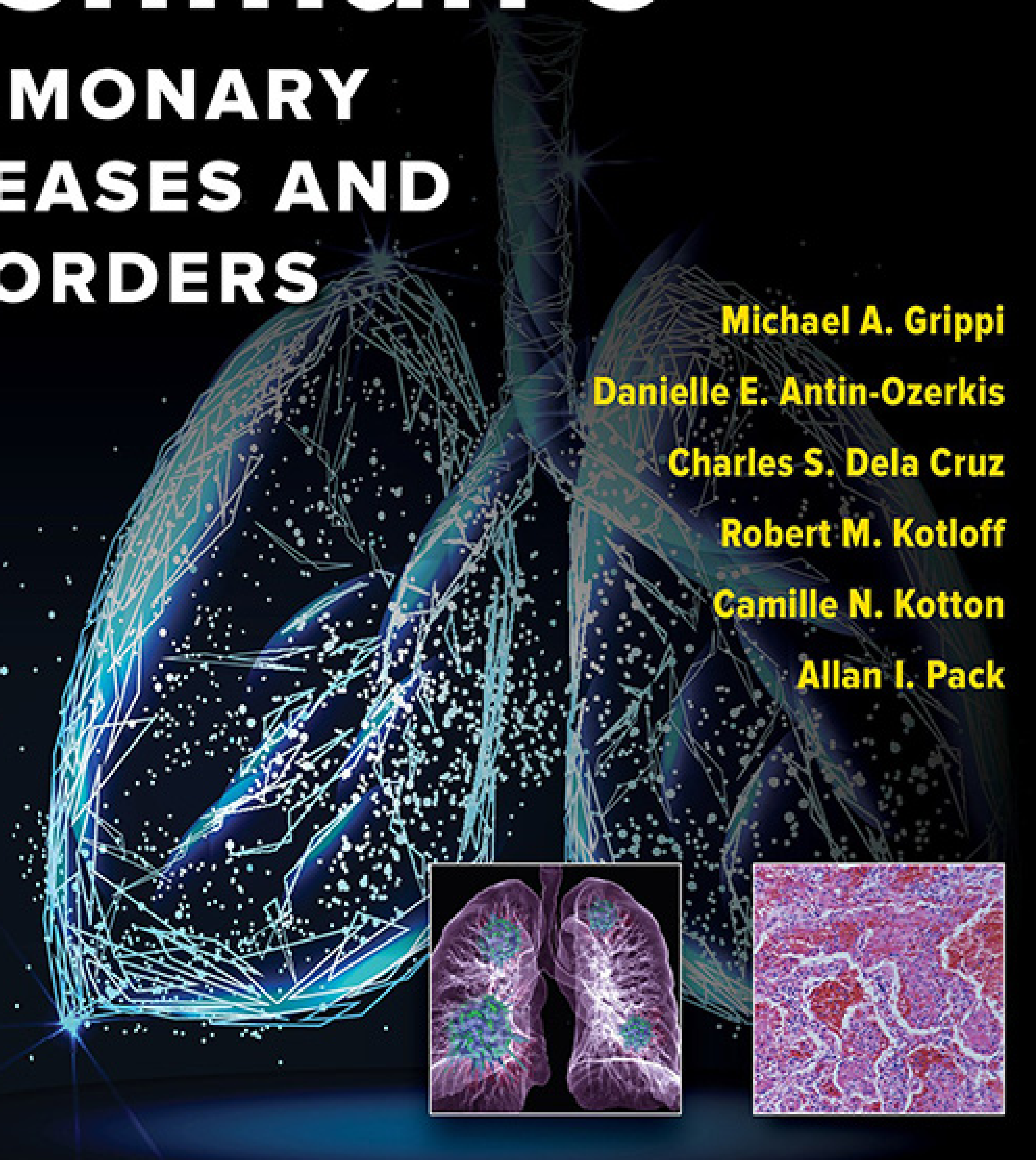
SIXTH EDITION

Fishman's
PULMONARY DISEASES AND DISORDERS

Michael A. Grippi
Danielle E. Antin-Ozerkis
Charles S. Dela Cruz
Robert M. Kotloff
Camille N. Kotton
Allan I. Pack



Mc
Graw
Hill

Fishman's Pulmonary Diseases and Disorders

Volume 1

NOTICE

Medicine is an ever-changing science. As new research and clinical experience broaden our knowledge, changes in treatment and drug therapy are required. The authors and the publisher of this work have checked with sources believed to be reliable in their efforts to provide information that is complete and generally in accord with the standards accepted at the time of publication. However, in view of the possibility of human error or changes in medical sciences, neither the authors nor the publisher nor any other party who has been involved in the preparation or publication of this work warrants that the information contained herein is in every respect accurate or complete, and they disclaim all responsibility for any errors or omissions or for the results obtained from use of the information contained in this work. Readers are encouraged to confirm the information contained herein with other sources. For example and in particular, readers are advised to check the product information sheet included in the package of each drug they plan to administer to be certain that the information contained in this work is accurate and that changes have not been made in the recommended dose or in the contraindications for administration. This recommendation is of particular importance in connection with new or infrequently used drugs.

Fishman's Pulmonary Diseases and Disorders

Sixth Edition

Volume 1

EDITOR-IN-CHIEF

Michael A. Grippi, MD

Pulmonary, Allergy, and Critical Care Division
Department of Medicine
Perelman School of Medicine at the University of Pennsylvania
Philadelphia, Pennsylvania

EDITORS

Danielle E. Antin-Ozerkis, MD

Medical Director, Yale Center for Interstitial Lung Diseases
Associate Professor of Medicine
Section of Pulmonary, Critical Care and Sleep Medicine
Yale School of Medicine
New Haven, Connecticut

Charles S. Dela Cruz, MD, PhD

Associate Professor of Medicine
Section of Pulmonary, Critical Care and Sleep Medicine
Associate Professor of Microbial Pathogenesis
Director, Center of Pulmonary Infection Research and Treatment
Yale School of Medicine
New Haven, Connecticut

Robert M. Kotloff, MD

Craig and Elaine Dobbin/Nancy P. Blumenthal
Professor of Advanced Lung Disease
Perelman School of Medicine at the University of Pennsylvania
Philadelphia, Pennsylvania

Camille Nelson Kotton, MD

Associate Professor, Harvard Medical School
Clinical Director, Transplant and Immunocompromised Host
Infectious Diseases
Infectious Diseases Division, Massachusetts General Hospital
Boston, Massachusetts

Allan I. Pack, MBChB, PhD

John Miclot Professor of Medicine
Division of Sleep Medicine
Department of Medicine
Perelman School of Medicine at the University of Pennsylvania
Philadelphia, Pennsylvania

Mc
Graw
Hill

New York Chicago San Francisco Lisbon London Madrid Mexico City
Milan New Delhi San Juan Seoul Singapore Sydney Toronto

Copyright © 2023 by McGraw Hill LLC. All rights reserved. Except as permitted under the United States Copyright Act of 1976, no part of this publication may be reproduced or distributed in any form or by any means, or stored in a database or retrieval system, without the prior written permission of the publisher.

ISBN: 978-1-26-047406-0
MHID: 1-26-047406-2

The material in this eBook also appears in the print version of this title: ISBN: 978-1-26-047398-8,
MHID: 1-26-047398-8.

eBook conversion by codeMantra
Version 1.0

All trademarks are trademarks of their respective owners. Rather than put a trademark symbol after every occurrence of a trademarked name, we use names in an editorial fashion only, and to the benefit of the trademark owner, with no intention of infringement of the trademark. Where such designations appear in this book, they have been printed with initial caps.

McGraw Hill eBooks are available at special quantity discounts to use as premiums and sales promotions or for use in corporate training programs. To contact a representative, please visit the Contact Us page at www.mhprofessional.com.

Library of Congress Cataloging-in-Publication Data

Names: Grippi, Michael A., editor.
Title: Fishman's pulmonary diseases and disorders / editor-in-chief, Michael A. Grippi ; co-editors, Danielle E. Antin-Ozerkis, Charles S. Dela Cruz, Robert M. Kotloff, Camille N. Kotton,
Allan I. Pack
Other titles: Pulmonary diseases and disorders
Description: Sixth edition. | New York : McGraw-Hill Education, [2023] | Includes bibliographical references and index. | Summary: "A presentation of pulmonary and critical care medicine with the underlying basic and applied science upon which the clinical material is based. The book includes relevant respiratory biology and underlying cellular and molecular mechanisms, and incorporates of a number of videos designed to complement and, at times, accentuate information contained within the text"– Provided by publisher.
Identifiers: LCCN 2021052087 | ISBN 9781260473988 (hardcover ; set ; alk. paper) | ISBN 9781260474060 (ebook)
Subjects: MESH: Lung Diseases
Classification: LCC RC756 | NLM WF 600 | DDC 616.2/4–dc23/eng/20220510
LC record available at https://lccn.loc.gov/2021052087

TERMS OF USE

This is a copyrighted work and McGraw-Hill Education and its licensors reserve all rights in and to the work. Use of this work is subject to these terms. Except as permitted under the Copyright Act of 1976 and the right to store and retrieve one copy of the work, you may not decompile, disassemble, reverse engineer, reproduce, modify, create derivative works based upon, transmit, distribute, disseminate, sell, publish or sublicense the work or any part of it without McGraw-Hill Education's prior consent. You may use the work for your own noncommercial and personal use; any other use of the work is strictly prohibited. Your right to use the work may be terminated if you fail to comply with these terms.

THE WORK IS PROVIDED "AS IS." McGRAW-HILL EDUCATION AND ITS LICENSORS MAKE NO GUARANTEES OR WARRANTIES AS TO THE ACCURACY, ADEQUACY OR COMPLETENESS OF OR RESULTS TO BE OBTAINED FROM USING THE WORK, INCLUDING ANY INFORMATION THAT CAN BE ACCESSED THROUGH THE WORK VIA HYPERLINK OR OTHERWISE, AND EXPRESSLY DISCLAIM ANY WARRANTY, EXPRESS OR IMPLIED, INCLUDING BUT NOT LIMITED TO IMPLIED WARRANTIES OF MERCHANTABILITY OR FITNESS FOR A PARTICULAR PURPOSE. McGraw-Hill Education and its licensors do not warrant or guarantee that the functions contained in the work will meet your requirements or that its operation will be uninterrupted or error free. Neither McGraw-Hill Education nor its licensors shall be liable to you or anyone else for any inaccuracy, error or omission, regardless of cause, in the work or for any damages resulting therefrom. McGraw-Hill Education has no responsibility for the content of any information accessed through the work. Under no circumstances shall McGraw-Hill Education and/or its licensors be liable for any indirect, incidental, special, punitive, consequential or similar damages that result from the use of or inability to use the work, even if any of them has been advised of the possibility of such damages. This limitation of liability shall apply to any claim or cause whatsoever whether such claim or cause arises in contract, tort or otherwise.

DEDICATION

This book is dedicated to the many clinicians worldwide who have devoted themselves to caring for those affected by SARS-CoV-19 and to the scientists who developed vaccines and therapeutic modalities directed against the virus.

MAG: To my wife, Barbara, and to our daughters, Kristen and Amy, for their steadfast support over the years, and to their families—Emily, Ali, Sawyer, Sophie, Levi, and Kieran.

DAO: To my husband, Eric, and our daughters, Orly and Daya. If you are going to spend a pandemic with anyone, you might as well laugh a lot. And to my patients, from whom I learn every day.

CDC: I would like to thank my family, friends, and all the mentors in pulmonary and critical care medicine who helped support me throughout my career. I would also like to thank my patients, from whom I have learned so much and who have been the motivation for my current work.

RMK: To my wife, Debbie, and my sons, Eric, Brian, and Ethan, for their unwavering love and support. And to the memory of my parents, Jean and Leon Kotloff, for instilling in me the principles by which I live my life and practice my profession.

CNK: Thanks to my husband, Darrell Kotton, and to our wonderful sons, David and Benjamin, for their thoughtfulness and support, especially as we navigated our family through the peaks of the COVID-19 pandemic. And thanks to my patients over the years, who have taught me so much about medicine, but also about resilience, optimism, and hope.

AIP: To my very supportive wife, Frances; my long-collaborating Administrative Assistant, Daniel Barrett; my four children, Alison, Angela, Andrew, and Allan Junior; and our 11 grandchildren.

This page intentionally left blank

CONTENTS

VOLUME 1

PART 1: Perspectives

PART 2: Scientific Basis of Lung Function in Health and Disease

SECTION 1 Genetic, Cellular, and Structural Basis of Normal Lung Function

SECTION 2 Physiological Principles of Normal Lung Function

SECTION 3 Lung Immunology

SECTION 4 Lung Injury and Repair

PART 3: Symptoms and Signs of Respiratory Disease

SECTION 5 Clinical Approach to the Patient

SECTION 6 Diagnostic Procedures

PART 4: Obstructive Lung Diseases

SECTION 7 Chronic Obstructive Pulmonary Disease

SECTION 8 Asthma

SECTION 9 Other Obstructive Disorders

PART 5: Interstitial and Inflammatory Lung Diseases

PART 6: Drug-Induced Lung Diseases

PART 7: Other Infiltrative and Airspace Disorders

PART 8: Disorders of the Pulmonary Circulation

PART 9: Disorders of the Pleural Space

VOLUME 2

PART 10: Diseases of the Mediastinum

PART 11: Disorders of the Chest Wall, Diaphragm, and Spine

PART 12: Occupational and Environmental Disorders

SECTION 10 Occupational Disorders

SECTION 11 Environmental Disorders

PART 13: Pulmonary Complications of Nonpulmonary Disorders

PART 14: Sleep and Sleep Disorders

PART 15: Surgical Aspects of Pulmonary Medicine

PART 16: Cancer and Other Malignancies of the Lungs

PART 17: Infectious Diseases of the Lungs

SECTION 12 General Concepts

SECTION 13 Common Syndromes in Pulmonary Infectious Diseases

SECTION 14 Major Pathogens in Pulmonary Infections

PART 18: Respiratory Failure

SECTION 15 Lung Failure

SECTION 16 Respiratory Pump Failure

SECTION 17 Management and Therapeutic Interventions

APPENDIXES

CONTRIBUTORS

Gerald F. Abbott, MD, FACR
Department of Radiology
Division of Thoracic Imaging & Intervention
Massachusetts General Hospital
Associate Professor, Harvard Medical School
Boston, Massachusetts
Chapter 117

Abass Alavi, MD, PhD (hon.), DSci (hon.)
Professor of Radiology and Neurology
Perelman School of Medicine at the University of Pennsylvania
Pennsylvania University Hospital
Philadelphia, Pennsylvania
Chapter 30

Timothy E. Albertson, MD, MPH, PhD
Chair, Internal Medicine, Distinguished Professor of Medicine
Pharmacology & Toxicology, Anesthesia & Emergency Medicine
Department of Internal Medicine
Division of Pulmonary, Critical Care and Sleep Medicine
University of California
Department of Emergency Medicine, University of California, Davis, Sacramento
Veterans Administration Northern California Health Care System, Department of Medicine
Mather, California
Chapter 66

John S. Albin, MD, PhD
Instructor, Harvard Medical School
Assistant in Medicine, Division of Infectious Diseases
Massachusetts General Hospital
Boston, Massachusetts
Chapter 131

Micheala A. Aldred, PhD
Professor of Medicine
Catherine and Lowe Berger and Pauline L. Ford Chair of Pulmonary Medicine
Department of Medicine
Division of Pulmonary, Critical Care, Sleep & Occupational Medicine
Indiana University School of Medicine
Indianapolis, Indiana
Chapter 7

Timothy Craig Allen, MD, JD, FCAP
Professor and Chair
Department of Pathology
The University of Mississippi Medical Center
Jackson, Mississippi
Chapter 67

Konstantinos-Dionysios Alysandratos, MD, PhD
Assistant Professor of Medicine
The Pulmonary Center and Department of Medicine
Boston University School of Medicine
Attending Physician
Department of Medicine
Boston Medical Center
Boston, Massachusetts
Chapter 8

