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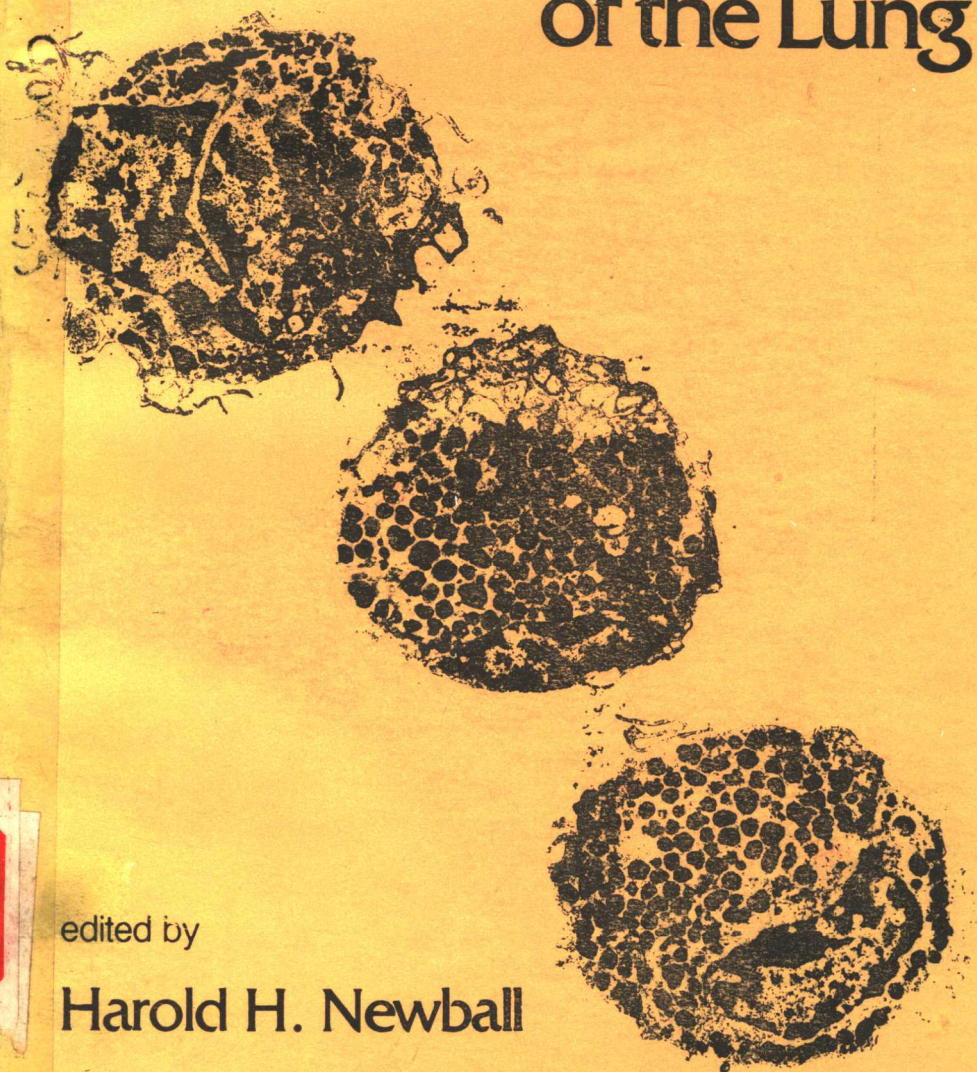

edited by

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IMMUNOPHARMACOLOGY OF THE LUNG

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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 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 respiratoty 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

Most lung diseases involve inflammatory mechanisms in one fashion or another. The elements of inflammatory processes may include: mediators of immediate hypersensitivity reactions, lymphokines, and proteolytic enzymes from mast cells, neutrophils, and macrophages, all of which may induce pathologic manifestations of the inflammatory response.

The mediators of immediate hypersensitivity reactions are numerous, with an ever increasing number. Histamine, for many decades, was considered to be the predominant mediator of immediate hypersensitivity reactions. This assumption was primarily justified by the observation that antigen-challenged, sensitized guinea pigs die of acute bronchospasm, and that this response is completely ablated by antihistamines. Recent data, however, question the importance of histamine in immediate type hypersensitivity reactions, and indeed suggest that histamine is probably of little importance in generating the symptom complex observed during many IgE-mediated reactions. This experimental data is supported by our clinical acumen which shows that antihistamines are ineffective in the therapy of bronchial asthma.

The past several years have seen the discovery of a number of potent and fascinating molecules (e.g., leukotrienes, platelet activating factor) that on a molar basis are 1000-fold more potent than histamine. These exciting discoveries have increased our knowledge of the mediators that may be operative in immunopharmacologic lesions of the lung, such as bronchial asthma. In this monograph, we have attempted to place the role of these newly discovered mediators in perspective, and to point out some of the complexities arising from these data, thus emphasizing the many questions that remain to be resolved.

