesis in human cells are described. Human bronchus and peripheral lung can be maintained as explants in vitro and as xenotransplants in immunodeficient animals. Within a controlled experimental setting, the interactions between the target tissue and chemical carcinogens can be studied.

In the last section of this monograph, Straus, Janis, and Moran review the biological properties of lung cancer. The clinical management of lung cancer, which causes the death of 90,000 people in the United States per year, is discussed by Cohen.

In Chapter 4, Nettesheim and Griesemer have chronicled the advance in respiratory carcinogenesis which has become an integral facet of cancer research. While many investigators have made significant findings, Umberto Saffiotti can be singled out for his contribution which encompasses the development of an animal model of human lung cancer, the direction of a comprehensive program in chemical carcinogenesis, and the role of a scientific expert in the intense debate concerning environmental carcinogenesis. He has also found the energy to aid young investigators. As a recipient of his encouragement and that of Charles A. Leone, Donald J. Svoboda, and many others I am most appreciative.

Claude Lenfant has had the forethought to include *Pathogenesis and Therapy of Lung Cancer* in his comprehensive series of monographs. The contributors to this volume of the series are representative of the multidisciplinary spectrum of investigators concerned with human lung cancer. Their efforts have been markedly aided by Claude Lenfant and the staff of Marcel Dekker, Inc. I am grateful to all for suggestions, cooperation, and patience.

Curtis C. Harris  
Bethesda, Maryland

## INTRODUCTION

The marked increase in lung cancer incidence in several countries became a matter of serious public concern in the early 1950s. Epidemiologic studies suggested a causal relationship with tobacco smoking, occupational exposures, and with air pollution. Advances in carcinogenesis research suggested a major role of chemical and physical factors in the causation of respiratory cancers.

At that time, research was focusing on the mechanisms of action of carcinogens in some target tissues (e.g., skin, liver). Understanding of the pathogenesis of the major forms of cancer known from human pathology was hampered, however, by the lack of animal models on which they could be reproduced and experimentally studied.

Since lung cancer was found to be a major cause of death in the United States and several other countries primarily due to environmental factors, it was particularly frustrating that no adequate experimental model was available for a direct study of its causative and pathogenetic mechanisms. The challenge posed by such a situation stimulated a small number of investigators in the late 1950s and early 1960s to embark on a long-range research effort to develop animal models and to elucidate the conditions of exposure, penetration, and interaction of inhaled particles and carcinogens in the respiratory tract.

These efforts bore fruits in the decade of the 1960s with the development and establishment of reproducible animal models for the induction of bronchogenic carcinomas, which were quite similar to their human counterpart.

In the last decade, these models have made it possible to undertake a systematic study of the pathogenic mechanisms of lung cancer and their possible inhibition. A variety of respiratory carcinogens were identified. Combined and synergistic effects were demonstrated. Morphological and biochemical methods were used to define the early stages of respiratory tract response to carcinogens and their subsequent evolution into invasive carcinomas. The cells of origin in bronchogenic carcinomas were identified and new classifications of lung cancers based on cellular characteristics were developed. Cell kinetics in the respiratory epithelium were studied in detail. The role of inhaled particulate matter in carcinogenesis was investigated. Methods were developed for the *in vitro* culture of respiratory tissues and cells first from animals and then from human sources, thus allowing comparisons to be made between the

response of animals and humans to respiratory carcinogens under controlled experimental conditions. These tissue culture methods made it possible to identify critical metabolic steps in the activation of environmental carcinogens by the respiratory epithelium, including the specific chemical product resulting from the interaction between the widespread environmental carcinogen benzo[a]pyrene and DNA in respiratory tissues from animals and from humans.

The marked interindividual variation observed in the human response to respiratory carcinogens suggests the possibility of identifying markers of high and low susceptibility. Studies of the pharmacologic inhibition of respiratory carcinogenesis by specific compounds, such as vitamin A derivatives, developed into a systematic study of anticarcinogenic mechanisms, which opens up the possibility of a pharmacologic prophylactic intervention in individuals at high risk for lung cancer.

These many advances have brought the clinical and the laboratory sides of research on lung cancer much closer together than they had ever been, and we can now look forward to a period of further substantial progress in the understanding and in the effective prevention and control of this leading form of cancer.

This book gives a comprehensive view of the state of our present knowledge on lung cancer and shows what can be accomplished by a determined group of laboratory and clinical investigators who share the intellectual goal of understanding and controlling one of the most threatening neoplastic diseases of our time.

**Umberto Saffiotti**  
Bethesda, Maryland

## NOTE FROM THE EXECUTIVE EDITOR

*Pathogenesis and Therapy of Lung Cancer* is the second "clinical" volume of the series "Lung Biology in Health and Disease." It is included in this series for two reasons. First, it addresses a major health problem. Indeed, cancer in general constitutes the third most important cause of death in this country (after coronary and cerebral vascular diseases). Among all types of cancers, cancer of the lung is the most prevalent; and indications are that this prevalence is increasing. This does not come as a surprise, for the lung is the "port of entry" for so many contaminants, pollutants, and noxious agents which may be carcinogenic.

The second reason for including this volume in the series is that the differentiation that characterizes the malignant process greatly affects all of the functions of the lung, both respiratory and nonrespiratory. Since one of the objectives of this series of monographs was to assemble a scholarly review of all biological processes occurring in, or relevant to, the lung, a volume devoted to the cancer of the lung was clearly a necessity.

It is fortunate for the series that Dr. Curt Harris accepted the editing of this volume. He assembled a group of experts from this country and from Europe and together they have composed a volume that reviews and discusses etiology, pathogenesis, and clinical aspects—including therapy—of lung cancer. Although cancer of the lung has been the topic of many books, few, if any, are as comprehensive as Dr. Harris'. For this reason, the volume will be of interest and a challenge to clinical and experimental investigators. This contribution is both an asset to this series of monographs and a tribute to Dr. Harris' leadership and foresight.

Claude Lenfant  
Bethesda, Maryland

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