Brian J. Anderson, MD, MSCE
Assistant Professor of Medicine
Department of Medicine
Division of Pulmonary, Allergy & Critical Care Medicine
Hospital of the University of Pennsylvania
Philadelphia, Pennsylvania
Chapter 146

Danielle E. Antin-Ozerkis, MD
Medical Director, Yale Center for Interstitial Lung Diseases
Associate Professor of Medicine
Section of Pulmonary, Critical Care and Sleep Medicine
Yale School of Medicine
New Haven, Connecticut
Chapter 52

Reuben J. Arasaratnam, MD, MPH
Staff Physician, Section of Infectious Diseases
VA North Texas Health Care System
Assistant Professor of Medicine
Division of Infectious Diseases and Geographic Medicine
UT Southwestern Medical Center
Dallas, Texas
Chapter 137

Silvia Asioli, MD
Team Leader of Haematopathology and Consultant
Department of Anatomic Pathology
Ospedale GB Morgagni
Forlì, Italy
Chapter 119

Olga I. Astapova, MD, PhD
Assistant Professor, Department of Medicine
Division of Endocrinology
University of Rochester Medical Center
University of Rochester School of Medicine and Dentistry
Rochester, New York
Chapter 62

Joshua H. Atkins, MD, PhD, FASA
Associate Professor of Anesthesiology & Critical Care
Department of Anesthesiology and Critical Care
Perelman School of Medicine at the University of Pennsylvania
Attending Physician, Co-Chair Airway Safety Committee
Director of Anesthesia for Head and Neck Surgery
Medical Director In-situ Simulation
Department of Anesthesiology and Critical Care
Hospital of the University of Pennsylvania
Philadelphia, Pennsylvania
Chapter 145

Marwan M. Azar, MD
Assistant Professor of Medicine/Infectious Diseases
Section of Infectious Diseases
Department of Internal Medicine
Yale University School of Medicine
Department of Laboratory Medicine
Yale University School of Medicine
New Haven, Connecticut
Chapter 134

Tara M. Babu, MD, MSCI
Acting Assistant Professor
Department of Medicine
Division of Allergy & Infectious Diseases
University of Washington
Seattle, Washington State
Chapter 137

Nathan C. Bahr, MD
Associate Professor
Department of Internal Medicine
Division of Infectious Diseases
University of Kansas Medical Center
Kansas City, Kansas
Chapter 133

Stephen R. Baldassarri, MD, MHS
Department of Internal Medicine
Section of Pulmonary, Critical Care, and Sleep Medicine
Yale School of Medicine
New Haven, Connecticut
Chapter 41

Debasree Banerjee, MD, MS
Assistant Professor, Department of Medicine, Brown University
Director, Critical Care Consult, Rhode Island Hospital
Providence, Rhode Island
Chapter 96

Tami J. Bang, MD
Assistant Professor
Department of Radiology, Division of Cardiothoracic Imaging
University of Colorado—Anschutz Medical Campus
Aurora, Colorado
Chapter 61

Eduardo J. Mortani Barbosa Jr., MD
Assistant Professor of Radiology
Director of Thoracic CT modality
Department of Radiology
Perelman School of Medicine at the University of Pennsylvania
Philadelphia, Pennsylvania
Chapter 28

Peter J. Barnes, DM, DSc, FRCP, FCCP, FMedSci, FRS
Professor of Thoracic Medicine
National Heart & Lung Institute, Imperial College London
London, United Kingdom
Chapter 45

Sonja D. Bartolome, MD
Professor, Department of Internal Medicine, University of Texas
Southwestern Medical Center
Dallas, Texas
Chapter 97

Cynthia M. Beall, PhD
Professor, Anthropology
Case Western Reserve University
Cleveland, Ohio
Chapter 91

Matthew C. Bell, MD
Assistant Professor of Medicine and Pediatrics
Department of Pediatrics
Division of Allergy & Immunology
University of Arkansas for Medical Sciences
Arkansas Children's Hospital
Little Rock, Arkansas
Chapter 43

Seth A. Bellister, MD
Department of Trauma and Acute Care Surgery
Christus Mother Frances Hospital
Tyler, Texas
Chapter 104

Ghada Bourjeily, MD
Professor of Medicine
Warren Alpert Medical School of Brown University
Associate Chief for Academic Advancement and
Research in Women's Services
Women's Medicine Collaborative of Lifespan
Department of Medicine
The Miriam Hospital
Providence, Rhode Island
Chapter 96

James P. Bridges, PhD
Associate Professor
Department of Medicine
National Jewish Health
Denver, Colorado
Chapter 5

Carl D. Britto, MBBS, DPhil
Clinical Fellow in Pediatrics, Harvard Medical School
Resident in Pediatrics, Department of Pediatrics
Boston Children's Hospital
Boston, Massachusetts
Chapter 124

Clemente J. Britto, MD
Assistant Professor of Medicine
Associate Director, Yale Adult Cystic Fibrosis Program
Department of Internal Medicine
Division of Pulmonary, Critical Care and Sleep Medicine
Yale University School of Medicine
New Haven, Connecticut
Chapter 19

Nathan E. Brummel, MD, MSCI, FCCM
Associate Professor of Medicine
Department of Internal Medicine
Division of Pulmonary, Critical Care, and Sleep Medicine
The Ohio State University Columbus, Ohio
Chapter 151

A. Cole Burks, MD
Assistant Professor of Medicine
Division of Pulmonary and Critical Care Medicine
University of North Carolina at Chapel Hill
Interventional Pulmonology, University of North Carolina Medical Center
Chapel Hill, North Carolina
Chapter 112

William W. Busse, MD
Emeritus Professor of Medicine
Department of Medicine
Division of Allergy, Pulmonary and Critical Care Medicine
University of Wisconsin School of Medicine and Public Health
Madison, Wisconsin
Chapter 43

Marcus W. Butler, MD, FRCPI
Associate Professor
University College Dublin School of Medicine
Consultant Respiratory Physician
St. Vincent's University Hospital
Dublin, Ireland
Chapter 24

Hilary C. Cain, MD, MS
Associate Professor of Medicine
Section of Pulmonary, Critical Care and Sleep Medicine
Yale School of Medicine
New Haven, Connecticut
Section Chief, Pulmonary Medicine
VA Connecticut Healthcare System
West Haven, Connecticut
Chapter 65

Jeffrey P. Callen, MD, FACP, MAAD, MACR
Professor of Medicine (Dermatology)
Chief, Division of Dermatology
University of Louisville School of Medicine
Louisville, Kentucky
Chapter 27

Edward J. Campbell, MD
Heredilab, Inc.
Salt Lake City, Utah
Chapter 18

Wellington V. Cardoso, MD, PhD
Professor of Medicine and Genetics & Development
Columbia Center for Human Development
Department of Medicine
Columbia University Medical Center
New York, New York
Chapter 4

Brenna Carey, MS, PhD
Assistant Professor of Medicine
Department of Pediatrics, University of Cincinnati
Cincinnati Children's Hospital Medical Center
Cincinnati, Ohio
Chapter 70

Laurie L. Carr, MD
Associate Professor of Medicine
Division of Oncology
National Jewish Health and University of Colorado
Denver, Colorado
Chapter 114

Rodrigo Cartin-Ceba, MD, MSc
Professor of Medicine, Mayo Clinic College of
Medicine and Science
Consultant, Department of Medicine
Division of Pulmonary Medicine, Mayo Clinic
Phoenix, Arizona
Chapter 74

David M. Center, MD
Gordon and Ruth Snider Professor of Pulmonary Medicine
Associate Provost for Translational Research
Professor of Medicine
Department of Medicine
Boston University
Chief, Pulmonary, Allergy, Sleep and Critical Care Medicine
Boston Medical Center
Boston, Massachusetts
Chapter 20

Georgios Chamilos, MD
Professor of Medicine
Department of Internal Medicine
School of Medicine, Stavrakia, Voutes
University of Crete Heraklion
Crete, Greece
Chapter 132

Giuliana Cerro Chiang, MD
Fellow in Pulmonary & Critical Care Medicine
Department of Medicine
Cedars-Sinai Medical Center
Los Angeles, California
Chapter 54

Edward S. Chen, MD
Assistant Professor
Division of Pulmonary and Critical Care Medicine
Johns Hopkins University School of Medicine
Attending Physician, Department of Medicine
Division of Pulmonary and Critical Care Medicine
Johns Hopkins Hospital
Baltimore, Maryland
Chapter 53

James A. Chenoweth, MD, MAS
Assistant Professor, Emergency Medicine
Department of Emergency Medicine
University of California, Davis
Sacramento, California
Veterans Administration Northern
Department of Medicine California Health Care System
Mather, California
Chapter 66

Asha N. Chesnutt, MD
The Oregon Clinic
Pulmonary, Critical Care & Sleep Medicine
Portland, Oregon
Chapter 140

Humberto K. Choi, MD
Assistant Professor of Medicine of Lerner College of Medicine of Case
Western Reserve University
Respiratory Institute, Cleveland Clinic
Cleveland, Ohio
Chapter 109

David C. Christiani, MD, MPH, MS
Elkan Blout Professor of Environmental Genetics
Department of Environmental Health
Harvard T.H. Chan School of Public Health
Professor of Medicine
Harvard Medical School
Physician, Pulmonary and Critical Care Division
Department of Medicine
Massachusetts General Hospital
Boston, Massachusetts
Chapter 88

Jason D. Christie, MD, MSCE
Professor of Medicine and Epidemiology
Division of Pulmonary, Allergy, and Critical Care
Department of Medicine
Perelman School of Medicine at the University of Pennsylvania
Philadelphia, Pennsylvania
Chapter 141

Geoffrey L. Chupp, MD
Professor of Medicine
Yale School of Medicine
Director, Yale Center for Asthma and Airway Disease
Director, Pulmonary Function Laboratory, Yale New Haven Hospital
New Haven, Connecticut
Chapters 43 and 46

Andrew Churg, MD, PhD
Professor of Pathology, University of British Columbia Pathologist
Vancouver General Hospital
Vancouver, British Columbia, Canada
Chapter 37

Brian J. Clark, MD
Assistant Professor, Section of Pulmonary, Critical Care and Sleep Medicine
Yale School of Medicine
New Haven, Connecticut
VA Connecticut Healthcare System
West Haven, Connecticut
Chapter 71

Lauren Cohn, MD
Associate Professor
Department of Medicine, Section of Pulmonary,
Critical Care and Sleep Medicine
Yale School of Medicine, New Haven, Connecticut
VA Connecticut Healthcare System
West Haven, Connecticut
Chapters 23 and 71

Gregory P. Cosgrove, MD
Associate Professor
Department of Medicine
Division of Pulmonary Sciences and Critical Care Medicine
University of Colorado—Anschutz Medical Campus
Denver, Colorado
Chapter 58

Gerard Joseph Criner, MD
Chair and Professor of Thoracic Medicine and Surgery
Department of Thoracic Medicine and Surgery
Lewis Katz School of Medicine at Temple University
Philadelphia, Pennsylvania
Chapter 84

Megan Rose Curtis, MD, MS
Research Fellow, Harvard Medical School
Associate Physician, Division of Infectious Diseases,
Brigham and Women's Hospital
Boston, Massachusetts
Chapter 122

James B. Cutrell, MD
Associate Professor of Internal Medicine
Program Director, Infectious Diseases Fellowship Program
Director, Antimicrobial Stewardship, Clements University Hospital and UTSW Health Systems
Department of Internal Medicine
Division of Infectious Diseases and Geographic Medicine
University of Texas Southwestern Medical Center
Dallas, Texas
Chapter 136

Erin DeBiasi, MD
Assistant Professor of Medicine
Department of Internal Medicine
Section of Pulmonary,
Critical Care, and Sleep Medicine
Yale School of Medicine
New Haven, Connecticut
Chapters 47 and 64

Malcolm M. DeCamp, MD, FACS
Professor and Chair, Division of Cardiothoracic Surgery
University of Wisconsin Hospitals and Clinics
Madison, Wisconsin
Chapter 81

Roy H. Decker, MD, PhD
Professor, Department of Therapeutic Radiology
Yale School of Medicine
Radiation Oncologist
Yale New Haven Hospital
New Haven, Connecticut
Chapter 57

Marc Decramer, MD, PhD
Emeritus Professor of Medicine
University of Leuven
Laboratory of Respiratory Diseases and Thoracic Surgery (BREATHE)
Department of Chronic Diseases and Metabolism (CHROMETA), KU-Leuven
Leuven, Belgium
Chapter 3

Charles S. Dela Cruz, MD, PhD
Associate Professor of Medicine
Section of Pulmonary, Critical Care and Sleep Medicine
Associate Professor of Microbial Pathogenesis
Director, Center of Pulmonary Infection Research and Treatment
Yale School of Medicine
New Haven, Connecticut
Chapters 19 and 108

Horace M. DeLisser, MD
Associate Professor of Medicine
Department of Medicine
Associate Dean for Diversity and Inclusion
Perelman School of Medicine at the University of Pennsylvania
Philadelphia, Pennsylvania
Chapters 105 and 152

Bradley M. Dennis, MD
Associate Professor of Surgery
Division of Acute Care Surgery,
Vanderbilt University School of Medicine
Trauma Medical Director, Vanderbilt University Medical Center
Associate Chief of Staff, Vanderbilt University Hospital
Nashville, Tennessee
Chapter 104

Jessy Deshane, PhD
Associate Professor
Department of Medicine
Division of Pulmonary Allergy and Critical Care Medicine
University of Alabama at Birmingham
Birmingham, Alabama
Chapter 25

Himanshu Deshwal, MD
Fellow in Pulmonary Disease and Critical Care Medicine
Division of Pulmonary, Critical Care, and Sleep Medicine
New York University Grossman School of Medicine
New York, New York
Chapter 105

Joshua M. Diamond, MD, MSCE
Associate Professor of Medicine
Department of Medicine
Division of Pulmonary, Allergy and Critical Care Medicine
University of Pennsylvania
Philadelphia, Pennsylvania
Chapter 121

David M. DiBardino, MD
Assistant Professor of Clinical Medicine
Section of Interventional Pulmonology
Division of Pulmonary, Allergy and Critical Care
Perelman School of Medicine at the University of Pennsylvania
Philadelphia, Pennsylvania
Chapter 33

Burton F. Dickey, MD
Clifton Howe Distinguished Professor of Pulmonary Medicine
University of Texas MD Anderson Cancer Center
Houston, Texas
Chapter 6

John D. Dickinson, MD, PhD
Assistant Professor of Medicine
Department of Internal Medicine
Division of Pulmonary, Critical Care, and Sleep Medicine
University of Nebraska Medical Center
Omaha, Nebraska
Chapter 6

Jennifer J. Dorsch, MD
Assistant Professor of Clinical Medicine
Perelman School of Medicine at the University of Pennsylvania
Division of Sleep Medicine,
The Hospital of the University of Pennsylvania
Associate Director, Sleep Non-Invasive Ventilation Program
Philadelphia, Pennsylvania
Chapter 142

Jonathan E. Dowell, MD
Professor of Internal Medicine
Division of Hematology/Oncology
UT Southwestern
Dallas, Texas
Chapter 116

Mark T. Dransfield, MD
Professor of Medicine, Endowed Chair in Pulmonary Disease
Division of Pulmonary, Allergy, and Critical Care Medicine
Lung Health Center
University of Alabama at Birmingham
Birmingham VA Medical Center
Birmingham, Alabama
Chapter 38

Benjamin J. Drapkin, MD, PhD
Assistant Professor of Internal Medicine
Division of Hematology/Oncology
UT Southwestern
Dallas, Texas
Chapter 116

M. Bradley Drummond, MD, MHS
Associate Professor of Medicine
Division of Pulmonary Diseases and Critical Care Medicine
University of North Carolina at Chapel Hill
Attending Physician
University of North Carolina at Chapel Hill Medical Center
Chapel Hill, North Carolina
Chapter 40