Perhaps the most exciting new data relate to the chemical definition of several mediators. In the case of the leukotrienes (SRS-A), many investigators provided data that led to the experiments by C. Parker (Chapter 2), and B. Samuelsson and his colleagues which indicate that leukotrienes are products of arachidonic acid via the lipoxygenase pathway. In the last two years, the structure of platelet activating factor has been delineated by Pinckard and Hanahan—it is likewise a lipid, acetyl glyceryl ether phosphorylcholine (AGEPC).

While much attention has been given to the possible role of these low molecular weight mediators (histamine, AGEPC, leukotrienes) in inflammatory

processes, little data has been available pertaining to the possible role of high molecular weight mediators which are also actively secreted during IgE-mediated events. Recent studies with mast cells have shown that during secretory events high molecular weight mediators are actively secreted, and they do possess biological activities. Thus, during IgE-mediated events, heparin bound to a large molecular weight proteoglycan is secreted, and is biologically active. Our studies with the human lung mast cell model also show that biologically active molecules are secreted bound to large molecular weight complexes. We have described the IgE-mediated secretion of four high molecular weight mediators from human lung mast cells (Chapter 6): a lung Hageman factor activator (LHFA), a lung prekallikrein activator (LPKA), a lung kallikrein-like activity (LK-A), and a molecule exhibiting tosyl arginine methyl ester (TAMe) esterase activity. In vitro, these high molecular weight mediators are capable of generating kinins from plasma kininogen, and activating human Hageman factor. This was the first description of mediators, released by IgE mediated mechanisms, that are capable of interacting with the coagulation, and the kallikrein-kinin systems to generate biologically active peptides. In fact, this represents the only known immunologic pathway into the plasma cascade systems. These high molecular weight mediators may participate not only in immediate type inflammatory processes, but may also function in important aspects of the entire inflammatory response. While the role of these high molecular weight mediators in immediate hypersensitivity reactions and in other inflammatory processes is not clear, they do represent a first and important interface between IgE-mediated reactions and the Hageman factor dependent pathways of the inflammatory response.

The identification and characterization of several mediators of the inflammatory response provide the potential for the synthesis of antagonists and the definition of biochemical pathways; these in turn provide the potential for the development of pharmacological agents that can inhibit various aspects of the inflammatory process. Thus, the next decade of studies on the mechanisms and therapy of inflammatory processes will be fruitful. It must be recognized, however, that inflammatory disorders of the lung are extremely complex, and that we have only begun to understand the mechanisms by which inflammatory processes injure the lung.

The contributors to this book are recognized internationally as authorities on the topics that they have written. All of the authors are pioneers in their field of research, and their contributions to this volume are truly at the cutting edge of research. I highly commend the reader to this monograph.

Harold H. Newball

INTRODUCTION

> Healing is a matter of time, but it is sometimes also a matter of opportunity. However, knowing this, one must attend in medical practice not primarily to plausible theories, but to experience combined with reason. . .
>
> *Hippocrates, 5th Century B.C.*

During the last ten to fifteen years we have witnessed the birth and maturation of modern immunology. First it was a science limited to molecular biology – today it is a clinical and therapeutic instrument which has revolutionized many concepts of, and approaches to clinical medicine. In the 5th Century B.C. Hippocrates, the founder of medicine, was speaking about a matter of opportunity, medical practice, plausible theories, and reason. No other words could apply more appropriately to immunology today.

A fallout of the many advances has been the evolution of a new discipline: immunopharmacology. Because the lung is such a unique organ with regard to immune reactions, it was only natural that immunopharmacology should be applied to that organ.

This volume, edited by Harold Newball, gives us the state of the art of immunopharmacology of the lung. But it does more than that: it takes us into the future. By asking questions, it points to new research directions which will pave the way to new observations. The authorship of this volume is truly remarkable: it brings together foremost researchers and clinicians who are at the cutting edge of their field. That such an authorship could be assembled is a tribute to the editor of this monograph, and, in turn, the volume is one more asset of the series "Lung Biology in Health and Disease."

Undoubtedly, this volume will contribute greatly to the goals of the series. Hence, it is with great pleasure that I express my appreciation to all who made this book possible.

Claude Lenfant, M.D.
Bethesda, Maryland

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1

Pharmacologic Modulation of the Immune Release of Mediators from Mast Cells and Basophils

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I. Introduction

All lung diseases, with the possible exception of direct trauma, involve inflammatory processes in one fashion or another. We can now classify these elements of inflammatory processes into rather simple categories: (a) they may involve immediate hypersensitivity reactions, the sequelae of IgE-mediated processes, and the release of mediators by mast cells and basophils; (b) they may involve the action of a variety of chemotactic stimuli that attract neutrophils and stimulate these cells and macrophages to release proteolytic enzymes which, over a period of time, have the potential for the destruction of almost every element that constitutes lung tissue; (c) they may involve lymphocytes capable of releasing destructive lymphokines with direct pathologic manifestations. There is, additionally, ample evidence that the plasma cascade systems, as illustrated by the activation of the Hageman factor-dependent pathways (kinin generation, and the

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