

# ASTHMA AND COPD SECOND EDITION



Basic Mechanisms and Clinical Management

Edited by

Peter J. Barnes

Jeffrey M. Drazen

Stephen I. Rennard

Neil C. Thomson



# Asthma and COPD

## Basic Mechanisms and Clinical Management

Second Edition



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## Preface to the 2nd Edition

In the 6 years since the publication of the first edition of *Asthma and COPD* there has been substantial progress in understanding the biological basis of both of these obstructive diseases. In contrast both our understanding of the physiological basis of these conditions and their treatment has improved very little. We firmly believe that the progress made in understanding the basic disease biology that has accrued since 2002 will lead, in the years to come to new and better treatments of these crippling obstructive airway diseases. As our knowledge advances, we now appreciate the areas of overlap and distinction between these two conditions which share many physiological similarities. Most of the chapters of this book highlight both the similarities and differences between these conditions.

In this era of widely available information on the internet it is reasonable to ask what value is served by a book of this type? The answer is simple. The editors have assembled the world's experts on these topics and commissioned them to write succinct reviews focusing on their particular area of expertise. For the student of the biology or treatment of these conditions, this compilation is an important resource of up-to-date information. For the researcher or clinician, the investigative or clinical problems that each of face on a daily basis are clearly illuminated by topic experts. We hope that you will find this summary of value to you in understanding these two highly variegated, closely similar but clearly distinct entities at the biological and clinical level.

Peter J. Barnes  
Jeffery M. Drazen  
Stephen I. Rennard  
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## About the Editors

**Peter J Barnes, DM, DSc, FRCP, FMedSci, FRS**, is a Professor of Thoracic Medicine at the National Heart and Lung Institute, Head of Respiratory Medicine at Imperial College, and Honorary Consultant Physician at Royal Brompton Hospital, London. He qualified at Cambridge and Oxford Universities and was appointed to his present post in 1987. He has published over 1000 peer-review papers on asthma, COPD, and related topics and has edited over 40 books. He is also amongst the top 50 most highly cited researchers in the world and has been the most highly cited clinical scientist in the United Kingdom and the most highly cited respiratory researcher in the world over the last 20 years. He was elected a Fellow of the Royal Society in 2007, the first respiratory researcher for over 150 years. He is currently a Member of the Scientific Committee of the WHO/NIH global guidelines on asthma (GINA) and COPD (GOLD). He also serves on the Editorial Board of over 30 journals and is currently an Associate Editor of Chest and Respiratory Editor of PLoS Medicine. He has given several prestigious lectures, including the Amberson Lecture at the American Thoracic Society and the Sadoul Lecture at the European Respiratory Society.

**Neil C Thomson, MD, FRCP**, is a Professor of Respiratory Medicine at the University of Glasgow, Head of Respiratory Medicine within the Division of Immunology, Infection & Inflammation, and Honorary Consultant at Gartnavel General Hospital, Glasgow. He graduated from the University of Glasgow and undertook postgraduate training in Glasgow, London and McMaster University, Canada. He is a former Member of the Committee for Safety of Medicine and former Chair of

the Scientific Committee of the British Lung Foundation. He has co-edited several textbooks on asthma and COPD and published over 150 peer-reviewed papers on asthma. His current research interests include corticosteroid insensitivity in smokers with asthma, biomarkers in asthma and COPD and assessment of novel treatments for asthma.

**Jeffrey M Drazen, MD**, was born in St. Louis, Missouri. He graduated from Tufts University with a major in Physics, and from Harvard Medical School. He served his medical internship and residency at Peter Bent Brigham Hospital in Boston and was a Clinical Fellow and Research Fellow at Harvard Medical School and Harvard School of Public Health. Thereafter, he joined the Pulmonary Divisions of the Harvard hospitals and served for many years as Chief of the Combined Pulmonary Divisions at Beth Israel and Brigham and Women's Hospitals.

Currently, he is a Senior Physician at the Brigham and Women's Hospital, and the Distinguished Parker B. Francis Professor of Medicine at Harvard Medical School, as well as Professor of Physiology, Harvard School of Public Health, and adjunct Professor of Medicine at Boston University School of Medicine.

He has served on the NIH Respiratory and Applied Physiology Study Section, the NIH Pulmonary Disease Advisory Council, the NIH Lung Biology and Pathology Study Section, and the NHLBI Advisory Council.

Through his research, he defined the role of novel endogenous chemical agents in asthma. This led to four new licensed pharmaceuticals for asthma used in the treatment of millions of people worldwide. He has published nearly 500 papers and edited 6 books.

He has been a member of the Editorial Boards of many prestigious journals, including the *Journal of Applied Physiology*, *American Journal of Physiology*, *Pulmonary Pharmacology*, *Experimental Lung Research*, *Journal of Clinical Investigation*, *American Journal of Respiratory Cell and Molecular Biology*, and the *American Journal of Medicine*. In addition, he has been an associate editor of the *Journal of Clinical Investigation* and the *American Review of Respiratory Disease*.