Hilary M. DuBrock, MD
Assistant Professor, Department of Internal Medicine
Mayo Clinic
Rochester, Minnesota
Chapter 97

Daniel G. Dunlap, MD
Assistant Professor of Medicine
Division of Pulmonary, Allergy, and Critical Care Medicine
University of Pittsburgh
Pittsburgh, Pennsylvania
Chapter 34

Ghassan El-Haddad, MD
Section Head, Radionuclide Therapy Program
Associate Member, Interventional Radiology
Associate Member, Cancer Physiology
H. Lee Moffitt Cancer Center and Research Institute
Associate Professor of Radiology and Oncologic Sciences
University of South Florida
Tampa, Florida
Chapter 30

Davide Elia, MD
Unità di Pneumologia e Terapia Semi-Intensiva Respiratoria
Servizio di Fisiopatologia Respiratoria ed Emodinamica Polmonare
Ospedale San Giuseppe, MultiMedica IRCCS
Milano, Italy
Chapter 59

Richard I. Enelow, MD
Professor of Medicine, and of Microbiology and Immunology
Geisel School of Medicine at Dartmouth
Dartmouth-Hitchcock Medical Center
Lebanon, New Hampshire
Chapter 56

Kyle B. Enfield, MD, MS
Associate Professor of Medicine
Section Chief, Critical Care
Department of Medicine
Division of Pulmonary and Critical Care Medicine
University of Virginia School of Medicine
Associate Chief Medical Officer for Critical Care UVA Health
Charlottesville, Virginia
Chapter 127

Perenlei Enkhbaatar, MD, PhD, FAHA
Professor, Department of Anesthesiology
Director, Translational Intensive Care Unit
Charles Robert Allen Professor in Anesthesiology
The University of Texas Medical Branch
Galveston, Texas
Chapter 93

Gary R. Epler, MD
Clinical Associate Professor
Harvard Medical School
Pulmonary and Critical Care Medicine
Brigham and Women's Hospital
Boston, Massachusetts
Chapter 49

Rodolfo A. Estrada, MD
Assistant Professor of Medicine
Division of Pulmonary and Critical Care
UT Health San Antonio/University of Texas Health Science Center San Antonio
San Antonio, Texas
Chapter 79

Peter F. Fedullo, MD
Clinical Professor of Medicine
University of California San Diego Health
Division of Pulmonary, Critical Care, and Sleep Medicine
San Diego, California
Chapter 73

David Feller-Kopman, MD
Professor of Medicine, Department of Medicine, Geisel School of Medicine
Chief, Pulmonary and Critical Care Medicine,
Dartmouth Hitchcock Medical Center
Lebanon, New Hampshire
Chapter 76

Thomas W. Ferkol, MD
Alexis F. Hartmann M.D. Professor of Pediatrics
Department of Pediatrics
Professor, Department of Cell Biology and Physiology
Washington University School of Medicine
St. Louis Children's Hospital
St. Louis, Missouri
Chapter 6

Timothy M. Fernandes, MD, MPH
Associate Clinical Professor of Medicine
University of California, San Diego School of Medicine
Division of Pulmonary, Critical Care and Sleep Medicine
La Jolla, California
Chapter 73

Barry G. Fields, MD, MSEd
Associate Professor of Medicine
Division of Pulmonary, Allergy, Critical Care, and Sleep Medicine
Emory University School of Medicine
Sleep Physician, Sleep Medicine Center, Atlanta VA Health Care System
Atlanta, Georgia
Chapter 98

Michael C. Fishbein, MD
Distinguished Professor of Pathology and Medicine
Department of Pathology and Laboratory Medicine
David Geffen School of Medicine at UCLA
Ronald Reagan Medical Center
Los Angeles, California
Chapter 68

Christopher Gange, MD
Assistant Professor, Radiology and Biomedical Imaging
Yale University School of Medicine
Thoracic Radiologist
Yale New Haven Hospital
New Haven, Connecticut
Chapter 63

David E. Gerber, MD
David Bruton, Jr. Professorship in Clinical Cancer Research
Departments of Internal Medicine and Population and Data Sciences
Division of Hematology/Oncology
UT Southwestern
Dallas, Texas
Chapter 116

Ghislaine Gayan-Ramirez, PhD
Professor at University of Leuven
Laboratory of Respiratory Diseases and Thoracic Surgery (BREATHE)
Department of Chronic Diseases and Metabolism (CHROMETA),
KU-Leuven
Leuven, Belgium
Chapter 3

Subha Ghosh, MD, MBA
Assistant Professor, Lerner College of Medicine of Case Western Reserve University
Staff Physician
Imaging Institute, Section of Thoracic Imaging
Cleveland Clinic Foundation
Cleveland, Ohio
Chapter 105

Timothy D. Girard, MD, MSCI, ATSF
Associate Professor of Critical Care Medicine
Department of Critical Care Medicine
University of Pittsburgh
Pittsburgh, Pennsylvania
Chapter 151

Mark T. Gladwin, MD
Vice President for Medical Affairs, UM Baltimore
John Z. and Akiko K. Bowers Distinguished Professor and Dean, University of Maryland School of Medicine
Baltimore, Maryland
Chapter 95

Stanley Goldfarb, MD
Former Associate Dean for Curriculum
Perelman School of Medicine at the University of Pennsylvania
Philadelphia, Pennsylvania
Chapter 17

Michael A. Grippi, MD
Pulmonary, Allergy, and Critical Care Division
Department of Medicine
Perelman School of Medicine at the University of Pennsylvania
Philadelphia, Pennsylvania
Chapters 1, 10, 27, 31, 102, and 139

Marco Guazzi, MD, PhD
Professor of Cardiology,
University of Milano School of Medicine
Head of Cardiology Division
San Paolo University Hospital
Milano, Italy
Chapter 32

Mridu Gulati, MD, MPH
Associate Professor
Departments of Internal Medicine
Section of Pulmonary, Critical Care and Sleep Medicine
Yale School of Medicine
New Haven, Connecticut
Chapter 55

Akash Gupta, MD
Instructor, Harvard Medical School
Assistant in Medicine, Department of Medicine
Division of Infectious Diseases
Massachusetts General Hospital
Boston, Massachusetts
Chapter 130

Nishant Gupta, MD, MS
Associate Professor
Division of Pulmonary, Critical Care and Sleep Medicine
University of Cincinnati
Cincinnati, Ohio
Chapter 61

Indira Gurubhagavatula, MD, MPH, FAASM
Associate Professor of Medicine, Division of Sleep Medicine
Perelman School of Medicine at the University of Pennsylvania
Corporal Michael Crescenz VA Medical Center
Philadelphia, Pennsylvania
Chapter 100

Jacob Gutsche, MD
Associate Professor
Department of Anesthesiology and Critical Care
Perelman School of Medicine at the University of Pennsylvania
Philadelphia, Pennsylvania
Chapter 149

Duc M. Ha, MD, MAS
Assistant Professor of Medicine
Department of Medicine
University of Colorado Anschutz Medical Campus
Staff Physician, Section of Pulmonary and Critical Care
Rocky Mountain Regional Veterans Affairs Medical Center
Aurora, Colorado
Chapter 42

Andrew R. Haas, MD, PhD
Associate Professor of Medicine
Director, Section of Interventional Pulmonary and Thoracic Oncology
Pulmonary, Allergy, and Critical Care Division
Perelman School of Medicine at the University of Pennsylvania
Philadelphia, Pennsylvania
Chapter 34

Ramsey R. Hachem, MD
Professor of Medicine
Division of Pulmonary and Critical Care Medicine
Department of Medicine
Washington University in St. Louis
Medical Director of Lung Transplantation
Barnes-Jewish Hospital
St. Louis, Missouri
Chapter 106

Chadi A. Hage, MD, ATSF
Professor of Medicine
University of Pittsburgh
Pulmonary, Allergy, and Critical Care Medicine
McGowan Institute for Regenerative Medicine
Medical Director, Lung Transplant
University of Pittsburgh Medical Center
Pittsburgh, Pennsylvania
Chapter 133

Kelly M. Hager, MD, MPH
Fellow, Yale Occupational and Environmental Medicine
Department of Medicine, Yale University School of Medicine
New Haven, Connecticut
Chapter 55

Stephen R. Hammes, MD, PhD
Professor and Chief, Division of Endocrinology
Department of Medicine
University of Rochester School of Medicine and Dentistry
Rochester, New York
Chapter 62

Sergio Harari, MD
Professor of Internal Medicine
University of Milan
Unità di Pneumologia e Terapia Semi-Intensiva Respiratoria
Servizio di Fisiopatologia Respiratoria ed Emodinamica Polmonare
Ospedale San Giuseppe, MultiMedica IRCCS
Department of Medical Sciences, San Giuseppe Hospital
MultiMedica IRCCS
Department of Clinical Sciences and Community Health
Università degli Studi di Milano
Milan, Italy
Chapter 59

Howard M. Heller, MD, MPH
Assistant Professor of Medicine, Harvard Medical School
Infectious Disease Division, Massachusetts General Hospital
Boston, Massachusetts
Chapter 138

Michael J. Herriges, PhD
Post-doctoral Fellow
Center for Regenerative Medicine (CReM) of Boston
University and Boston Medical Center
Boston, Massachusetts
Chapter 8

Søren Hess, MD
Chief Physician, Head of Section (Nuclear Medicine & PET)
Department of Radiology and Nuclear Medicine
Hospital South West Jutland
Esbjerg, Denmark
Clinical Associate Professor, Head of Research (Imaging)
Research Unit for Radiology and Nuclear Medicine
Department of Regional Health Research, Faculty of Health Sciences
University of Southern Denmark
Odense, Denmark
Chair, Danish Society of Clinical Physiology and Nuclear Medicine
Aarup, Denmark
Chapter 30

Janet Hilbert, MD
Associate Professor of Clinical Medicine
Medical Director of Yale Noninvasive Ventilation Program
Division of Pulmonary and Critical Care Medicine
Yale University
New Haven, Connecticut
Chapter 148

Robert J. Homer, MD, PhD
Professor of Pathology
Yale University School of Medicine
New Haven, Connecticut
Chapter 63

Gary B. Huffnagle
Department of Internal Medicine
Department of Molecular Cell and Developmental Biology
Division of Pulmonary and Critical Care Medicine
University of Michigan Medical Center
Ann Arbor, Michigan
Chapter 120

Rocio M. Hurtado, MD
Assistant Professor of Medicine, Harvard Medical School
Director, Mycobacterial Center, Division of Infectious Diseases
Massachusetts General Hospital
Boston, Massachusetts
Chapter 131

Louise C. Ivers, MD, MPH
Professor of Medicine, Professor of Global Health and Social Medicine, Harvard Medical School
Director, Center for Global Health, Massachusetts General Hospital
Boston, Massachusetts
Chapter 135

Karen R. Jacobson, MD, MPH
Associate Professor of Medicine
Section of Infectious Diseases
Boston University School of Medicine and Boston Medical Center
Boston, Massachusetts
Chapter 130

Frank J. Jacono, MD
Virginia Hubbell Chair in Pulmonary and Critical Care and Tenured Professor of Medicine
Case Western Reserve University School of Medicine
Division Chief, Pulmonary, Critical Care & Sleep Medicine
University Hospitals Cleveland Medical Center
Cleveland VA Medical Center, VA Northeast Ohio Health System
Cleveland, Ohio
Chapter 11

Tulip Ajit Jhaveri, MBBS
Assistant Professor of Medicine, University of Mississippi School of Medicine
Attending Physician, Division of Infectious Diseases, University of Mississippi Medical Center
Jackson, Mississippi
Chapter 122

David H. Johnson, MD
R. Ellwood Jones, M.D. Distinguished Professorship in Clinical Education
Department of Internal Medicine
Division of Hematology/Oncology
UT Southwestern
Dallas, Texas
Chapter 116

Austin J. Jolly
MD/PhD Student, Department of Medicine
University of Colorado Anschutz Medical Campus
Aurora, Colorado
Chapter 90

Christopher M. Kapp, MD
Clinical Instructor of Medicine, Department of Medicine, University of Illinois at Chicago College of Medicine
Interventional Pulmonologist and Pulmonary Critical Care Medicine Physician, Department of Medicine, University of Illinois Hospital
Chicago, Illinois
Chapter 76

Joel D. Kaufman, MD, MPH
Professor
Departments of Environmental & Occupational Health Sciences
University of Washington
Medicine, and Epidemiology
Seattle, Washington
Chapter 89

Joshua B. Kayser, MD, MPH, MBE, FCCM
Professor of Clinical Medicine and Medical Ethics & Health Policy
Department of Medicine
Department of Medical Ethics & Health Policy
Perelman School of Medicine University of Pennsylvania
Philadelphia, Pennsylvania
Chapter 152

Michael P. Keane, MD, FRCP, FRCPI
Professor of Medicine
Dean and Head of School of Medicine
University College Dublin
Consultant Respiratory Physician
St. Vincent's University Hospital
Dublin, Ireland
Chapter 24

Andrea Kelly, MD MSCE
Attending Physician, Division of Endocrinology and Diabetes
Children's Hospital of Philadelphia
Professor of Pediatrics
Perelman School of Medicine at the University of Pennsylvania
Philadelphia, Pennsylvania
Chapter 48

Jeffrey A. Kern, MD
Professor of Medicine
National Jewish Health
University of Colorado, Denver
Chief, Oncology Division
Vice-Chair, Department of Medicine
National Jewish Health
Denver, Colorado
Chapter 107

Nick H. Kim, MD
Professor of Medicine
Section Chief, Pulmonary Vascular Medicine
Medical Director, Pulmonary Thromboendarterectomy Program
Pulmonary, Critical Care, and Sleep Medicine
University of California San Diego
La Jolla, California
Chapter 72

Corrine R. Kliment, MD, PhD
Assistant Professor
Department of Medicine
Division of Pulmonary, Allergy and Critical Care Medicine
University of Pittsburgh
University of Pittsburgh Medical Center
Pittsburgh, Pennsylvania
Chapter 18

Robert A. Klocke, MD
Emeritus Professor of Chairperson
Department of Medicine
Jacobs School of Medicine and Biomedical Sciences
University at Buffalo
Buffalo, New York
Chapters 15 and 16

Marin H. Kollef, MD
Director, Critical Care Research
Director, Respiratory Care Services Barnes-Jewish Hospital
Virginia E. and Sam J. Golman Chair in Respiratory Intensive Care Medicine
Professor of Medicine
Division of Pulmonary and Critical Care Medicine
Washington University School of Medicine
St. Louis, Missouri
Chapter 129

Dimitrios P. Kontoyiannis, MD, ScD, FACP, FIDSA
Frances King Black Endowed Professor, Infectious Diseases
Deputy Head
Division of Internal Medicine
The University of Texas MD Anderson Cancer Center
Adj Professor Baylor College of Medicine
Adj Professor University of Houston
Houston, Texas
Chapter 132

Robert M. Kotloff, MD
Craig and Elaine Dobbin/Nancy P. Blumenthal
Professor of Advanced Lung Disease
Perelman School of Medicine at the University of Pennsylvania
Philadelphia, Pennsylvania
Chapters 94 and 103

Darrell N. Kotton, MD
David C. Seldin Professor of Medicine
The Pulmonary Center and Department of Medicine
Boston University School of Medicine
Director, Center for Regenerative Medicine (CReM) of Boston
University and Boston Medical Center
Attending Physician
Department of Medicine
Boston Medical Center
Boston, Massachusetts
Chapters 8 and 39

Mary Elizabeth Kreider, MD, MSCE
Professor of Clinical Medicine
Vice Chief for Education and Faculty Development
Fellowship Program Director
Director, ILD Program
Division of Pulmonary and Critical Care Medicine
Perelman School of Medicine at the University of Pennsylvania
Philadelphia, Pennsylvania
Chapter 86

Arnold S. Kristof, MDCM, FRCPC
Associate Professor of Medicine
Meakins-Christie Laboratories and Translational Research in Respiratory
Diseases Program
Research Institute of the McGill University Health Centre
Departments of Critical Care and Medicine, McGill University
Montreal, Quebec
Chapter 60

Meir Kryger, MD, FRCPC
Professor, Pulmonary, Critical Care, and Sleep Medicine
Yale School of Medicine
New Haven, Connecticut
Chapters 47 and 101

Ricardo M. La Hoz, MD
Director, Solid Organ Transplant Infectious Diseases
Associate Professor of Internal Medicine
Department of Internal Medicine
Division of Infectious Diseases and Geographic Medicine
University of Texas Southwestern Medical Center
Dallas, Texas
Chapter 136

James H. Laird, MD
Resident Physician
Department of Therapeutic Radiology
Yale School of Medicine
Resident Physician
Yale New Haven Hospital
New Haven, Connecticut
Chapter 57

Daniel Langer, PT, PhD
Professor of Rehabilitation Sciences and Physiotherapy
Department of Rehabilitation Sciences
Research Group for Cardiovascular and Respiratory Rehabilitation
KU-Leuven
Respiratory Rehabilitation and Respiratory Division
University Hospital Leuven
Leuven, Belgium
Chapter 3

Kathleen A. Lee-Sarwar, MD, MS
Instructor, Harvard Medical School
Physician, Department of Medicine, Brigham and Women's Hospital
Boston, Massachusetts
Chapter 44

Andrew T. Levinson, MD, MPH
Associate Professor of Medicine, Clinician Educator
Program Director, Critical Care Medicine Fellowship
Warren Alpert Medical School of Brown University
Department of Medicine
Miriam Hospital and Rhode Island Hospital
Providence, Rhode Island
Chapter 96

Erik E. Lewis, MD
Fellow, Division of Cardiothoracic Surgery, University of Wisconsin
Hospitals and Clinics
Madison, Wisconsin
Chapter 81

Howard Y. Li, MD
Associate Professor
Department of Internal Medicine
Division of Pulmonary Disease and Critical Care Medicine
Virginia Commonwealth University
Director, Lung Cancer Screening
Medical Service
Section of Pulmonary and Critical Care Medicine
Hunter Holmes McGuire Veterans Affairs Medical Center
Richmond, Virginia
Chapter 107

Shu-Yi Liao, MD, MPH, MS, ScD
Assistant Professor of Medicine
Department of Medicine
National Jewish Health
Assistant Professor of Medicine
Department of Medicine
University of Colorado Anschutz Medical Campus
Physician
Department of Medicine
Division of Environmental & Occupational Health Sciences
National Jewish Health
Denver, Colorado
Chapter 88

Augusto A. Litonjua, MD, MPH
Professor of Pediatrics and Medicine
Department of Pediatrics and Department of Medicine
University of Rochester School of Medicine and Dentistry
Division Chief of Pediatric Pulmonary Medicine
Physician, Department of Pediatrics, Golisano Children's Hospital
Department of Medicine, Strong Memorial Hospital, University of
Rochester Medical Center
Rochester, New York
Chapter 44

Leslie A. Litzky, MD
Professor, Pathology and Laboratory Medicine
Perelman School of Medicine at the University of Pennsylvania
Chief of Surgical and Medical Pathology
Subspecialty Director, Thoracic Pathology
Hospital of the University of Pennsylvania
Philadelphia, Pennsylvania
Chapters 78 and 111

Jining Lu, PhD
Program Director
Division of Lung Diseases
National Heart, Lung, and Blood Institute
National Institutes of Health
Bethesda, Maryland
Chapter 4

Natalie S. Lui, MD
Assistant Professor of Cardiothoracic Surgery
Stanford University School of Medicine/Stanford Cancer Institute
Stanford, California
Chapter 82

Joseph P. Lynch, III, MD, FCCP, FERS
Holt and Jo Hickman Endowed Chair of Advanced Lung Disease and Lung Transplantation
Distinguished Professor of Clinical Medicine
Division of Pulmonary and Critical Care Medicine,
Clinical Immunology, and Allergy
David Geffen School of Medicine at UCLA
Los Angeles, California
Chapter 68

Kevin C. Ma, MD
Assistant Professor of Clinical Medicine
Section of Interventional Pulmonology and Thoracic Oncology
Division of Pulmonary, Allergy, and Critical Care
Perelman School of Medicine at the University of Pennsylvania
Philadelphia, Pennsylvania
Chapter 77

Roberto F. Machado, MD
Dr. Calvin H. English Professor of Medicine
Chief, Division of Pulmonary, Critical Care, Sleep, and Occupational Medicine
Department of Medicine
Indiana University
Indianapolis, Indiana
Chapter 95

Mitchell Machtay, MD
Professor of Radiation Oncology
Department of Radiation Oncology
Penn State University College of Medicine and Cancer Institute
Hershey, Pennsylvania
Chapter 115

Atul Malhotra, MD
Peter C. Farrell Presidential Chair and Tenured Professor of Medicine
University of California San Diego
Division of Pulmonary, Critical Care & Sleep Medicine
La Jolla, California
Chapter 10

Joshua Malo, MD
Associate Professor of Medicine, Clinical Scholar
Associate Director, Internal Medicine Residency
Program—Tucson Campus
Tucson, Arizona
Chapter 133

Scott Manaker, MD, PhD
Professor of Medicine
University of Pennsylvania
Hospital of the University of Pennsylvania
Philadelphia, Pennsylvania
Chapter 144

Jess Mandel, MD, MACP, ATSF
Kenneth M. Moser Professor of Medicine
Chief, Division of Pulmonary, Critical Care, and Sleep Medicine
Vice-Chair for Education, Department of Internal Medicine
UC San Diego School of Medicine
La Jolla, California
Chapter 72

Keshav Mangalick, MD
Resident Physician, Department of Medicine
New York University Grossman School of Medicine
Resident Physician, Department of Medicine
New York University Langone Health
New York, New York
Chapter 78

Patrick Mangialardi, DO
Senior Fellow, Pulmonary, Critical Care and Sleep Medicine
Department of Internal Medicine
Division of Pulmonary, Critical Care and Sleep Medicine
University of California, Davis, Sacramento
Veterans Administration Northern California Health Care System
Department of Medicine
Mather, California
Chapter 66

Nathaniel Marchetti, DO
Professor of Thoracic Medicine and Surgery
Department of Thoracic Medicine and Surgery
Lewis Katz School of Medicine at Temple University
Philadelphia, Pennsylvania
Chapter 84

Paul E. Marik, MD, FCCP, FCCM
Professor, Pulmonary and Critical Care Medicine
Department of Internal Medicine
Eastern Virginia Medical School
Norfolk, Virginia
Chapter 69

Fernando J. Martinez, MD, MS
Chief, Division of Pulmonary and Critical Care Medine
Joan and Sanford Weill Department of Medicine
Weill Cornell Medicine
NY Presbyterian Hospital
New York, New York
Chapter 50

Fiore Mastroianni, MD
Attending Intensivist and Pulmonologist
Department of Intensive Care and Pulmonary Medicine
Mather Hospital
Northwell Health
Port Jefferson, New York
Chapter 29

Aditi Mathur, MD
Attending Pulmonary Physician
Summit Health, Department of Pulmonary, Critical Care & Sleep Medicine
Hackensack University Medical Center
Montclair, New Jersey
Chapter 52

Michael A. Matthay, MD
Professor, Departments of Medicine and Anesthesia
Senior Associate Cardiovascular Research Institute
University of California San Francisco
Associate Director, Critical Care Medicine
University of California, San Francisco Medical Center
San Francisco, California
Chapter 140

Daniel N. Maxwell, MD
Fellow of Infectious Disease and Critical Care, UT Southwestern
Fellow of Infectious Disease and Critical Care
Parkland Hospital, Clements Hospital, North Texas VA Hospital
Dallas, Texas
Chapter 137

Paul H. Mayo, MD, FAACP
Professor of Clinical Medicine at the Donald and Barbara Zucker School of Medicine at Hofstra/Northwell
Academic Director of Critical Care
Division of Pulmonary, Critical Care, and Sleep Medicine
Department of Medicine
Northwell Health
New Hyde Park, New York
Chapter 29

Jeffrey Mazer, MD
Director of Pulmonary and Critical Care
Lovelace Medical Group
Albuquerque, New Mexico
Chapter 96

Peter J. Mazzone, MD, MPH
Section Head, Thoracic Oncology
Respiratory Institute
Cleveland Clinic
Cleveland, Ohio
Chapter 109

Cormac McCarthy, MD, PhD
Associate Professor of Medicine
School of Medicine, University College Dublin
Consultant Respiratory Physician, St. Vincent's University Hospital
Dublin, Ireland
Chapter 70

Daniel P. McCarthy, MD, MBA, MEM
Assistant Professor, Division of Cardiothoracic Surgery
University of Wisconsin Hospitals and Clinics
Madison, Wisconsin
Chapter 81

F. Dennis McCool, MD
Professor of Medicine, Warren Alpert Medical School of Brown University
Division of Pulmonary Critical Care and Sleep Medicine
Rhode Island Hospital
Providence, Rhode Island
Chapter 83

John E. McGinniss, MD
Assistant Professor of Medicine
Department of Medicine
Division of Pulmonary, Allergy, and Critical Care Medicine
Hospital of the University of Pennsylvania
Philadelphia, Pennsylvania
Chapter 121

Paul McLoughlin, MB, BCh, MRCPI, PhD
Professor of Physiology
University College Dublin
School of Medicine
Conway Institute of Biomedical and Biomolecular Research
St. Vincent's University Hospital
Dublin, Ireland
Chapter 24

Robert E. Merritt, MD, FACS
Professor of Surgery
Director, Division of Thoracic Surgery
Medical Director of Inpatient Services
The James Comprehensive Cancer Center
The Ohio State University Wexner Medical Center
Columbus, Ohio
Chapter 35

Joseph A. Miccio, MD
Assistant Professor of Radiation Oncology
Department of Radiation Oncology
Penn State University College of Medicine and Cancer Institute
Hershey, Pennsylvania
Chapter 115

Joseph P. Mizgerd, ScD
Jerome S. Brody, MD, Professor of Pulmonary Medicine
Professor of Medicine, Microbiology, and Biochemistry
Director, Pulmonary Center
Pulmonary Center, Boston University School of Medicine
Boston, Massachusetts
Chapter 20

Takudzwa Mkorombindo, MD
Division of Pulmonary, Allergy, and Critical Care Medicine
Lung Health Center
University of Alabama at Birmingham
Birmingham VA Medical Center
Birmingham, Alabama
Chapter 38

Edmund K. Moon, MD
Medical Director
Cell & Gene Therapy
Oncology R&D
Collegeville, Pennsylvania
Chapter 78

Richard E. Moon, MD, FACP, FCCP
Professor of Anesthesiology
Professor of Medicine
Duke University Medical Center
Durham, North Carolina
Chapter 92

Jorge I. Mora, MD
Associate Professor of Clinical Medicine
Perelman School of Medicine at the University of Pennsylvania
Associate Chief for Clinical Affairs and
Medical Director Division of Sleep Medicine
Hospital of the University of Pennsylvania
Director, Sleep Non-Invasive Ventilation Program
Philadelphia, Pennsylvania
Chapter 99

Alice Moroni, MD
Resident in Cardiology
University of Milano school of Medicine
Milano, Italy
Chapter 32

Joel Moss, MD, PhD
Senior Investigator, Pulmonary Branch
National Heart, Lung, and Blood Institute, National Institutes of Health
Clinical Center, National Institutes of Health
Bethesda, Maryland
Chapters 59, 60, and 62

Prerna Mota, MD
Assistant Professor of Medicine
Geisel School of Medicine at Dartmouth
Dartmouth-Hitchcock Medical Center
Lebanon, New Hampshire
Chapter 56

Susan Murin, MD, MBA
Professor and Associate Dean
Department of Internal Medicine
Division of Pulmonary, Critical Care and Sleep Medicine
University of California
Davis, Sacramento
Department of Medicine
Veterans Administration Northern California Health Care System
Mather, California
Chapter 66

Robert Naeije, MD, PhD
Professor of Physiology
Department of Physiology
Erasme Campus of the Free University of Brussels
Brussels, Belgium
Chapter 13

Girish B. Nair, MD, MS, FACP, FCCP
Division of Pulmonary and Critical Care
Beaumont Health
Associate Professor of Medicine
OUWB School of Medicine
Royal Oak, Michigan
Chapter 125

Camille Nelson Kotton, MD
Associate Professor, Harvard Medical School
Clinical Director, Transplant and Immunocompromised Host
Infectious Diseases
Infectious Diseases Division, Massachusetts General Hospital
Boston, Massachusetts
Chapters 123 and 138

Natalia Neparidze, MD
Associate Professor
Research DART Leader, Multiple Myeloma and Gammopathies Program
Section of Hematology
Department of Internal Medicine and Yale Cancer Center
Yale University School of Medicine
New Haven, Connecticut
Chapter 63

Nikolaus C. Netzer, MD, PhD
Prof. Prof.(Hon)/Director Hermann Buhl Institute for Hypoxia and Sleep Medicine Research
University Innsbruck
Innsbruck, Austria
Scientific Medical Director, Terra X Cube
Institute of Mountain Emergency Medicine
Eurac Research
Bozen, Italy
Chapter 91

Michael S. Niederman, MD, MACP, FCCP, FCCM, FERS
Professor of Clinical Medicine
Division of Pulmonary and Critical Care Medicine
New York Presbyterian/Weill Cornell Medical Center
Weill Cornell Medical College
New York, New York
Chapter 125

Paul W. Noble, MD
Professor of Medicine and Chair, Department of Medicine
Vera and Paul Guerin Family Distinguished Chair in Pulmonary Medicine
Medical Director, Women's Guild Lung Institute
Cedars-Sinai Medical Center
Los Angeles, California
Chapter 54

Eliezer Zachary Nussbaum
Fellow in infectious diseases
Department of infectious disease
Massachusetts General Hospital
Boston, Massachusetts
Chapter 134

Matthias Ochs, MD
Professor and Chair, Institute of Functional Anatomy, Charité—Universitätsmedizin Berlin, Germany
Chapter 2

Philip G. Ong, MD
Associate Professor of Medicine, Division of Pulmonary and Critical Care
UT Health San Antonio/University of Texas Health Science Center San Antonio
San Antonio, Texas
Chapter 79

David E. Ost, MD, MPH
Professor of Medicine, Department of Pulmonary Medicine
The University of Texas MD Anderson Cancer Center
Houston, Texas
Chapter 110

Gustavo Pacheco-Rodriguez, PhD
Staff Scientist, Pulmonary Branch
National Heart, Lung, and Blood Institute
National Institutes of Health
Bethesda, Maryland
Chapter 62

Allan I. Pack, MBChB, PhD
John Miclot Professor of Medicine
Division of Sleep Medicine
Department of Medicine
Perelman School of Medicine at the University of Pennsylvania
Philadelphia, Pennsylvania
Chapters 10 and 12

Henry S. Park, MD, MPH
Assistant Professor, Department of Therapeutic Radiology
Yale School of Medicine
Radiation Oncologist
Yale New Haven Hospital
New Haven, Connecticut
Chapter 57

John E. Parker, MD
Professor of Pulmonary Critical Care and Sleep Medicine
Department of Medicine
West Virginia University
Morgantown, West Virginia
Chapter 87

Nicholas J. Pastis, MD
Professor of Medicine
Director of Interventional Pulmonology
Interventional Pulmonology Fellowship Program Director
The Ohio State University Wexner Medical Center
Columbus, Ohio
Chapter 118

Susheel P. Patil, MD, PhD
Clinical Associate Professor of Medicine
Pulmonary, Critical Care, and Sleep Medicine
University Hospitals Cleveland Medical Center
Cleveland, Ohio
Chapter 100