In 2000, he assumed the post of Editor-in-Chief of the *New England Journal of Medicine*. During his tenure, the journal has published major papers advancing the science of medicine, including the first descriptions of SARS and papers modifying the treatment of cancer, heart disease, and lung disease. The journal, which has more than half a million readers every week, has the highest impact factor of any medical journal publishing original research.

**Stephen I Rennard, MD**, is Larson Professor of Medicine in the Pulmonary and Critical Care Medicine Section of the Department of Internal Medicine at the University of Nebraska Medical Center in Omaha, Nebraska, and courtesy Professor of the Department of Pathology and Microbiology and the Department of Genetics, Cell Biology and Anatomy. He received an AB with honors in Folklore and Mythology from Harvard University and an MD with honors from the Baylor College of Medicine, Houston, Texas. He completed internal medicine training at Barnes Hospital, Washington University, St. Louis, Missouri and trained in Pulmonary Diseases at the National

Institutes of Health where he remained for seven years, conducting research in the cell biology of lung disease.

He joined the University of Nebraska in 1984 as Chief of Pulmonary and Critical Care, a position he retained until 1997. He was the Director of the Nebraska Office of Tobacco Control and Research from 1997 until 2008.

Dr. Rennard currently serves on the Board of Directors of the COPD Foundation and the Alpha-1 Foundation. He is a member of the American Thoracic Society Committee on Corporate Relations and the National Heart Lung Education Program Executive Committee. He is an external advisor to the Thomas Petty Aspen Lung Conference and the University of California-Davis Pulmonary Training Grant.

Dr. Rennard is active in several professional societies and has previously served on the Board of Directors for the American Thoracic Society, the Council of the American Lung Association and was a Governor for the American College of Chest Physicians. He served on the American Board of Internal Medicine, Pulmonary Section and was a member of the expert panel which prepared the global GOLD guidelines for COPD for the WHO/NHLBI. He has served on several task force committees, including the ATS/ERS task force that prepared the ATS/ERS joint COPD Standards.

Professor Rennard maintains an active program of clinical investigation in COPD and smoking cessation and a program of basic research in the mechanisms of lung tissue repair and remodeling, including the role of stem cells in disease pathogenesis and repair.



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# 1

## PART

# Definitions, Epidemiology, and Genetics of Asthma and COPD





## Definitions

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Definitions of diseases evolve over time as our understanding of them changes. For example, until recently, the presence or absence of *reversibility* was considered to be the key distinction between asthma and chronic obstructive pulmonary disease (COPD) – with reversible airflow obstruction the hallmark of asthma, and irreversible airflow obstruction the hallmark of COPD. Better understanding of both diseases has brought new definitions that acknowledge the overlap and highlight the similarities and differences between them. The important change in our understanding is the recognition that chronic inflammation underlies both diseases. The nature of the inflammation differs, however, as does the response to anti-inflammatory medications, as described in detail in later chapters. This chapter draws heavily on the latest information on asthma and COPD that is included in the guidelines on the diagnosis and management of these diseases from two widely respected global initiatives, the Global Initiative for Asthma (GINA) [1] and the Global Initiative for Chronic Obstructive Lung Disease (GOLD) [2], as updated in 2006.

## DEFINITIONS

**Asthma**

Most of the definitions for asthma have emphasized the characteristics of fluctuations over time in bronchoconstriction and the reversible nature of the disease [1, 3]. As the pathophysiological basis of asthma became clearer, definitions began to include a statement about the pathological characteristics. The 2006 revision

of the GINA Guidelines [1] proposes an operational description of asthma as:

*a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role. The chronic inflammation is associated with airway hyperresponsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or in the early morning. These episodes are usually associated with widespread, but variable, airflow obstruction within the lung that is often reversible either spontaneously or with treatment.*

This is very similar to the definition proposed by the National Asthma Education and Prevention Program in their 1997 guidelines [3]. Both definitions imply that asthma is one disorder, rather than multiple complex disorders and syndromes – a notion that is receiving increasing attention [4, 5].

**COPD**

Until quite recently, definitions of COPD used to include the terms “chronic bronchitis” and “emphysema”. The GOLD Guidelines, first published in 2002 [6], and revised in 2006 [2], the American Thoracic Society/European Respiratory Society (ATS–ERS) Guidelines published in 2004 [7], and the NICE Guidelines [8, 9] published in 2004 deliberately omitted these terms and used just the umbrella term COPD. The main reason for this is that the use of many different terms for COPD has led to confusion on the part of health-care providers and the public. This in turn has stood in the way of COPD becoming widely recognized.