Tyler J. Peck, MD
Instructor of Medicine, Harvard Medical School
Physician, Division of Pulmonary, Critical Care, and Sleep Medicine
Beth Israel Deaconess Medical Center
Boston, Massachusetts
Chapter 75

Jay I. Peters, MD
Professor of Medicine, Division of Pulmonary and Critical Care
UT Health San Antonio/University of Texas Health Science Center San Antonio and the South Texas Veterans Health Care System
San Antonio, Texas
Chapter 79

Steve G. Peters, MD
Professor of Medicine
Division of Pulmonary/Critical Care Medicine
Mayo Clinic
Rochester, Minnesota
Chapter 94

Sara Piciucchi, MD
Team Leader of Thoracic Radiology and Consultant
Department of Radiology
Ospedale GB Morgagni
Forlì, Italy
Chapter 119

Grace W. Pien, MD, MSCE
Program Director, Sleep Medicine Fellowship Program
Assistant Professor of Medicine
Pulmonary and Critical Care Division
Johns Hopkins School of Medicine
Baltimore, Maryland
Chapter 98

Gerald B. Pier, PhD
Professor of Medicine (Microbiology and Immunology)
Department of Medicine, Harvard Medical School
Senior Investigator, Department of Medicine
Brigham and Women's Hospital
Boston, Massachusetts
Chapter 124

Venerino Poletti, MD
Professor of Pulmonary Medicine, Dipartimento di Medicina Specialistica e Sperimentale (DIMES)
Università di Bologna
Bologna, Italy
Honorary Professor of Pulmonary Medicine
Department of Clinical Medicine
Aarhus University Hospital
Aarhus, Denmark
Head & Professor, Department of Pulmonology, Ospedale GB Morgagni
Forlì, Italy
Chapter 119

Jennifer D. Possick, MD
Associate Professor of Medicine
Department of Internal Medicine
Section of Pulmonary,
Critical Care, and Sleep Medicine
Yale School of Medicine
Director, Winchester Center for Lung Disease
Yale-New Haven Hospital
New Haven, Connecticut
Chapter 64

Niall T. Prendergast, MD
Research Fellow, Division of Pulmonary,
Allergy, and Critical Care Medicine
Attending Physician, Department of Medicine
University of Pittsburgh Medical Center
University of Pittsburgh
Pittsburgh, Pennsylvania
Chapter 151

Gregory P. Priebe, MD
Associate Professor of Anaesthesia, Harvard Medical School
Senior Associate in Critical Care Medicine
Department of Anesthesiology, Critical Care and Pain Medicine
Associate in Pediatrics
Department of Pediatrics, Division of Infectious Diseases
Boston Children's Hospital
Boston, Massachusetts
Chapter 124

Benjamin A. Raby, MD, CM, MPH
Professor of Pediatrics
Division of Pulmonary Medicine
Boston Children's Hospital
Harvard Medical School
Boston, Massachusetts
Chapter 9

Christopher H. Rassekh, MD, FACS
Professor of Clinical Otorhinolaryngology: Head and Neck Surgery
Department of Otorhinolaryngology: Head and Neck Surgery
Perelman School of Medicine at the University of Pennsylvania
Attending Physician, Co-Chair Airway Safety Committee
Director of Risk Reduction, Professional Practice, and
Salivary Gland Center
Department of Otorhinolaryngology: Head and Neck Surgery
Hospital of the University of Pennsylvania
Philadelphia, Pennsylvania
Chapter 145

John P. Reilly, MD, MSCE
Assistant Professor of Medicine
Division of Pulmonary, Allergy, and Critical Care
Department of Medicine
Perelman School of Medicine at the University of Pennsylvania
Philadelphia, Pennsylvania
Chapter 141

Stephen I. Rennard, MD
Internal Medicine, Division of Pulmonary, Critical Care, Sleep & Allergy
University of Nebraska Medical Center
Omaha, Nebraska
Chapter 41

Alejandro Restrepo, MD
Clinical Assistant Professor
Department of Medicine
UTMB Health
League City, Texas
Chapter 137

Scott I. Reznik, MD
Associate Professor
Department of Cardiovascular and Thoracic Surgery
University of Texas Southwestern Medical Center
Dallas, Texas
Chapter 113

Andrew L. Ries, MD, MPH
Professor of Medicine and Public Health
Associate Vice Chancellor for Health Sciences Academic Affairs
University of California, San Diego
San Diego, California
Chapter 42

M. Patricia Rivera, MD
C. Jane Davis & C. Robert Davis Distinguished
Professor in Pulmonary Medicine
Chief, Division of Pulmonary and Critical Care Medicine
University of Rochester
Associate Director of DEI, Wilmot Cancer Center
University of Rochester Medical Center
Rochester, New York
Chapter 112

Kenneth B. Roberts, MD
Professor, Department of Therapeutic Radiology
Yale University School of Medicine
Attending Physician, Department of Radiation Oncology
Yale-New Haven Health System
New Haven, Connecticut
Chapter 57

Matthew B. Roberts, MBBS, MPH&TM, FRACP
Infectious Diseases Physician, Infectious Diseases Unit
Royal Adelaide Hospital
Adelaide, South Australia
Chapter 123

Carolyn L. Rochester, MD
Professor, Section of Pulmonary, Critical Care and Sleep Medicine
Yale School of Medicine
New Haven, Connecticut
VA Connecticut Healthcare System
West Haven, Connecticut
Chapter 71

Karen Rodriguez, MD
Department of Radiology
Division of Thoracic Imaging & Intervention
Massachusetts General Hospital
Instructor, Harvard Medical School
Boston, Massachusetts
Chapter 117

Josanna M. Rodriguez-Lopez, MD
Instructor of Medicine, Harvard Medical School
Physician, Division of Pulmonary and Critical Care Medicine
Massachusetts General Hospital
Boston, Massachusetts
Chapter 75

William N. Rom, MD, MPH
Sol and Judith Bergstein Professor, Emeritus
Department of Medicine
Division of Pulmonary, Critical Care, and Sleep Medicine
NYU Grossman School of Medicine
Research Scientist
NYU School of Global Public Health
New York, New York
Chapter 85

Ilene M. Rosen, MD, MSCE
Assistant Dean for Graduate Medical Education
Vice Chair for Education, Department of Medicine
Associate Professor of Medicine
Division of Sleep Medicine
Perelman School of Medicine at the University of Pennsylvania
Philadelphia, Pennsylvania
Chapter 98

Leonid Roshkovan, MD
Department of Radiology
Hospital of the University of Pennsylvania
Perelman School of Medicine at the University of Pennsylvania
Philadelphia, Pennsylvania
Chapter 28

Andrew T. Roth, MD
Fellow
Department of Medicine
Division of Pulmonary and Critical Care Medicine
Washington University School of Medicine
St. Louis, Missouri
Chapter 129

Ami Rubinowitz, MD
Associate Professor of Radiology & Biomedical Imaging
Yale School of Medicine
Thoracic Imaging Section
Yale-New Haven Hospital
New Haven, Connecticut
Chapter 55

Lisa Ruvuna, MD
Fellow, Division of Pulmonary Sciences and Critical Care Medicine
University of Colorado Anschutz Medical Campus
University of Colorado School of Medicine
Denver, Colorado
Chapter 36

Edward T. Ryan, MD
Professor of Medicine, Harvard Medical School
Professor of Immunology and Infectious Diseases
Harvard T.H. Chan School of Public Health
Director, Global Infectious Diseases, Massachusetts General Hospital
Boston, Massachusetts
Chapter 135

Coralynn Sack, MD, MPH
Assistant Professor
Departments of Medicine and Environmental &
Occupational Health Sciences
University of Washington
Seattle, Washington
Chapter 89

Moiz Salahuddin, MD
Interventional Pulmonary fellow, Interventional Pulmonology
MD Anderson Cancer Center
Houston, Texas
Chapter 110

Amali E. Samarasinghe, MS, PhD
Plough Foundation Endowed Chair of Excellence
Director of the Pediatric Asthma Research Center
Associate Professor, Department of Pediatrics, Division of Pulmonology
University of Tennessee Health Science Center
Le Bonheur Children's Hospital
Children's Foundation Research Institute
Memphis, Tennessee
Chapter 21

Rahul G. Sangani, MD
Associate Professor, Section of Pulmonary, Critical Care and Sleep Medicine
West Virginia University Department of Medicine
Morgantown, West Virginia
Chapter 87

Thomas F. Scanlin, MD
Chief, Division of Pediatric Pulmonary Medicine and
The Cystic Fibrosis Center
Professor, Department of Pediatrics,
Rutgers, Robert Wood Johnson Medical School
New Brunswick, New Jersey
Chapter 48

Edward S. Schulman, MD
Professor of Medicine
Division of Pulmonary, Critical Care and Sleep Medicine
Director, Allergy and Asthma Research Center
Drexel University College of Medicine
Philadelphia, Pennsylvania
Chapter 21

Richard J. Schwab, MD
Professor of Medicine
Perelman School of Medicine at the University of Pennsylvania
Chief, Division of Sleep Medicine
The Hospital of the University of Pennsylvania
Philadelphia, Pennsylvania
Chapter 99

David A. Schwartz, MD
Distinguished Professor of Medicine and Immunology
Anschutz Medical Campus
University of Colorado Denver
Aurora, Colorado
Chapter 90

Bernardo Selim, MD
Associate Professor of Medicine
Medical Director of Respiratory Care Unit
Division of Pulmonary and Critical Care Medicine
Mayo Clinic
Rochester, Minnesota
Chapter 148

Mithu Sen, MD, FRCPC, DABSM, ABIM, FCCP, FCCM, FAASM
Professor of Medicine, University of Western Ontario
Schulich School of Medicine & Dentistry
Department of Medicine
Division of Respirology, Critical Care, & Sleep Medicine
London, Canada
Chapter 101

David S. Seres, MD
Professor of Medicine in the Institute of Human Nutrition
Director of Medical Nutrition
Associate Clinical Ethicist
Department of Medicine
Columbia University Irving Medical Center
New York, New York
Chapter 150

Hari M. Shankar, MD
Assistant Professor of Clinical Medicine
Department of Medicine
Division of Pulmonary, Allergy & Critical Care Medicine
Hospital of the University of Pennsylvania
Philadelphia, Pennsylvania
Chapter 146

Adrian Shifren, MBBCh, FCCP
Associate Professor of Medicine
Washington University School of Medicine
St. Louis, Missouri
Chapters 15 and 16

Joseph B. Shrager, MD
Professor of Cardiothoracic Surgery
Chief, Division of Thoracic Surgery
Director, Thoracic Oncology CCP
Stanford University School of Medicine/Stanford Cancer Institute
Stanford, California
Chapter 82

Costi D. Sifri, MD
Becton, Dickinson and Company Endowed Chair of Infectious Diseases and International Health Division of Infectious Diseases and International Health Department of Medicine, University of Virginia School of Medicine
Attending Physician and Director, Hospital Epidemiology/Infection Prevention & Control UVA Health
Charlottesville, Virginia
Chapter 127

Gerard A. Silvestri, MD, MS
Hillenbrand Professor of Thoracic Oncology
Senior Vice-Chair of Faculty Development
Department of Medicine
Medical University of South Carolina
Charleston, South Carolina
Chapter 118

Kimberly A. Smith, PhD
Research Associate
Department of Pediatrics
Northwestern University
Chicago, Illinois
Chapter 72

Nilam J. Soni, MD
Professor of Medicine, Academic Hospitalist
UT Health San Antonio/University of Texas Health Science Center San Antonio and the South Texas Veterans Health Care System
San Antonio, Texas
Chapter 79

Akshay Sood, MD, MPH
Professor, Department of Internal Medicine
University of New Mexico School of Medicine
Albuquerque, New Mexico
Chapter 36

Shweta Sood, MD, MS
Assistant Professor of Clinical Medicine
Medical Director of Perelman Harron Lung Center
Division of Pulmonary and Critical Care Medicine
The Perelman School of Medicine at the University of Pennsylvania
Philadelphia, Pennsylvania
Chapter 86

Ulrich Specks, MD
Professor of Medicine, Mayo Clinic College of Medicine and Science
Consultant, Department of Medicine
Division of Pulmonary and Critical Care Medicine
Mayo Clinic
Rochester, Minnesota
Chapter 74

Peter H.S. Sporn, MD
Professor of Medicine
Cell and Developmental Biology, and Medical Education
Northwestern University Feinberg School of Medicine
Chicago, Illinois
Chapter 21

Theodore J. Standiford, MD
Professor of Medicine
Chief, Division of Pulmonary and Critical Care Medicine
University of Michigan Medical Center
Ann Arbor, Michigan
Chapter 120

Robert C. Stansbury, MD
Associate Professor
Department of Medicine
Section of Pulmonary, Critical Care and Sleep Medicine
West Virginia University
Morgantown, West Virginia
Chapter 87

Daniel H. Sterman, MD, FCCP, ATSF, DAABIP
Thomas & Suzanne Murphy Professor of Pulmonary & Critical Care Medicine
Departments of Medicine and Cardiothoracic Surgery
Director, Division of Pulmonary, Critical Care & Sleep Medicine
Director, Multidisciplinary Pulmonary Oncology Program
Principal Investigator, NYU Pulmonary Oncology Research Team (NYU PORT)
NYU Grossman School of Medicine/NYU Langone Health
New York, New York
Chapters 33, 34, and 78

Kingman P. Strohl, MD
Professor, Medicine and Physiology & Biophysics
Case Western Reserve University
Cleveland, Ohio
Chapter 91

Erik R. Swenson, MD
Professor of Medicine and Physiology
Division of Pulmonary, Critical Care and Sleep Medicine
University of Washington School of Medicine
Attending Physician
Pulmonary, Critical Care and Sleep Medicine
VA Puget Sound Health Care System
Seattle, Washington
Chapter 143

Flora K. Szabo, MD, PhD
Assistant Professor of Pediatrics
Department of Pediatrics
Division of Gastroenterology, Hepatology and Nutrition
Children's Hospital of Richmond, VCU
Richmond, Virginia
Chapter 48

Nichole T. Tanner, MD, MSCR
Professor of Medicine
Co-Director, Hollings Lung Cancer Screening Program
Division of Pulmonary, Critical Care, Allergy and Sleep Medicine
Medical University of South Carolina
Core Investigator
Health Equity and Rural Outreach Innovation Center (HEROIC)
Ralph H. Johnson Veterans Affairs Hospital
Charleston, South Carolina
Chapter 118

Lynn T. Tanoue, MD, MBA
Professor of Medicine and Vice-Chair for Clinical Affairs
Department of Internal Medicine
Yale School of Medicine
Director, Lung Screening and Nodule Program
Yale Cancer Center, Yale New Haven Hospital
New Haven, Connecticut
Chapters 64 and 108

Kelan G. Tantisira, MD, MPH
Professor of Pediatrics
Chief, Department of Pediatrics
Division of Pediatric Respiratory Medicine
University of California San Diego and Rady Children's Hospital
San Diego, California
Chapter 9

Luis F. Tapias, MD
Assistant Professor of Surgery
Mayo Clinic College of Medicine and Science
Thoracic Surgeon, Mayo Clinic
Rochester, Minnesota
Chapter 80

Tachira Tavarez, MD, MSc
Clinical Associate, Neurosciences Critical Care
NIH T32 Post-Doctoral Research Fellow in Critical Care
Departments of Neurology, Anesthesiology & Critical Care Medicine
The Johns Hopkins University School of Medicine
Baltimore, Maryland
Chapter 150

Abdellatif Tazi, MD, PhD
Professor of Pulmonology, Medical School, Université Paris Cité, INSERM UMR 976
Human Immunology Pathophysiology and Immunotherapy
Head of Respiratory Department, National Reference Center for Histiocytoses
St. Louis Hospital, AP-HP
Paris, France
Chapter 59

Victor J. Thannickal, MD
Professor and Harry B. Greenberg Chair
John W. Deming Department of Medicine
Tulane University School of Medicine
New Orleans, Louisiana
Chapters 25 and 26

Sritika Thapa, MD
Clinical Instructor, Pulmonary, Critical Care, and Sleep Medicine
Yale School of Medicine
New Haven, Connecticut
Chapter 101

Jeffrey C. Thompson, MD, MTR
Assistant Professor of Medicine
Section of Interventional Pulmonology and Thoracic Oncology
Division of Pulmonary, Allergy, and Critical Care
Perelman School of Medicine at the University of Pennsylvania
Philadelphia, Pennsylvania
Chapter 77

Gregory Tino, MD
Associate Professor of Medicine
Perelman School of Medicine at the University of Pennsylvania
Chief, Department of Medicine
Penn Presbyterian Medical Center
Philadelphia, Pennsylvania
Chapters 31 and 51

Karen J. Tietze, PharmD
Professor of Clinical Pharmacy
Department of Pharmacy Practice
Philadelphia College of Pharmacy
St. Joseph's University
Philadelphia, Pennsylvania
Chapter 144

Martin J. Tobin, MD
Professor of Medicine
Division of Pulmonary and Critical Care Medicine
Loyola University of Chicago Stritch School of Medicine and Hines VA Hospital
Chicago, Illinois
Chapter 147

Kevin P. Toole
College of Science
University of Notre Dame
Notre Dame, Indiana
Chapter 58

Katrina E. Traber, MD, PhD
Assistant Professor of Medicine
Boston University
Pulmonary, Allergy, Sleep and Critical Care Medicine
Boston Medical Center
Boston, Massachusetts
Chapter 20

Bruce C. Trapnell, MD
Professor, Departments of Medicine and Pediatrics, University of Cincinnati
Attending Physician, Department of Medicine University of Cincinnati Medical Center
Attending Physician, Department of Pediatrics, Cincinnati Children's Hospital Medical Center
Cincinnati, Ohio
Chapter 70

John Treanor, MD
Emeritus Professor of Medicine
University of Rochester Medical Center
Rochester, New York
Chapter 126

Jun-Chieh J. Tsay, MD, MSc
Assistant Professor, Department of Medicine
Division of Pulmonary, Critical Care, and Sleep Medicine
NYU Grossman School of Medicine
Department of Medicine
VA New York Harbor Healthcare System
New York, New York
Chapter 85

Homer L. Twigg III, MD
Professor of Medicine
Department of Medicine
Division of Pulmonary, Critical Care, Sleep, and Occupational Medicine
Indiana University
Indianapolis, Indiana
Chapters 22 and 63

George E. Tzelepis, MD
Professor of Medicine
National and Kapodistrian University of Athens Medical School
Athens, Greece
Chapter 83

Asad Ali Usman, MD, MPH
Instructor of Anesthesiology and Critical Care
University of Pennsylvania
Hospital of the University of Pennsylvania
Philadelphia, Pennsylvania
Chapter 149

Omar S. Usmani, MBBS, PhD, FHEA, FRCP, FERS
Professor of Respiratory Medicine
National Heart and Lung Institute, Imperial College London
Royal Brompton Hospital and St. Mary's Hospital London
London, United Kingdom
Chapter 45

Anil Vachani, MD, MS
Associate Professor of Clinical Medicine
Section of Interventional Pulmonology
Division of Pulmonary, Allergy and Critical Care
Perelman School of Medicine at the University of Pennsylvania
Philadelphia, Pennsylvania
Chapter 33

Judith A. Voynow, MD
Edwin L. Kendig Jr. Professor of Pediatric Pulmonary Medicine
Department of Pediatrics
Virginia Commonwealth University School of Medicine
Children's Hospital of Richmond at VCU
Richmond, Virginia
Chapter 48

Peter D. Wagner, MD
Emeritus Distinguished Professor of Medicine and Bioengineering
Department of Medicine, University of California San Diego
La Jolla, California
Chapter 14

James M. Walter, MD
Assistant Professor
Department of Internal Medicine
Division of Pulmonary and Critical Care Medicine
Northwestern University Feinberg School of Medicine
Chicago, Illinois
Chapter 128

Tisha S. Wang, MD
Professor of Clinical Medicine
UCLA Department of Medicine
UCLA Division of Pulmonary, Critical Care, and Sleep Medicine
Ronald Reagan Medical Center
Los Angeles, California
Chapter 68

John K. Waters, MD
Assistant Professor
Department of Cardiovascular and Thoracic Surgery
University of Texas Southwestern Medical Center
Dallas, Texas
Chapter 113

Timothy E. Weaver, PhD
Professor of Pediatrics (retired)
Division of Pulmonary Biology
Cincinnati Children's Hospital Medical Center
Department of Pediatrics
University of Cincinnati College of Medicine
Trout Run, Pennsylvania
Chapter 5

Andrew Weber, MD
Attending Intensivist and Pulmonologist
Department of Intensive Care and Pulmonary Medicine
Mather Hospital
Northwell Health
Port Jefferson, New York
Chapter 29

Scott T. Weiss, MD, MS
Professor of Medicine, Harvard Medical School
Physician, Department of Medicine, Brigham and Women's Hospital
Boston, Massachusetts
Chapter 44

Matthew Wemple, MD
Clinical Associate Professor of Medicine
Division of Pulmonary, Critical Care and Sleep Medicine
University of Washington School of Medicine
Intensivist, Medical Director, MICU
Pulmonary, Critical Care and Sleep Medicine
VA Puget Sound Health Care System
Seattle, Washington
Chapter 143

Jeffrey A. Whitsett, MD
Kindervelt Professor of Pediatrics
Co-Director, Perinatal Institute
Chief, Division of Neonatology and Pulmonary Biology
Cincinnati Children's Hospital Medical Center
University of Cincinnati College of Medicine
Cincinnati, Ohio
Chapter 5

Kathryn A. Wikenheiser-Brokamp, MD, PhD
Professor, Department of Pathology & Laboratory Medicine
Cincinnati Children's Hospital Medical Center and University of Cincinnati
Cincinnati, Ohio
Chapter 61

Andrew A. Wilson, MD
Associate Professor of Medicine
The Pulmonary Center and Department of Medicine
Boston University School of Medicine
Director, The Alpha-1 Center of Boston University and
Boston Medical Center
Attending Physician
Department of Medicine
Boston Medical Center
Boston, Massachusetts
Chapter 39

Christopher E. Winstead-Derlega, MD
Undersea & Hyperbaric Fellow
Department of Emergency Medicine
The Outer Banks Hospital
Nags Head, North Carolina
Chapter 92

Robert A. Wise, MD
Professor of Medicine
Johns Hopkins University School of Medicine
Attending Physician
Johns Hopkins Hospital
Johns Hopkins Bayview Medical Center
Baltimore, Maryland
Chapter 40

Christine Won, MD, MS
Associate Professor of Medicine
Section of Pulmonary, Critical Care and Sleep Medicine
Yale University School of Medicine
Chapter 47

Cameron D. Wright, MD
Professor of Surgery, Harvard Medical School
Thoracic Surgeon, Massachusetts General Hospital
Boston, Massachusetts
Chapter 80

Joanne L. Wright, MD, FRCP(C)
Professor of Pathology, University of British Columbia
Pathologist, St. Paul's Hospital
Vancouver, British Columbia, Canada
Chapter 37

Richard G. Wunderink, MD
Professor of Medicine
Department of Medicine
Division of Pulmonary and Critical Care
Northwestern University Feinberg School of Medicine
Medical Director, Medical Intensive Care Unit,
Northwestern Memorial Hospital
Chicago, Illinois
Chapter 128

Hemang Yadav, MBBS
Assistant Professor of Medicine
Division of Pulmonary and Critical Care Medicine
Mayo Clinic
Rochester, Minnesota
Chapter 94

Henry K. Yaggi, MD, MPH, BA
Professor of Internal Medicine
Vice Chief of Research in Pulmonary, Critical Care & Sleep Medicine
Associate Director of Yale Pulmonary Critical Care Fellowship Program
Director of Yale Centers for Sleep Medicine
Division of Pulmonary and Critical Care Medicine
Yale University
New Haven, Connecticut
Chapter 148

Ying Yang, PhD
Columbia Center for Human Development
Department of Medicine
Columbia University Medical Center
New York, New York
Chapter 4

Jason X.-J. Yuan, MD, PhD
Professor and Director, Department of Medicine
University of California, San Diego
La Jolla, California
Chapter 72

Tanzira Zaman, MD
Assistant Professor of Medicine, Department of Medicine
Medical Director, Interstitial Lung Disease Program
Cedars-Sinai Medical Center
Los Angeles, California
Chapter 54

Yong Zhou, PhD
Associate Professor
Department of Medicine
University of Alabama at Birmingham
Birmingham, Alabama
Chapter 26

PREFACE

This, the 6th edition of *Fishman's Pulmonary Diseases and Disorders*, represents a major update of the prior edition. The book continues to incorporate broad and authoritative discussions of topics relevant to pulmonary physicians and those interested in sleep medicine and associated disorders; it also includes core topics of importance to the practice of critical care medicine. As in previous editions, the 6th relies heavily upon expert presentations of many basic science areas that, in the Editors' opinions, constitute an important substrate for clinically based discussions. The clinical sections of the book have been extensively revamped and expanded.

Notable content additions include important information on the respiratory effects of vaping, more detailed discussion of the idiopathic interstitial pneumonitides, an expanded presentation on the imaging and work-up of lung nodules, consideration of immunotherapy in the treatment of lung cancer, information on COVID-19–related lung disease and its management, and comprehensive discussion of noninvasive ventilation, including its use in ambulatory and ICU settings. In addition, new chapters on cystic lung disease, lung cancer screening, the lung microbiome, developmental lung disorders, nocardiosis and actinomycosis, and application of ECMO have been included. The work is extensively referenced, with more than 22,000 citations.

Remarkably, all the material presented was prepared during an unprecedented global pandemic caused by the coronavirus, SARS-CoV-2. At the time of the 6th edition's publication, more than 6.3 million deaths due to COVID-19 had been reported worldwide. The impact that the pandemic has had on all aspects of society, including health care, has been extraordinary. The fact that this edition was orchestrated during a time when those most engaged in its preparation were also heavily involved in caring for patients with coronavirus-related respiratory disease is noteworthy. The dedication of the scientists and clinicians globally who contributed to the volume during this time is duly recognized and greatly appreciated. In fact, the 6th edition is the result of contributions from 328 authors from many countries around the world, reflecting expertise that is truly global in nature; 141 are new to the publication.

Illustrations remain a pivotal component of the book, with nearly 2500 included in the book and online on *AccessMedicine.com.*

Preparation of this edition required the work of many. The Editors wish to express their sincere gratitude to the clinicians and scientists who contributed content. They are among the leading authorities on the topics on which they have written. The Editorial group itself includes three new members. Each has stepped up to the challenge and has invested considerable time and energy in helping to prepare the work. On a personal note, I'd like to express my sincere gratitude to all my Editor colleagues who collaborated in the book's development.

Finally, the Editors wish to thank key individuals on the McGraw-Hill staff who played important roles during the project, including Jason Malley, Executive Editor, Medical Publishing; Christie Naglieri, Senior Project Development Editor; and Leah Carton, Associate Editor.

Michael A. Grippi, M.D.

PART 1

Perspectives

CHAPTER 1

Milestones in the History of Pulmonary Medicine*

Michael A. Grippi

Clinical, scientific, and technologic aspects of medicine have evolved over more than 2000 years, and the study of lung function and pulmonary diseases has been an integral part of its growth and development. About 3 centuries ago, progress toward scientific medicine accelerated markedly, and it has continued to gain speed ever since. In the 17th century, research and experimentation began to tilt clinical medicine toward the exact sciences; by the 18th century, pathology had become an integral part of clinical medicine, and clinical–pathologic correlations succeeded empiricism, dogmatism, and metaphysics. The age of the great clinicians dawned in Europe in the early 19th century, when autopsies became legal and socially acceptable, and when physicians who cared for patients actually *performed* the autopsies.

The road to our current understanding and practice of pulmonary medicine and science has been somewhat convoluted.[1–3] However, it is possible to retrace the scientific trail by examining iconic figures and addressing milestones (Table 1-1). This chapter traces the course of scientific pulmonary medicine over the last two millennia. By necessity, what follows constitutes a limited overview of *selected* aspects of the history of the field, including alveolar–capillary gas exchange, lung volumes, mechanics of breathing, control of breathing, ventilation–perfusion relationships, and scientific advancements impacting clinical medicine, including chest imaging, lung transplantation, bronchoscopic techniques, and advances in critical care. Indeed, much of the content of the book addresses the many advances in respiratory disorders achieved over the last 50 years.

ALVEOLAR–CAPILLARY GAS EXCHANGE

In reflecting on the history of the science and thinkers largely responsible for our current understanding of the central role of the lungs in gas exchange, the following are considered: the ancient Greeks, William Harvey and the Oxford physiologists, the "phlogiston theory," theories of blood gas diffusion and "secretion" of oxygen, and the physical chemistry of blood gas transport.

Ancient Greek Medicine

The beginnings of scientific medicine can be traced to ancient Greece in the sixth century BC. At that time, natural philosophers speculated that air, or an essential ingredient in air, was inspired to generate a "vital essence" for distribution throughout the body.

Hippocrates, the "father of medicine," is as much a symbol of the Greek physician of the fifth and fourth centuries BC as the name of a real figure (Fig. 1-1). As an individual, he exemplified the caring physician who kept accurate records, made cautious inferences, and relied more on nature, rest, and diet than on drugs for treatment. His name has been immortalized by affixing it to three major components of Greek medicine, even though none appears to be the work of a single individual.

The first is the *Hippocratic corpus*, a collection of about 70 works that includes case reports, textbooks, lectures, and notebooks. The collection contains a description of Cheyne–Stokes respiration and the use of *Hippocratic succussion* for the diagnosis of fluid and air in the pleural space. The second is a collection of aphorisms—a compilation of brief generalizations related to medicine. The third, which is more likely attributable to Pythagoras (c. 530 BC) than Hippocrates (who lived about a century later), is the *Hippocratic oath*, which not only represents the spirit of the physician of ancient Greece, but which has endured to modern times as a reflection of the physician's code of ethics.

Another Greek, Aristotle, not only had an enduring influence on the intellect of humankind in his own time, but also for two millennia thereafter. Not until the 17th century were Aristotle's doctrine of the four elements (earth, air, fire, and water) and that of Hippocrates (blood, phlegm, yellow bile, and black bile) laid to rest, thereby clearing the way for modern scientific medicine.

Soon after Aristotle, in about 300 BC, an extraordinary medical school was founded at Alexandria in Egypt. One of the first teachers at the school, Erasistratus, postulated that the "pneuma," or spirit essential for life, is generated from interplay between air and blood.

About four centuries after Erasistratus, Galen (Fig. 1-2) drew upon the medical, philosophic, and anatomic knowledge of his day to fashion a remarkable physiologic schema.[3,4] His construct was largely teleologic. Unfortunately, it was so convincing that even though it was ultimately proved to be fanciful, it sufficed to retard scientific progress for a millennium and a half. Galen was a talented individual who was well educated, well read, and well positioned in society to popularize his beliefs. Moreover, his concepts fit well into the tenets of Christianity, which was then in its ascendency; to controvert his authority was tantamount to blasphemy. Among his long-lasting, albeit erroneous, postulates were the following: invisible pores in the ventricular septum that enabled the bulk of the blood to flow from the right ventricle to the left ventricle, thereby bypassing the lungs; a diminutive pulmonary circulation that served only to nourish the lungs; and two-way traffic in the pulmonary veins that enabled inspired air and "effluent waste vapors" to go their respective ways (Fig. 1-3).

Voices raised in protest to Galen's theories were without lasting effect. In the 13th century, Ibn al-Nafis, writing in his *Canon of Avicenna*, objected that blood does not traverse the ventricular septum from right to left, as Galen had proposed. However, this insight attracted little attention. Three hundred years later, Vesalius voiced similar misgivings. In the 16th century, Michael Servetus, a polymath trained in theology, geography, and anatomy, pictured the pulmonary circulation as the vehicle by which the "inhaled spirit" could be distributed throughout the body. In his theologic treatise, *Christianismi Restitutio*, he pointed out that blood could not traverse the septum between the right and left ventricles, and that the lumen of the pulmonary artery was too large for a nutrient vessel. He became a hunted heretic, wanted for execution by both the Catholic Church and Calvin. He was warned by Calvin to stay out of Geneva. Both Servetus and Calvin then behaved predictably: Servetus showed up at a church where Calvin was preaching, and Calvin had him captured and burned at the stake. In 1559, Realdus Columbus of Cremona, a pupil of Vesalius, rediscovered the pulmonary circulation, as did Andreas Caesalpinus in 1571. Despite these challenging observations, Galen's schema was to last for more than another half century—until the physiologic experiments of William Harvey.

William Harvey and the Oxford Physiologists

William Harvey's (Fig. 1-4) discovery of the circulation of the blood[5] was preceded by anatomic observations on the valves in systemic veins made by his mentor, Fabricus ab Aquapedente. Harvey's

---

*This chapter is a revision of the original chapter written by Alfred P. Fishman.

TABLE 1-1 Landmark Figures in the Evolution of Modern Pulmonary Medicine

Alveolar–Capillary Gas Exchange

Ancient Greek Medicine

- Hippocrates of Cos (c. 460–359 BC)
- Aristotle (384–322 BC)
- Erasistratus of Chios (c. 300–250 BC)
- Galen of Pergamon (AD 129–99)
- Ibn al-Nafis (c. 1210–1288)
- Leonardo da Vinci (1452–1519)
- Miguel Servetus (1511–1553)
- Andreas Vesalius of Brussels (1514–1564)
- Realdus Columbus of Cremona (1516–1559)
- Andreas Caesalpinus of Pisa (1519–1603)

William Harvey and the Oxford Physiologists

- Galileo Galilei (1564–1642)
- William Harvey (1578–1657)
- Giovanni Alfonso Borelli (1608–1679)
- Marcello Malpighi (1628–1694)
- Robert Boyle (1627–1691)
- Richard Lower (1631–1691)
- Robert Hooke (1635–1703)
- John Mayow (1640–1679)

Phlogiston: The Rise and Fall

- Georg Ernst Stahl (1660–1734)
- John Black (1728–1799)
- Joseph Priestley (1733–1804)
- Carl Wilhelm Scheele (1742–1782)

Respiration and Metabolism

- Antoine Laurent Lavoisier (1743–1794)
- John Dalton (1766–1844)
- Julius Robert von Mayer (1814–1878)
- Carl von Voit (1831–1908)
- Nathan Zuntz (1847–1920)

The Blood Gases

- Joseph Black (1728–1799)
- John Dalton (1766–1844)
- Heinrich Gustav Magnus (1802–1870)
- Felix Hoppe-Seyler (1825–1895)
- Paul Bert (1833–1886)
- Christian Bohr (1855–1911)
- John Scott Haldane (1860–1936)
- August Krogh (1874–1949)

Diffusion or Secretion of Oxygen

- Joseph Barcroft (1872–1947)
- Marie Krogh (1874–1943)

The Physical–Chemical Synthesis

- Lawrence J. Henderson (1878–1942)

Mechanics of Breathing

- John Hutchinson (1811–1861)
- Karl Ludwig (1816–1895)
- Franciscus Cornelius Donders (1818–1889)
- Fritz Rohrer (1888–1926)
- Wallace Osgood Fenn (1893–1971)

Control of Breathing

The Central Respiratory Centers

- Thomas Lumsden (1874–1953)
- Hans Winterstein (1878–1963)
- Merkel Henry Jacobs (1884–1970)

The Peripheral Chemoreceptors

- Ewald Hering (1834–1918)
- Joseph Breuer (1842–1925)
- Cornelius Heymans (1892–1968)

Scientific Basis of Clinical Medicine

Pathologic Anatomy

- Gioranni Battista Morgagni (1682–1771)
- Leopold Auenbrugger (1727–1809)
- Jean Nicolas Corvisart (1755–1821)
- René Théophile Hyacinthe Laënnec (1781–1826)

Microbiology

- Robert Koch (1843–1910)

Physiology of the Pulmonary Circulation

- Claude Bernard (1813–1878)
- Auguste Chauveau (1827–1917)
- Étienne Jules Marey (1830–1904)
- Dickinson W. Richards (1895–1973)
- André Frederic Cournand (1895–1988)
- Werner Forssmann (1904–1979)

Thoracic Imaging

- Wilhelm Conrad Roentgen (1845–1923)
- Godfrey N. Hounsfield (1919–2004)

Bronchoscopy

- Gustav Killian (1860–1921)
- Chevalier Jackson (1865–1958)
- Shigeto Ikeda (1925–2001)

Lung Transplantation

- Vladimir P. Demikhov (1916–1998)
- James D. Hardy (1918–2003)
- Joel D. Cooper

small book, *De Motu Cordis*, published in 1628, not only corrected a self-perpetuating error in Galenical teaching, but also marked the birth of modern physiology. The time, however, was not yet ripe to relate the function of the heart to the physiology of breathing. To his dying day, Harvey clung to the idea that the main function of breathing was to cool the heart. Moreover, since he made no use of the microscope, he could not picture how the pulmonary arteries made connections with the pulmonary veins. Galileo invented the compound microscope in 1610. In 1661, using the compound microscope, Marcello Malpighi reported that alveoli were covered by capillaries and that blood and air were kept separate by the continuous alveolar–capillary barrier.

Figure 1-1 The Hippocrates of Ostia. This damaged bust is believed to represent Hippocrates as perceived in antiquity. It was found in a family tomb in excavations near Ostia. *(Reproduced with permission from Dr. Dickinson W. Richards.)*

Figure 1-2 Galen of Pergamon as depicted in medieval times. No authentic reproduction exists of Galen in ancient times. *(Reproduced with permission from Galen's Therapeutica, published in Venice in 1500.)*

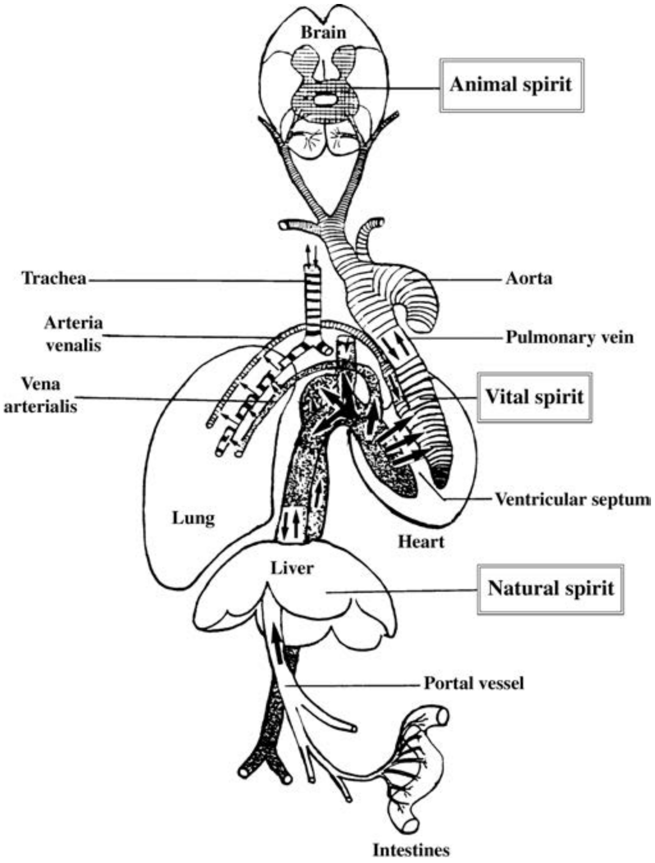


Figure 1-3 Galen's scheme of the circulation. The diagram shows the source and distribution of the three types of spirits. The validity of this scheme depended on invisible pores in the ventricular septum, two-way traffic in the pulmonary vein, and selective permeability of the mitral valve for sooty wastes but not for spirit-containing blood. Vena arterialis, pulmonary vein; arteria venalis, pulmonary artery. *(Modified with permission from Singer C. A Short History of Scientific Ideas to 1900. London: Oxford University Press; 1959.)*

Figure 1-4 William Harvey (1578–1657). This portrait of William Harvey is part of a family group in which William Harvey and his five brothers are gathered around their father, William Harvey.

Harvey's description in 1628 of the circulation of the blood had three major consequences for pulmonary medicine: (1) it oriented pulmonary medicine toward the basic sciences and away from philosophy and empiricism; (2) it demolished the Galenic concept of the movement of the blood; and (3) it set the stage for an upcoming generation of physiologists at Oxford University to explore breathing in chemical and physical terms.

The physiologists working at Oxford in the 1660s were greatly impressed by Harvey's disciplined approach to scientific inquiry. Many were medical practitioners who conducted research as a sideline. Four, in particular, began the systematic study of air and its constituents, thereby laying the foundations for contemporary respiratory physiology and medicine: Robert Boyle (Fig. 1-5), Robert Hooke, Richard Lower, and John Mayow.

In 1660, Robert Boyle proved by means of his air pump that air is necessary for life. In 1667, Robert Hooke showed that insufflation of the lungs with air while breathing movements were arrested could keep an open-chest animal alive; that is, that movement of the lungs was not essential for life. Richard Lower, the first to practice blood transfusion, took advantage of Hooke's continuously inflated lung preparation in the dog to observe that dark venous blood becomes bright red as it traverses lungs insufflated with air. In 1674, Mayow interpreted the change in the color of blood from venous to arterial as due to the uptake of "nitroaerial particles" (later to be called "oxygen") from the air.

Phlogiston: the Rise and Fall

Unfortunately, the discoveries and insights of the Oxford physiologists went largely unnoticed during the century that followed, overshadowed by the "phlogiston theory" of combustion. The theory, advanced by Stahl, postulated that all combustible materials were composed of two ingredients: phlogiston, a principle that transformed into fire when heated, and an ash that was left behind after the fiery phlogiston escaped. The phlogiston theory was sufficiently malleable to accommodate almost every new discovery that could have overthrown it, including the rediscovery of carbon dioxide in 1754 by John Black, and the independent discoveries of oxygen by Priestley and Scheele. Although the respiratory gases had been discovered by the end of the 18th century and many of their properties characterized, the discoveries were misapplied to support, rather than destroy, the phlogiston theory. The phlogiston theory was finally undone by the experiments of Lavoisier.

Figure 1-5 Robert Boyle (1627–1691). This engraving, from an original painting by Johann Kerseboom, hangs in the Royal Society, London. Boyle's invention of a pneumatic air pump and his publications concerning "the spring of air and its effect" stimulated considerable research on the physical properties of air and its role in respiration and combustion. He strongly influenced Hooke, Lower, and Mayow at Oxford.

Respiration and Metabolism

From the time of Hippocrates until early in the 20th century, debate had continued about the site of heat production in the body. In 1777, Lavoisier suggested that air was composed of one respirable gas (which he later named "oxygine") and another (nitrogen) that remained unchanged in the course of respiration. Between 1782 and 1784, Lavoisier and Laplace concluded, on the basis of calorimetric experiments on guinea pigs, that "respiration is therefore a combustion, admittedly very slow, but otherwise exactly similar to that of charcoal" (Fig. 1-6). The similarity between respiration and combustion had previously been recognized by the Oxford physiologists, especially Mayow.[6] By 1783, Lavoisier was accumulating evidence against the phlogiston theory and began to replace it with an entirely new system of chemistry.

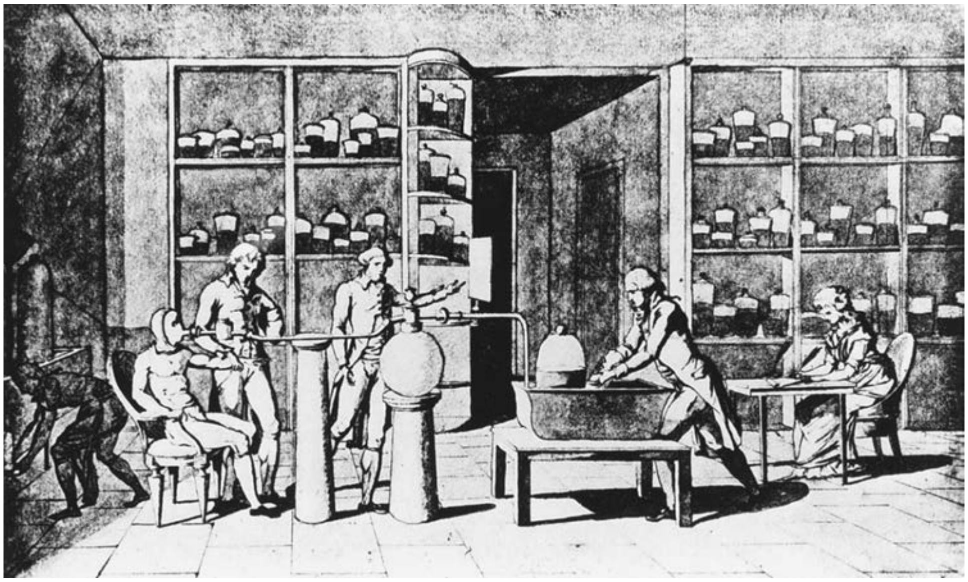


Figure 1-6 Scene from the laboratory of Antoine Laurent Lavoisier (1743–1794). His wife is acting as his assistant, and Sequin is the subject. Studies such as this led to the conclusion that respiration and combustion are similar processes.

As noted previously, the ancients pictured the heart as the heat generator. Lavoisier favored the lungs. Others held that combustion occurred in the blood. Although Spallanzani had shown in the 18th century that isolated tissues take up oxygen and evolve carbon dioxide, the idea that combustion occurred in the tissues was slow to gain acceptance. However, the hypothesis gained strength through the work of Pflüger in 1878. He measured oxygen consumption and carbon dioxide production in dogs and calculated respiratory quotients. His research substantiated a concept that had been enunciated, but not named, by Lavoisier.[7]

Once the idea that oxidation occurred in the tissues had become generally accepted, investigators delved into the processes involved in utilization of foodstuffs by the tissues, energetics, growth, and repair. Carl von Voit and Max von Pettenkofer, using a respiration chamber, drew upon chemical balances and respiratory quotients in humans to distinguish the nature of the foodstuffs being burned and to show that the amounts of fat, protein, and carbohydrate burned varied with the mechanical work done by the subject. Between 1842 and 1845, Julius Robert von Mayer formulated the law of conservation of energy. Subsequently, Max Rubner showed that the law applied to the living body, and Herman von Helmholtz showed that its relevance to metabolism could be demonstrated experimentally. Application of these principles at the bedside was greatly facilitated by the development of a portable metabolic apparatus by Nathan Zuntz. Pioneering bedside studies of metabolic states were conducted by a succession of distinguished investigators, including Magnus-Levy, Graham Lusk, F. G. Benedict, and Eugene F. DuBois.

■ The Blood Gases

The Oxford physiologists set the stage for the discovery of the blood gases. Using his vacuum pump, Robert Boyle extracted "air" from blood. John Mayow came close to discovering oxygen by showing that only a portion of air was necessary for life—the "nitroaerial spirits"—which were removed both by respiration and fire (combustion). One of his famous experiments entailed enclosing a mouse and a lighted lamp in an airtight container; the lamp went out first and then the mouse died. However, Mayow did not realize that the "nitroaerial spirits" could be isolated as a gas.[6]

One hundred years after Mayow, Joseph Priestley (Fig. 1-7) exposed a mouse to the gas released from heated mercuric oxide and found that the gas supported life better than air did; he also noticed that a flame burned more vigorously in this gas than in air. Priestley was not alone in his preoccupation with flame. In 1773, about a year before Priestley had obtained oxygen by heating mercuric oxide, Scheele discovered oxygen independently because of his interest in fire, and he designated oxygen as "fire air."

In 1662, Van Helmont, a Capuchin friar and talented chemist, as well as a mystic with a drive to quantify, discovered carbon dioxide, coined the word *gas*, and called carbon dioxide "wild gas" ("gas sylvestre"). In 1755, Joseph Black rediscovered carbon dioxide. He showed that calcium carbonate (limestone) and magnesium carbonate (magnesia alba) lost weight on heating, releasing "fixed air" (CO_2) in the process. This fixed air extinguished both flame and life. Lavoisier knew of the observations of Black and of Priestley

Figure 1-7 Joseph Priestley (1733–1804), the discoverer of oxygen. This figure shows a silver medal struck in his honor in 1783. A Presbyterian minister, he was radical in his religious and political beliefs, inventive in science, and conservative in the interpretation of his findings. *(Reproduced with permission from Fishman AP, Richards DW. Circulation of the Blood: Men and Ideas. New York, NY: Oxford University Press; 1964.)*

Figure 1-8 Christian Bohr (1855–1911). At work in his laboratory, Bohr *(far right)* and his associates systematically explored the interplay between the respiratory gases and hemoglobin that led to the discovery of the "Bohr effect." *(Reproduced with permission from Fishman AP, Richards DW. Circulation of the Blood: Men and Ideas. New York, NY: Oxford University Press; 1964.)*

and Scheele. He decided in 1778 that the gas obtained from heating mercuric oxide was not "fixed air" or "common air," but "highly respirable air" (oxygen).

The story of hemoglobin, the essential element in the transport of the respiratory gases by the blood, begins with Hoppe-Seyler, who, between 1866 and 1871, crystallized hemoglobin, explored its chemical properties, and assigned it a proper role in the transport of oxygen by the blood. At the turn of the 19th century, Dalton reported his experiments with the respiratory gases, which led to the development of his atomic theory. In 1872, taking advantage of Dalton's law, Paul Bert published the first oxygen dissociation curve, that is, oxygen content at different barometric pressures; he pictured the curve as hyperbolic. Christian Bohr (Fig. 1-8) subsequently identified its s-shaped contour, and in 1904, together with Hasselbach and August Krogh, showed that increasing carbon dioxide tension in blood drives out oxygen, that is, the "Bohr effect." Shortly thereafter, the influence of various factors, for example, temperature and electrolytes, on the affinity of oxygen for hemoglobin (and, consequently, on the position of the oxygen dissociation curve) was explored in detail by Barcroft and associates. In 1914, Christiansen, Douglas, and Haldane reported that an increase in the oxygen tension of the blood drives out carbon dioxide, that is, the "Haldane effect." In 1967, a new dimension was added to the understanding of the position and configuration of the oxygen dissociation curve by the demonstration that diphosphoglycerate, a chemical constituent of red cells, regulates the release of oxygen from oxyhemoglobin.

■ Diffusion or Secretion of Oxygen

Bohr is a central figure as an investigator and mentor in respiratory physiology.[8] In 1904, he raised a troublesome issue that was not easily resolved, primarily because of limitations in methodology at the time. He postulated that even though diffusion could account for oxygen uptake at rest, it could not suffice during strenuous exercise, particularly at altitude. He held that oxygen *secretion* had to be involved.[9] He clung to this misconception during his lifetime, a conviction supported by two major lines of evidence. The first was indirect: Oxygen secretion by the swim bladder of fish showed by extrapolation that active transport of oxygen in the lungs was possible. The second was based on observations made during Bohr's expedition to Pike's Peak in 1912, during which it was erroneously demonstrated that with exercise at altitude, arterial oxygen tension exceeded alveolar oxygen tension.

However, even before the report from high altitude, Bohr's former assistant, August Krogh, and his wife, Marie Krogh (Fig. 1-9) had marshaled new evidence to show that "the absorption of oxygen and the elimination of carbon dioxide in the lungs takes place by diffusion and diffusion alone." The final blow to the secretion theory was delivered by Marie Krogh.[10] Based on the single-breath carbon monoxide method for determining diffusing capacity that she and her husband had developed in 1910,[11] she was able to account for oxygen uptake in the lungs by diffusion alone, even during strenuous exercise under conditions of low oxygen tension. Refinements in the carbon monoxide method by Roughton and others extended

Figure 1-9 August and Marie Krogh in 1922, at the time of their first visit to the United States so that August Krogh could deliver the Silliman Lecture at Yale. They demonstrated that diffusion, without secretion, could account for the transfer of O_2 and CO_2 across the alveolar–capillary membranes of the lungs. *(Reproduced with permission of their daughter, Dr. Bodil Schmidt-Nielsen.)*

Figure 1-10 Two founders of contemporary respiratory physiology in 1936. Sir Joseph Barcroft (1872–1947) *(left)* proved, in experiments on himself, that diffusion was the mechanism for gas exchange in the lungs and pioneered current understanding of the respiratory functions of the blood. Lawrence J. Henderson (1878–1942) *(right)* provided a mathematical analysis of blood as a physiochemical system and stimulated research on the complex interplay involved in respiratory gas exchange during exercise. *(Reproduced with permission from Fishman AP, Richards DW. Circulation of the Blood: Men and Ideas. New York, NY: Oxford University Press; 1964.)*

its clinical applicability and provided further evidence against the secretion theory.[12] Despite these observations, Haldane would not let go. Throughout his life, despite mounting evidence to the contrary, he adhered to the idea that oxygen was secreted by the alveolar membrane.

The issue was finally settled by Joseph Barcroft (Fig. 1-10). Using a chamber to reproduce the circumstances of hypoxia and strenuous exercise assessed during the Pike's Peak expedition, he found that under all conditions, the oxygen saturation of arterial blood was less than that of arterial blood exposed to a sample of alveolar gas obtained at the same time. He subsequently confirmed these results by experiments done at high altitude at Cerro de Pasco (1921–1922).

■ The Physical–Chemical Synthesis

Lawrence J. Henderson undertook the herculean task of depicting the reactions of oxygen and carbon dioxide in blood, not as cause and effect, but as interplay among physiochemical variables and functions (Fig. 1-10). His theoretical considerations and practical applications in the Fatigue Laboratory at Harvard University were greatly abetted by close collaboration with Van Slyke, Wu, and McLean at the Rockefeller Institute in New York, who were exploring the exchanges of blood constituents between red cells and plasma. In 1828, Henderson presented his synthesis in the form of a d'Ocagne nomogram that displayed changes in the various elements that entered into the exchange of the respiratory gases between alveolar gas and blood: plasma; the red cell; hemoglobin; and chloride, bicarbonate, and hydrogen ions. He presented nomograms not only for the normal subject at rest and during exercises, but also for individuals with anemia, nephritis, diabetic coma, and other major clinical entities. Henderson dealt with steady-state observations. Roughton and associates enlarged the physiochemical horizons further by discovering carbonic anhydrase in the red cell and addressing transient phenomena related to transport of respiratory gases and carbon monoxide in blood.

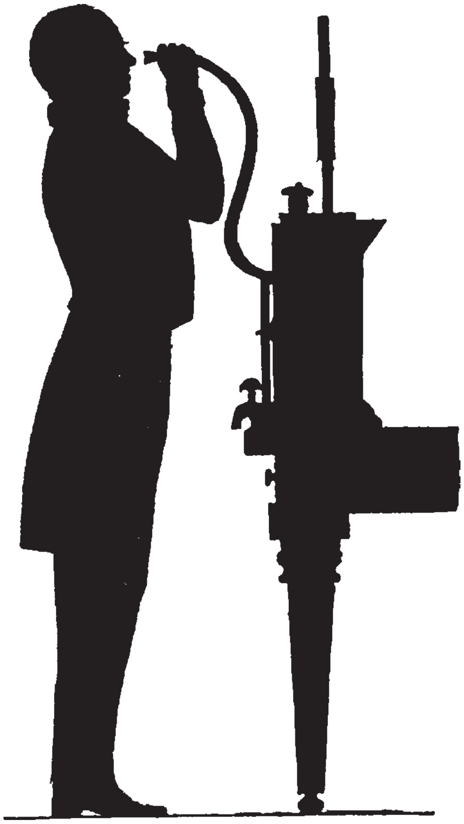


Figure 1-11 John Hutchinson's illustration of a subject about to undergo measurements of lung volumes. *(Reproduced with permission from Hutchinson J. On the capacity of the lungs, and on the respiratory functions, with a view of establishing a precise and easy method of detecting disease by the spirometer. Med Chir Trans. 1846;29:137–252.)*

LUNG VOLUMES

Although Humphrey Davy had determined his own lung volume using hydrogen as the test gas in 1800,[13] it was not until the 1840s that John Hutchinson laid the groundwork for modern pulmonary function testing. He devised a spirometer and used it to determine the subdivisions of the lung in a large number of healthy subjects, relating the measurements to height and age (Fig. 1-11). The many refinements since then are too numerous for mention in this chapter. A big step forward was the invention of the body plethysmograph many years later, which made possible the determination of the thoracic gas volume and airway resistance.

MECHANICS OF BREATHING

The ancients wondered how air moved into and out of the lungs; as far back as the time of Erasistratus, the diaphragm was recognized as involved in breathing. Galen was aware that the lungs fill the chest cavity and are moved by the actions of the thorax, and that the large airways enlarge and lengthen during inspiration. He marveled at the long course of the nerves to the diaphragm and the innervation of the intercostal muscles. After Galen, interest in the mechanics of breathing waned except for sporadic observations and experiments by anatomists, notably Leonardo da Vinci and Andreas Vesalius. Interest in respiratory mechanics resumed in the 16th century, largely as a result of progress in physics and mathematics, as exemplified in the works of Borelli and Galileo.

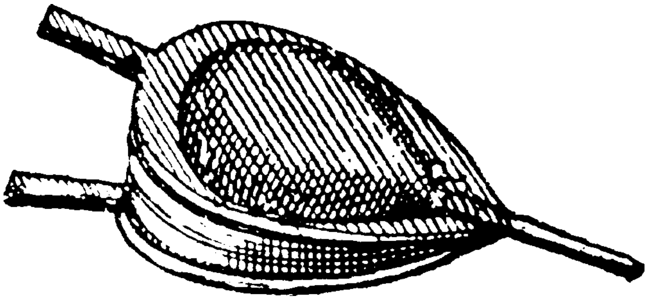


Figure 1-12 Mayow's model of the chest and lungs. The bellows encloses a bladder, the neck of which opens to the outside. A glass window on the upper side makes it possible to observe the bladder during inflation and deflation. *(Reproduced with permission from Mayow J: Medico-Physical Works, Crum A, Brown, Dobbin L [trans]. Edinburgh, Alembic Club, Reprints, no 17, 1957. [Translated from Tractatus quinque medico-physics, 1674.])*

The Respiratory Muscles

Mayow, one of the Oxford physiologists, drew heavily on the work of colleagues, including Boyle and Hooke, to develop considerable insight into the mechanics of breathing. He also built the first model on record of the chest as a bellows, which contained a bladder within it (Fig. 1-12). He understood that air moved into the lungs as the chest expanded because of the pressure and elasticity of ambient air; he also appreciated that the chest expands because of the action of the intercostal muscles (internal and external), that the diaphragm is the primary muscle of inspiration, and that normal expiration is passive. After Mayow, little research was done on the role of the respiratory muscles in breathing until the mid-19th century, when Donders distinguished between the respective roles played by the inspiratory muscles and elastic forces.

Elastic Properties of Lungs and Chest Wall

Until the 20th century, observations on the elastic properties of the lungs and chest wall in humans were fragmentary. Access to the pleural space was the major limiting factor. With few exceptions—notably Neergaard and Wirz, who used pleural pressures to determine elastic recoil in normal human subjects, and Christie, who recorded pleural pressures to demonstrate loss of pulmonary elasticity in emphysematous patients—measurements in humans were largely confined either to therapeutic interventions, for example, induction of a pneumothorax or aspiration of pleural fluid, or experiments done at autopsy. The number of observations on the mechanical properties of the lungs increased dramatically when it was shown by Buytendijk, in 1949, and again by Dornhurst and Leathart, in 1952, that esophageal pressures provided an accurate measure of pleural pressures.

The role of alveolar surface tension in determining the elastic forces in the lungs began to be widely appreciated in the late 1950s, although the stage had been set long before. In 1812, Laplace had published the law of surface tension. The implication of this law for the lungs was appreciated initially in 1929 when Neergaard compared pressure–volume curves of lungs filled with air with those filled with fluid. He concluded that unopposed surface tensions would favor alveolar collapse. Then, between 1954 and 1960, a remarkable outpouring of papers from different laboratories showed that a unique surfactant lined the alveoli, and that this material was absent in premature infants with hyaline membrane disease (and alveolar collapse); these papers prompted extensive research on the chemical and physical properties of surfactant and on its sites of formation and removal.

Airway Resistance

A giant step forward occurred in 1916 when Rohrer, as part of his doctoral dissertation, presented a conceptual framework for determining flow and resistance in airways. His equations were based on precise anatomic measurements of airway dimensions in a human cadaver, coupled with aerodynamic principles. During the following decade, he and his coworkers, Neergaard and Wirz, applied Poiseuille's law for laminar flow and his equations to the determination of airway resistance. Use of Fleisch's pneumotachograph, coupled with periodic interruptions of airflow, permitted measurement of alveolar pressure. Clinically useful measurements of alveolar pressure became available in 1956 with the introduction by DuBois and associates of the whole-body plethysmograph, which they coupled with the application of Boyle's law.

Synthesis of Mechanics

During the decade between 1915 and 1926, Rohrer and his colleagues provided a remarkably comprehensive synthesis of respiratory mechanics that included a description of the static pressure–volume characteristics of the respiratory system and the work of breathing; they also developed the principle of optimal frequencies of breathing to minimize respiratory work. Together with von Neergaard and Wirz, Rohrer developed and tested, experimentally, concepts involving pressures, flows, and volumes. The full significance of Rohrer's work was not appreciated until the publications by Fenn and his group at the University of Rochester, starting in the 1940s. The contributions of W. O. Fenn, H. Rahn, and A. B. Otis to our present understanding of the mechanics of breathing are significant, and there is little doubt that this group shaped much of the contemporary thinking of respiratory physiologists and pulmonary physicians.[14–17]

CONTROL OF BREATHING

The control of breathing is a complex process that depends on the integrity of the entire respiratory system—lungs, airways, circulation, and control systems.[18] Two dominant control systems exist. One is in the central nervous system; the other is outside the brain. Control mechanisms in the central nervous system are influenced by the state of wakefulness or alertness and are subject to voluntary control. These mechanisms are also influenced reflexively by a variety of peripheral receptors.

Localization of the Central Respiratory Centers

In 1812, Legallois, apparently intrigued by the gasping movements of the head after decapitation, identified an area in the medulla that was essential for life. In 1923, Lumsden systematically explored the effects of serial sectioning of the brain stem on respiration, marking the beginning of the era of contemporary research on rhythmic breathing. He designated an area in the caudal pons responsible for a sustained inspiratory drive as the "apneustic center," and an area in the rostral and lateral portions of the pons that presumably inhibited the apneustic drive as the "pneumotaxic center"; sectioning of the vagi exaggerated the inhibition of the apneustic drive by the pneumotaxic center. Sixteen years later, Pitts et al.,[19] using stereotactic stimulation of the cat medulla, identified inspiratory and expiratory centers and proposed a theory that could account for both rhythmic breathing and apneusis.

Chemical Stimulation of the Respiratory Centers

The chemical stimuli to breathing have been known for more than a century. In 1885, Miescher-Ruesch showed in humans that ventilation at rest is primarily regulated by carbon dioxide. Between 1887 and 1901, cross-perfusion experiments by Leon Fredericq underscored the role of carbon dioxide. However, it was not until 1905